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Case Report

Single Center Experience of Patients with Hepatocellular Carcinoma Undergoing Porta Hepatic Lymphadenectomy at the Time of Liver Transplant Between January 1, 1990, And December 31, 2010

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Hypothesis

The goal of this project is to determine the effectiveness of porta hepatis lymphadenectomy for hepatocellular carcinoma at the time of liver transplant.

Background/Introduction

Cancer of the liver and intrahepatic biliary ducts has the sixth highest incidence, and third highest mortality, worldwide [1]. The predominant types include hepatocellular carcinoma and cholangiocarcinoma. These are particularly devastating, within the United States, 5-year survival from diagnosis is approximately 22% [2]. Even for disease identified in the local stage, 5-year survival remains about 37% [2]. Overall mortality from primary liver cancer declined in the United States from 2016-2018, despite continuing to rise in select states and populations [3]. Hepatocellular carcinoma is the leading primary cancer of the liver, responsible for 4 out of 5 new liver cancer diagnoses [4]. Risk factors for hepatocellular carcinoma are heavily related to cirrhosis. While typically associated with chronic infections from hepatitis viruses or alcohol consumption, cirrhosis can also have environmental, autoimmune, genetic, or vascular origin. Cirrhosis of any etiology is associated with a 2% annual risk of HCC, and 80% of patients with HCC have cirrhosis [4]. Additionally, increased risk of HCC has been associated with metabolic syndrome and diabetes, and increased risk of primary liver cancer is associated with increasing Body Mass Index (BMI) [5-7]. While metabolic syndrome, diabetes, and obesity each can contribute to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD, formerly non-alcoholic fatty liver disease) which can progress to cirrhosis, up to 30% of cases of HCC in individuals with MASLD occur without cirrhosis [8].

Surgical resection and orthotopic liver transplantation offer potentially curative treatment for HCC. A variety of noncurative treatment options are also available including types of ablations and embolization, as well as chemotherapy, targeted molecular therapies, and immunotherapies. Surgical resection can be difficult. Metastatic and local extra-hepatic spread, post-resection liver function, and anatomic tumor location must be considered on a case-by-case basis. Importantly, resection does not eliminate any underlying liver pathology predisposing to HCC, thus the potential for disease recurrence persists following intervention. Liver transplantation was first demonstrated to be an effective strategy for HCC by Mazzaferro and colleagues, demonstrating a 4-year survival rate of 75%, and 4-year disease recurrence rate of 8%, following transplant [9]. This work produced the Milan criteria, primarily used in transplant centers today. These criteria include a single tumor 5cm or less, multi-

ple tumors each 3cm or less, no gross evidence of vascular invasion, and no metastasis [9]. Alternative, expanded criteria have been explored in attempts to allow greater access to liver transplantation, including the University of California San Francisco (UCSF) criteria which comprise a single tumor ≤6.5 cm diameter or 2 tumors, each ≤4.5 cm with total diameter ≤8 cm [10].

Metastatic disease is a contraindication to liver transplantation. Common sites of metastasis include lungs, bone, adrenals, lymph nodes, and peritoneum [11]. Evaluation for metastasis is accomplished during HCC workup and diagnosis and includes chest Computed Tomography (CT), abdomen and pelvis CT or Magnetic Resonance Imaging (MRI), and bone scan if clinically indicated; Positive Emission Tomography (PET) scan is not routinely recommended [11].

Reports of the occurrence of lymph node metastasis in HCC are variable, with incidence reported from 3.4% [12] to 7.5% [13,14]. For patients with HCC specifically being evaluated for transplantation, incidence has been reported at 6% [15]. Beyond being a contraindication for transplantation, presence of lymph node metastasis additionally portends significant decreases in 1- and 2-year survival [14]. Lymphadenectomy at the time of transplant or surgical resection is not strictly required for hepatic cancers. Some authors have argued in favour of routinely performing regional lymphadenectomy, specifically in the setting of liver resection for any primary or secondary hepatic tumour, citing the very low risk of the operation and frequency of lymph node metastasis with any hepatic tumour [14]. Alternatively, others have questioned the necessity of routine lymph node dissection. Grobmyer and colleagues evaluated a series of 100 patients undergoing liver resection for any primary or secondary hepatic tumour with preoperative CT, intraoperative clinical assessment of lymph nodes, and select preoperative PET scans [16]. They concluded negative predictive values of 95% for CT, 88% for PET, and 99% for intraoperative assessment, arguing in favour of performing lymphadenectomy on a case-by-case basis [16]. Notably, none of the 11 patients with HCC in their sample had any lymph node metastasis [16].

At our center, The University of Kansas Medical Center, it has been routine to perform intraoperative porta hepatis lymphadenectomy during orthotopic liver transplant to evaluate for metastatic disease. Little work has been done exploring the necessity of lymphadenectomy specifically for HCC in the setting of liver transplantation. The goal of this project is to determine the efficacy of porta hepatis lymphadenectomy for hepatocellular carcinoma at the time of liver transplant.

Methods

This is a retrospective chart review at a single institution, The University of Kansas Medical Center. Patients who were taken for orthotopic liver transplantation with an indication of HCC between January 1, 1990, and December 31, 2010, were identified. Charts were reviewed for porta hepatis lymph node final pathology reports. Patients were determined to be either positive or negative for lymph node metastasis at time of transplant.

A $X^{2\ test}$ was used to evaluate categorical values, being the presence or absence of lymph node metastasis. An incidence rate of 6% was used to determine the expected lymph node metastasis, as this rate was identified specifically in patients with HCC being evaluated for transplant [15].

Results

A total of 90 patients were identified with a diagnosis of hepatocellular carcinoma and underwent liver transplantation with hepatic lymphadenectomy, between January 1, 1990, and December 31, 2010, at The University of Kansas Medical Center. The final pathology report was negative for lymph node metastasis in all 90 patients. Zero patients were determined to have positive porta hepatis lymph nodes. Utilizing a 6% incidence of lymph node metastasis in patients with HCC evaluated for liver transplantation, 5 patients would have been expected to be positive for lymph node metastasis at time of transplant. This was determined to be significant ($p=0.02$).

Notably, one patient was determined to be positive for porta hepatis lymph node metastasis during intraoperative pathology evaluation. The transplant operation for this patient had to be aborted. The following day, pathology was reviewed, and this intraoperative report was determined to be a false positive, thus the final pathology report was negative for porta hepatis lymph node metastasis.

Discussion

This was a retrospective study looking at patients who received porta hepatis lymphadenectomy prior to liver transplant for HCC over a span of 20 years. Of those patients one had a positive lymph node thereby preventing him from having a liver transplant. On further testing the lymph node was found to be negative but he had already lost his chance for liver transplantation. The patient passed away due to cirrhosis related issues.

A RCT showed that those in early stage HCC who had a hepatectomy vs hepatectomy with lymphadenectomy had no significant difference in long term mortality [17]. Another study also showed lymphadenectomies did not improve overall survival, however lymph nodes metastasis worsen overall survival [18]. Although patients with primary and metastatic liver cancers present an overall low risk of metastatic disease present in perihepatic lymph node [16]. Therefore, there may be value in lymphadenectomy in those with high suspicion of lymph node disease for prognostic information, but less benefit in those with low suspicion [18]. The utilization of CT and PET to predict nodal metastases can be used in the decision for lymphadenectomy [16]. Another method of using serologic values can help predict the risk of metastatic lymph nodes [19].

Different criteria and adjustments have been made through the years to determine a fair way to distribute livers to those most in

need [20]. Despite the extensive process that our patient underwent, the ability of a positive lymphadenectomy to alter the course of the patient's treatment options meant the loss of a liver for that patient. In liver transplant there is always a risk that metastasis was missed and even in cases of liver transplants with no known lymph node metastasis there is a risk for recurrence [21]. Liver transplants in HCC increase survival rates in patients [22]. As shown in our study with some patients surviving up to a decade after transplantation. Thus, a failure to obtain a liver transplant likely led to him passing prematurely.

A limitation to this study was a lack of patients with a positive lymph node biopsy. The effects of transplanting a liver in a patient with positive lymph node on that patient's survival, quality of life, and risk of recurrence could not be evaluated. So, the consequences of a true positive lymph node could not be compared to the effects on our patient not obtaining a liver. Another limitation was the cause of death in patients that passed after the liver transplant. It could be further investigated if the cause was transplant or liver related vs other underlying condition or exogenous factors.

Conclusions

In summary, the impact of hepatic lymphadenectomy for those with HCC prior to undergoing liver transplant was not found to be beneficial for patient outcomes at our institution. With an overall low incidence of positive lymph node metastasis in HCC, performing hepatic lymphadenectomy appears to be better utilized on an individual basis instead of universally. Of note, the incidence of positive lymph nodes was significantly lower in our review than predicted based on previous studies. Additionally, the consequence of a false positive prevented someone found to be a suitable candidate based on the Milan criteria from receiving a liver transplant. Previous studies have found imaging techniques such as MRI, CT, and PET for evaluation of lymph node metastasis provide insight without the need for hepatic lymphadenectomy. HCC presents an overall low 5-year survival rate, however, with liver transplant survival rates improve. Due to benefits in the survival rate with a liver transplant and the risk of a positive lymph node preventing transplant, it was concluded that the need for hepatic lymphadenectomy should not be performed routinely for all patients with HCC prior to liver transplant.

Acknowledgement

None.

Conflict of Interest

None.

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