

Systematic Review

Surgical management of intrahepatic and hilar cholangiocarcinoma: liver resection versus liver transplantation

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ABSTRACT

The incidence of cholangiocarcinoma is increasing worldwide. Patients present with abdominal pain, whereas weight loss and malaise are symptoms of advanced disease. Jaundice occurs when there is hilar obstruction by the tumor. Surgical management involves resection of the affected hepatic segments or liver transplantation, which requires a dedicated multidisciplinary team approach, and promising outcomes are seen in high-volume centres. The authors employed a search strategy for databases like PubMed and Google Scholar. The authors then reviewed the articles using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines and compared data concerning postoperative complications, recurrence rates, five-year survival rates and prognosis. Liver resection confers long-term survival in patients with intrahepatic cholangiocarcinoma, though the prognosis and morbidity of this procedure are still gloomy. Liver transplantation could be an option, either in early stages diagnosed in the context of chronic liver diseases or locally advanced tumors, when neoadjuvant treatments have achieved sustained tumor response without extrahepatic tumor spread.

Keywords: Cholangiocarcinoma, Liver transplantation, Liver resection, Loco-regional therapy, Outcomes, Survival

INTRODUCTION

Cholangiocarcinoma ranks second amongst the primary neoplasms of the liver, accounting for 10-15% of such cases and is on an alarming rise worldwide.¹⁹

It originates from the biliary epithelium and histologically is adenocarcinoma in 95% of the cases. Anatomically, it is classified as per the tumor location into intrahepatic, hilar and extrahepatic cholangiocarcinomas.^{4,20} Curative resection offers the only chance for long-term survival in patients with hilar cholangiocarcinoma.⁵ However, treatment remains challenging and includes surgical resection combined with neoadjuvant or adjuvant therapies, external beam radiation therapy and systemic chemotherapy. Complete surgical resection (R0) is the only option for long-term survival, which varies from 20–40% at five years in most series reviewed.^{1,2,5} However,

there have been problems in the limited resection procedure regarding having free surgical margins in the resected proximal hepatic ducts and achieving long survivals without tumor recurrence.^{2,4} Although hepatic resection appears to be the primary treatment for cholangiocarcinoma, extensive perineural and lymphatic invasion, bilateral liver involvement, and vascular encasement preclude complete tumor resection.⁶ In patients with an unresectable tumor because of technical reasons or impaired hepatic function, and where conventional resection surgery was limited, total hepatectomy with liver transplantation has been carried out. Total hepatectomy followed by orthotopic liver transplant thus might offer a chance for significant improvement in the overall survival rates and availability of wide tumor-free margin without any underlying liver pathology.^{1,2} A protocol using preoperative irradiation and chemotherapy to control the tumor growth and decrease

the recurrence rates at the Mayo Clinic paved the way for managing this disease.² In the last few decades, as outcomes of liver transplantation have improved, the indications for the same have been extended to include other malignant conditions, including neuroendocrine liver metastases, colorectal liver metastases, and cholangiocarcinoma (both intrahepatic and hilar).^{3,7} This study, a systematic review thus, attempts to put the arguments about the two surgical modalities for treating cholangiocarcinoma at rest.

Aim

Aim of the study was to compare the outcomes for patients undergoing liver transplantation and liver resection in cases of cholangiocarcinoma.

METHODS

This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines based on the authors' predetermined inclusion criteria (Figure 1). Five authors screened the literature independently, and resolved discrepancies after reaching a consensus. Full-text articles of retrospective studies published in English, which reported outcomes of patients who underwent liver transplantation vs liver resection for hilar or intrahepatic cholangiocarcinoma, were included. A few articles relevant to the study, retrieved as full free texts from the reference list, were also included. Because of the limited number of related studies, retrospective investigations or observational studies were included. 1, 3, 5-year survival rates, as well as the rate of disease recurrence, were looked for in the selected articles. Articles of case series, letters, editorials, preclinical studies, and case reports mentioning other treatment modalities or those published in languages other than English were excluded.

Search strategy

"Cholangiocarcinoma" [Mesh] and "liver transplantation" [Mesh] were employed for the PubMed database for articles published from 1993 to October 2022. Another database searched was Google Scholar. Search terms used were "intrahepatic", "hilar", "cholangiocarcinoma", "Klatskin", "liver transplantation", and "liver resection". Quality appraisal was done using Newcastle Ottawa tool for non-randomized studies. Ethics approval was not required because this study was based on aggregate data.

RESULTS

Data extraction from electronic databases like PubMed and Google Scholar and further review of publications (1993 to 2022) led to the selection of 7 articles that compared the two surgical modalities for treating cholangiocarcinoma. The numbers and rates of R0 resections, survival rates at 1,3 and 5 years and the

recurrence rates of both modalities were noted in each study (Tables 1-3).

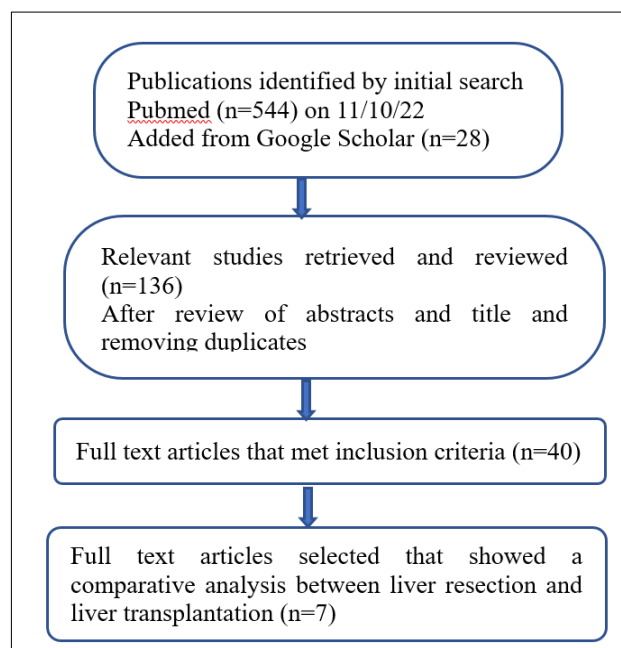


Figure 1: PRISMA flow diagram.

DISCUSSION

Cholangiocarcinoma presents a significant challenge to clinicians. Most of the time presents at a late stage when resection is often not the option available. In early disease, surrounding hilar structures, lymphatics, and peri neural and vascular involvement preclude complete resection.⁶ Concomitant primary sclerosing cholangitis (PSC) is not ideal for liver resection. Also, for diffuse and central disease, curative resection becomes difficult. In such difficult cases, liver transplantation looks promising as an alternative, allowing for wide excision margins and decreased possibility of tumor spillage, theoretically permitting R0 resection. It is an attractive option for those affected with PSC as it leaves no residual disease and offers normal liver function to the individuals.^{9,21} The use of neoadjuvant radiation therapy before transplantation was pioneered at the University of Nebraska. Sudan et al developed a protocol wherein 6000 cGy brachytherapy is delivered through percutaneous transhepatic catheters, and 5 F.U. intravenous infusion is delivered until transplantation.¹² A landmark study was done at the Mayo Clinic with more than a decade of experience since 1993. Results showcased promising outcomes in survival and tumor-free survival rates in selected patients suffering from unresectable disease, post-neoadjuvant chemoradiation and administration of 5 F.U. until transplantation. Moreover, a staging laparotomy was also performed to limit transplantation to patients with localized disease and no regional lymph nodal metastases.^{2,18} This modality required a multidisciplinary team approach.

Table 1: An overview of the studies.

Study	Study period	Type of study	Adjunctive therapy	Number of patients who underwent liver trans-plantation	Number of patients who underwent liver resection	Primary sclerosing cholangitis patients (n)
Rea et al ⁸	January 1993-August 2004	Nonrandomized trial, update to the initial Mayo series	Neoadjuvant for transplant group, adjuvant for resection group	38	26	22 in transplant, 2 in resection groups
Ethun et al ⁹	January 2000- March 2015	Multicentric, retrospective, intention-to-treat analysis	Neoadjuvant for transplant group, adjuvant for resection group	41	191	25 in transplant, 3 in resection groups
Iwatsuki et al ¹⁰	1981-1996	Retrospective, single centre	Patients variably received neoadjuvant/ adjuvant therapies as per the changes in protocol	38	34	1 in transplant group
Croome et al ⁶	1993-2013	Retrospective, single centre	Neoadjuvant for transplant group, Adjuvant for resection group	54	99	Not mentioned
Hong et al ¹¹	1985-2009	Retrospective, single centre	Neoadjuvant for transplant group, adjuvant for resection group	38	19	14 in transplant group
De Martin et al ¹²	2002-2015	Retrospective, multicentric	Patients variably received neoadjuvant and adjuvant therapies in both the groups	49	26	Not mentioned
Hue et al ¹³	2010-2016	Matched trial	Patients variably received neoadjuvant and adjuvant therapies in both the groups	57	57	Not mentioned

Table 2: Summary of overall survival and recurrence rates in the selected studies for both the modalities and conclusions derived.

Study	Recurrence after liver transplantation	Recurrence after liver resection	R0 resection (n)	Overall survival rates after liver transplantation % (1, 3, 5 year)	Overall survival rates after liver resection % (1, 3, 5 year)	Limitations	Conclusion
Rea et al ⁸	0, 5, 12% at (1, 3, 5 years)	5, 44, 58 % at (1, 3, 5 years)	23	92, 82, 82	82, 48, 21	No difference in survival rates between both groups in an intention-to-treat analysis	Liver transplantation with neoadjuvant therapy is an alternative to liver resection for selected patients with localized, node-negative hilar cholangiocarcinoma
Ethun et al ⁹	24%	37%	12	80, 58, 53	66, 29, 17	Small sample size, retrospective, selection bias	Resection for hilar cholangiocarcinoma that meets criteria for transplant (<3 cm and lymph node negative disease) is associated with significantly decreased survival compared to

Continued.

Study	Recurrence after liver transplantation	Recurrence after liver resection	R0 resection (n)	Overall survival rates after liver transplantation % (1, 3, 5 year)	Overall survival rates after liver resection % (1, 3, 5 year)	Limitations	Conclusion
							neoadjuvant therapy/ transplantation for the same criteria with unresectable disease, when performing an intention-to-treat analysis
Iwatsuki et al¹⁰	40 patients had tumor recurrence out of 72		20 in resection, 31 in transplant	60, 32, 25	74, 34, 9	Varied adjunct therapy, high recurrence rates, no 5-year survival in patients who had tumors with lymph node involvement	Negative tumor margins, negative lymph nodes and less tumor depth were statistically significant good prognostic factors

Table 3: Summary of overall survival and recurrence rates in the selected studies for both the modalities and conclusions derived.

Study	Recurrence after liver transplantation	Recurrence after liver resection	R0 resection (n)	Overall survival rates after liver transplantation % (1, 3, 5 year)	Overall survival rates after liver resection % (1, 3, 5 year)	Limitations	Conclusion
Croome et al⁶			90 in resection, 54 in transplant	90, 71, 59	81, 53, 36	Referral bias to a centre with multidisciplinary interest in hilar cholangiocarcinoma, varied adjunct therapy	Patients with clearly resectable de novo hilar cholangiocarcinoma undergo resection; patients with locally unresectable de novo hilar cholangiocarcinoma should be treated with neoadjuvant therapy and liver transplantation
Hong et al¹¹	40%			33 at 5 years	0 at 5 years	Retrospective design	Liver transplantation in combination with neoadjuvant and adjuvant therapy is superior to liver resection and adjuvant treatment in patients with locally advanced intrahepatic and hilar cholangiocarcinoma
De Martin et al¹²	18 patients	46 patients	23 in resection group	90, 76, 67	92, 59, 40	Small sample size, retrospective design, lack of an intention-to-treat analysis in the transplant group, missing data	Liver transplantation is an alternative curative option for intrahepatic and hilar cholangiocarcinoma with tumor size of ≤ 5 cm that has developed in the setting of cirrhosis
Hue et al¹³			42 in resection, 49 in transplant groups	87, 55, 39	82, 47, 35	A propensity matched study, missing data	Resection is preferable in patients with non-metastatic disease due to the similarity in outcomes and the risks associated with chronic immunosuppression associated with transplantation and the organ shortage

In this systematic review, a total of 900 patients were studied, 527 of which underwent hepatic resection and 373 liver transplantation. Recurrence rates were higher in patients who underwent liver resection. Five-year survival rates after transplantation ranged from 50-70% in all studies, compared to 20-30% in the resection group.

In the selected studies that mentioned patients affected with primary sclerosing cholangitis, most of these were a part of the liver transplantation group. Ethun et al reported that the patients who underwent transplantation had better survival rates than those who underwent resection, even after excluding patients with primary sclerosing cholangitis.⁹

The preoperative workup included investigations to prove the diagnosis, like brush biopsy, MRCP studies, and serum CA 19-9 >100 U/ml. Patients in the liver transplantation group underwent neoadjuvant chemotherapy and radiation. Also, they were started on 5 F.U. until surgery. Most of the studies carried out a staging laparotomy before proceeding with transplantation. Rea et al reported an update to the initial Mayo series.⁸ They compared patients with unresectable hilar cholangiocarcinoma or underlying primary sclerosing cholangitis treated with neoadjuvant chemoradiation and then transplantation to patients who underwent resection for resectable disease. According to them, an improvement in 1,3,5-year survival rates was found in patients who underwent liver transplantation compared to those who underwent liver resection, which persisted even in patients without primary sclerosing cholangitis. However, in an intention-to-treat analysis, no difference in survival was found between the said groups. They still concluded that neoadjuvant therapy followed by transplantation should be considered an alternative to resection for patients with localized disease.

Recently, Croome et al published a study comparing patients who underwent resection to those who underwent neoadjuvant therapy and transplantation for de novo disease.⁶ They again found improved survival rates in patients who underwent transplantation compared to resection. Intention to treat analysis demonstrated improved survival in the transplantation group. No difference was seen in subgroup analysis with variables like R0 resection and N0 disease. They, therefore, concluded that patients with clearly resectable de novo disease should undergo resection.

In a recent study, Hue et al identified patients with intrahepatic cholangiocarcinoma using the National Cancer Database (2010-2016) and further grouped them based on the surgical modalities and matched them 1:1 by propensity score.¹³ They analyzed the pathological and postoperative outcomes and the overall survival. They propounded that the patients who underwent transplantation had more pathologic tumors than those who underwent resection, T0 (7.7% versus 0.4%), T1 (47.7% versus 42.1%). However, there were no differences in the length of stay, mortalities and survival

outcomes or even unplanned readmissions before matching. After matching, there were no significant differences in the postoperative outcomes or survival rates between the transplantation and resection groups. They concluded that hepatectomy and liver transplantation were associated with similar postoperative outcomes and survival in patients with intrahepatic cholangiocarcinoma.

Also, in light of the resources and chronic immunosuppression required transplantation, hepatectomy seems preferable for localized intrahepatic cholangiocarcinoma.⁷ Predictors of recurrence in most studies were increasing age, Serum CA 19-9 >100 U/ml, higher tumor grade and perineural invasion. Patient selection is vital in determining the outcomes regarding recurrence after transplantation and the overall survival rates.²³

Limitations

This study could not analyze intrahepatic, hilar and proximal extrahepatic cholangiocarcinomas separately due to the gaps in the original articles. To extrapolate the results of this study, well-designed, prospective, multicentric randomized controlled trials are the absolute necessity to devise a protocol for adequately treating these patients. A regulated organ registry and a devised protocol for managing patients with intrahepatic and hilar cholangiocarcinoma seem paramount because of the rising cases.

CONCLUSION

This study systematically reviewed the recent comparative studies concerning liver transplantation and liver resection in hilar and intrahepatic cholangiocarcinoma cases. Most of the selected publications were non-randomized and retrospective studies. Patient characteristics and tumor pathology significantly change the outcomes regarding recurrence and survival rates.

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