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Hepatocellular Carcinoma Recurrence After Liver Transplantation: an Analysis of Risk Factors and Incidence from Oregon Health & Science University

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**Hepatocellular Carcinoma Recurrence After Liver Transplantation: An Analysis of Risk
Factors and Incidence from Oregon Health & Science University**

By

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degree of

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in

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and

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Research Question

What are the risk factors for incidence of hepatocellular carcinoma recurrence after liver transplantation? How does data collected from Oregon Health and Science University compare to the published literature?

Abstract

Hepatocellular carcinoma (HCC) is among the top ten most frequently diagnosed cancers in the United States, with liver transplantation widely accepted as the best treatment option for long term outcomes. The risk of HCC recurrence after liver transplantation is a growing concern among the medical community due to the scarcity of available organs for transplant. Scholars desire to understand HCC biology and risk factors associated with recurrence, for more accurate predictions of HCC recurrence in the future. A retrospective review from Oregon Health and Science University (OHSU) examined 69 HCC patients from February 27, 2002 to December 31, 2011. Data was collected and statistically analyzed for significant connections to incidence of HCC recurrence ($p < 0.05$). No statistical difference was observed between ten of the eleven risk factors and incidence of recurrence: age, ethnicity, gender, initial imaging, explant pathology, AFP levels, MELD scores, ischemia time, diagnoses, and donor type. A statistically significant association was identified between Milan criteria and HCC recurrence ($p = 0.004$). The incidence of HCC recurrence from the OHSU data set was 15.9%. The Milan findings support the nationwide acceptance of the risk factor, which underlies the MELD exception scores for transplantation. The other ten risk factors supported the lack of consensus among the research community and the idea that HCC biology is still not fully understood. This thesis determines

how data from OHSU compares to nationally reported data, in terms of similarities, differences, and future focuses of research.

Introduction/Background

Cancer is one of the leading causes of death in the United States, affecting millions of individuals each year. In 2015, 1,658,370 new diagnoses of cancer were predicted to affect individuals across the country (American Cancer Society, 2015). Cancer of the liver, specifically hepatocellular carcinoma (HCC), is among the ten most frequently diagnosed cancers, and is the fifth leading cancer that contributes to death in American males (American Cancer Society, 2015). Of the limited treatment options available, the most successful and durable treatment for HCC is liver transplantation. However, as with most malignancies, an underlying concern for recurrence after transplantation persists for HCC. Multiple authors have examined this issue, in an attempt to identify possible risk factors and to understand the underlying causes of recurrence. In this thesis, I will identify the incidence of and risk factors associated with HCC recurrence after liver transplantation. Furthermore, I will compare published literature to data collected from Oregon Health and Science University (OHSU).

Screening and Surveillance

Prior to diagnosis of HCC, patients considered at risk undergo screening and surveillance. Screening focuses on a wide array of patients without HCC risk factors, while surveillance focuses on an array of individuals with known risk factors for HCC (Bruix and Sherman, 2010). The goal of screening and surveillance is to identify early stage rather than late stage HCC. HCC development often stems from precursor diseases. Hepatitis B and C are common pathways for the development of cirrhosis, which is ultimately the biggest risk factor for HCC development

(Zarrinpar and Busuttil, 2013). Bruix and Sherman (2010), mention, “hepatitis B carriers were 100 times more likely to develop HCC than uninfected persons,” demonstrating the impact these diseases have on the likelihood of developing HCC. According to the American Cancer Society (2015), individuals with a high risk for developing precursor diseases are those with a history of intravenous drug use, excess alcohol consumption, and those unvaccinated for hepatitis B. Alcohol consumption, an environmental risk factor, serves as another pathway to cirrhosis, which can lead to the development of HCC. Other environmental risk factors exist, but most are rare and are not a large area of focus.

Serological and radiological tests are used to screen at risk patients for HCC. Serological tests refer to biochemical markers, primarily alpha-fetoprotein (AFP), while radiological tests refer to the use of various imaging techniques (Bruix and Sherman, 2010). These include ultrasound, computerized tomography (CT) scan, and magnetic resonance imaging (MRI). For more accurate early detection, both ultrasonography and AFP tests should be performed, which is done approximately every 6-12 months (Bruix and Sherman, 2010). Surveillance continues after an individual is diagnosed with HCC, with the time interval changing depending on the treatment option chosen.

Diagnosis

Diagnosis of HCC increased by 3.4% between 2007 and 2011, with the rate predicted to continue climbing in the near term (American Cancer Society, 2015). The most widely accepted diagnostic algorithm for the detection of HCC uses a combination of radiology, biopsy, and serology tests (Bruix and Sherman, 2010). Radiology techniques test for HCC with the use of an MRI or a CT scan. In addition to radiology tests, biopsies are performed to examine the pathology for a section of the affected liver tissue when classic imaging characteristics are not

present. Serological testing refers to the use of AFP, an indicator for tumor growth when present in high concentrations. AFP testing is not sensitive or specific, so it must be combined with the radiological and biopsy tests to make an accurate diagnosis of HCC (Bruix and Sherman, 2010). AFP levels can indicate treatment response, so it is important to measure levels prior to and after treatment.

Tumor Classification

The stage of a tumor is determined “based on the size of or extent of the primary tumor and whether it has spread to nearby lymph nodes or other areas of the body” (American Cancer Society, 2015). A major concern regarding HCC is metastasis, the spread of cancer to locations in the body that differ from the original location (Roberts, 2005). Metastasis is common among patients with HCC recurrence, with death occurring shortly after. Vascular invasion is often an early predictor of local and distant recurrence, which is why individuals may be unqualified for many treatments.

Individuals eligible for liver transplantation based on the results from the previously described tests, will be placed on a transplant waitlist with a score to reflect the state of their disease. The Model for End-Stage Liver Disease (MELD) was designed “as a severity index for patients with end-stage liver disease awaiting liver transplantation” (Kamath et al., 2001). The original goal of the MELD scoring system was to provide an objective ranking system within a group of heterogeneous individuals having liver dysfunction (Kamath et al., 2001). This original model did not include adjustments for HCC or other ailments involving diseases without liver dysfunction. In February 2002, the MELD score incorporated exception scores, which enabled patients without liver dysfunction to have MELD scores among individuals with liver dysfunction (Heimbach et al., 2015). The adjustments for HCC patients are often higher due to

specific HCC disease processes, including tumor size and vascular invasion. An individual's MELD score is updated every three months, which allows for adjustments based on the risk of progression of the tumor, which increases with time. The MELD score is a reflection of the risk of death in the patient, meaning it is possible for patients to be dropped from the list, depending on the severity of tumor progression (Heimbach et al., 2015).

The MELD system measures the mortality risk of patients, while several scoring systems have been developed to predict the likelihood of HCC recurrence after liver transplantation. The extents of Milan and University of California at San Francisco (UCSF) criteria are well established and accepted as methods for predicting HCC recurrence. Despite controversy regarding the relative efficacy of these criteria, these guidelines are widely accepted nationwide. To be within the Milan criteria a patient must have a single tumor ≤ 5 cm or up to 3 nodules ≤ 3 cm (Mazzaferro et al., 1996). The UCSF criteria states that patients within the criteria must have a single tumor ≤ 6.5 cm or up to three nodules ≤ 4.5 cm and a total diameter ≤ 8 cm (Bonadio et al., 2015). Individuals with vascular invasion, regardless of tumor size, do not fit within either criterion.

Treatment

Treatment options for HCC vary depending on the nature of the tumor and the predicted survival rate of the patient. Prior to opting for organ transplantation, multiple methods to limit tumor growth or even to downstage are applied. In the latter, tumors that are larger than Milan or UCSF criteria may undergo up front treatment such that the tumor(s) shrink and fall into these classification schemas. One method of up front treatment involves transarterial chemoembolization (TACE) a process which blocks blood flow to the tumor (American Cancer Society, 2015). Another preoperative treatment is radiofrequency ablation (RFA), which "causes

the ablation of tumor tissue through heat or local ischemic necrosis” (Wang et al., 2015).

Resection involves operations to remove a section of normal liver along with the tumor. These procedures are considered for patients within the Milan and UCSF criteria that have enough healthy liver tissue that can tolerate the stress of surgery (American Cancer Society, 2015).

Patients with combined poor life expectancy and tumors exceeding the Milan and UCSF criteria, are given the medication Sorafenib, which can temporarily extend survival time (Zarrinpar and Busuttil, 2013). Patients that do not have enough intrinsic liver function and tumors within the Milan and UCSF criteria are considered for liver transplantation. Many treatment options are available for HCC, but liver transplantation has been widely accepted as the most successful treatment for eliminating malignancy in the long term.

Liver transplantation operations were first documented in the early 1950’s, but were not considered successful until the late 1960’s (Zarrinpar and Busuttil, 2013). Since then, liver transplantation has become one of the most successful and widely accepted forms of treatment for HCC. Individuals considered for organ transplantation have tumors within the Milan or UCSF criteria, and are determined eligible by a multidisciplinary tumor board (Akoad and Pomfret, 2015). Two options are available for transplantation candidates, living donor transplantation or deceased donor transplantation. Nationwide, most patients are transplanted with deceased donor organs. While liver transplantation is considered the best method for removing HCC, recurrence is a prevailing issue. Researchers have developed various hypotheses of possible risk factors, in an attempt to reduce the number of individuals affected by HCC.

Individuals eligible for liver transplantation are placed on an organ waitlist, due to the scarce availability for organs. Allocation of livers depend on the compatibility between the patient and the donor, the patient’s urgency for the organ, and the region the organ is available in

(United Network for Organ Sharing, 2015). Individuals considered for transplantation have information sent to the United Network for Organ Sharing (UNOS) regarding their blood type, height, weight, and other medical factors. When donors are available, the same information is sent to UNOS, providing the basis to a compatibility test. Of the resulting matches, a list of individuals in the specific region is created. Of this list, the individual with the highest MELD scores and exception points is given priority for the organ (United Network for Organ Sharing, 2015).

Methodology

In order to compare data from OHSU to published literature, an extensive literature review was performed in the fields of hepatology, oncology, radiology, surgery, and transplantation. Research focusing on possible risk factors of HCC recurrence were chosen, compared, and summarized. These articles were supplemented with articles regarding MELD, Milan, and transplant guidelines and criteria. Articles including incidence of recurrence were compiled to develop a range of incidence for HCC recurrence after liver transplantation.

My advisor approved the research from OHSU through the institution's Institutional Review Board. A spreadsheet was created to organize data from OHSU, focusing on 69 HCC diagnosed patients who had deceased liver donor transplant surgery between February 27, 2002 and December 31, 2011. Data were collected from patient files within the hospital's EPIC charting system. Supplemental data was collected using files from the UNOS organization. Patients were de-identified prior to analysis.

Eleven variables were chosen as areas of focus, including age, ethnicity, gender, initial imaging, explant pathology, AFP levels, MELD scores, ischemia time, diagnoses, within Milan

pathology, and donor type. These values were statistically analyzed, using the statistical analysis program, IBM SPSS Statistics V22.0. A t-test was applied to continuous variables and a chi square test was performed for categorical variables. A p-value of 0.05 or less was used to determine significance. Continuous variables do not have a defined maximum value, while categorical variables have a yes or no answer. Examples of continuous variables are age and tumor size, and examples of categorical variables are ethnicity and gender.

Resulting trends from OHSU were compared to data collected during the literature review process. Similarities, discrepancies, incidence, conclusions, and gaps in the research were identified.

Literature Review

In recent years, the number of cancer research studies has grown exponentially in the attempt to identify risk factors, cures, and to understand the resilient nature of malignant tumors. HCC has become an area of increased interest due to the rising incidences of recurrence in patients after liver transplantation. While controversy exists, some agreement among researchers has identified several key risk factors for HCC recurrence after liver transplantation. The most notable risks are vascular invasion and whether an individual is within Milan criteria or not. In this literature review, I will identify the range of risk factors and incidence of HCC recurrence, to establish a basis of information that will be compared to collected data from OHSU.

Patients

Recipients of liver transplants undergo preoperative treatments, laboratory tests, and imaging to manage and document tumor extent and monitor for disease progression. Research studies with a focus on recipient characteristics examine preoperative elements as predictors of

recurrence. These studies concentrate on the analysis of tumor criteria, through comparison of preoperative tumor characteristics and the incidence of recurrence. Research studies performed by Bonadio et al. (2015) and Chaiteerakij et al. (2015) analyzed the predictive capacity of the Milan, UCSF and Asan criteria. Both studies demonstrated a relationship between patients “outside” the criteria and the incidence of recurrence. The study performed by Bonadio et al. (2015) was a multivariable analysis, concluding that recurrence was found in individuals exceeding the Asan criteria. This study argued that the Milan and UCSF criteria were not sufficient indicators of recurrence when compared to the Asan criteria (Bonadio et al., 2015). Although this argument about Asan criteria exists, the Milan criteria continues to be the most widely accepted system and underlies the MELD exception point system.

In addition to criteria analysis, Chaiteerakij et al. (2015) proposed that preoperative biomarkers, specifically AFP and des-gamma-carboxyprothrombin (DCP), should be used in recurrence predictions. Research by Varona et al. (2015) supplements the argument made by Chaiteerakij et al. (2015), in terms of the AFP biomarker. These two studies agree that biomarkers should be used in addition to criteria methods, but the studies propose different levels of AFP as the indicator of recurrence. Chaiteerakij et al. (2015) proposed a level ≥ 250 ng/mL, while Varona et al. (2015) proposed a lower level of ≥ 100 ng/mL. A study by Berry and Ioannou (2013) proposed an even lower level of ≥ 15 ng/mL. A consensus exists about use of AFP levels as an indicator of recurrence, but the level of concern has yet to have a consensus. AFP is not specific, and therefore there is multiple interpretations of laboratory data and wide variance in terms of how these values are applied clinically.

Donor

Another category of risk factors associated with HCC recurrence focuses on the characteristics of the donor. Research on this topic suggests that incidence of recurrence is not influenced by the biology of the recipient, but rather the source of the transplanted organ. The studies primarily focus on incidence of recurrence between recipients of living donor liver transplantations and deceased donor liver transplantations. Research conducted by Fisher et al. (2007) and Kornberg et al. (2015) concluded that living organ donor transplant recipients had a higher risk for recurrence than deceased organ donor recipients. Fisher et al. (2007) connected higher risk with surgical procedures, while Kornberg et al. (2015) associated higher risk with prolonged warm ischemia time. Despite the type of donor liver, neither study focused on waitlist time and the outcome of the patient. Patients undergoing living donor liver transplants have shorter waitlist times, and therefore might be transplanted before the full biology of the tumor is presented. Patients on the waitlist for deceased organs often have longer waitlist times, giving the tumor biology time to progress. These studies claim that living donor liver transplant recipients have a higher risk of recurrence, but the absence of waitlist time comparisons questions the validity of this argument. These studies demonstrate that it is difficult to draw conclusions based on the donor organ because of many elements, especially time.

Surgical

The transplant surgical procedure contributes another probable risk factor for recurrence. In studies focusing on this issue, the evidence is purely hypothesis based because there is not data to support a definitive hypothesis. Studies by Fisher et al. (2007), Wang et al. (2015), and Akoad and Pomfret (2015), hypothesize a connection between recurrence and the nature of the transplant operation. Fisher et al. (2007) suggest that tumor residue remains after transplantation

from a living donor liver. Wang et al. (2015) suggest that the amount of blood loss during the operation can be connected to recurrence. Akoad and Pomfret (2015) connect both suggestions, hypothesizing that the amount of manipulation during transplantation can leave residual malignancy, which can enter the blood stream. A method to quantitatively analyze surgical operations has yet to be developed, but literature predicts a connection between the nature of the operation and risk of recurrence.

Incidence

A common element reflected in the collected literature was the incidence of recurrence after liver transplantation. Recurrence most commonly arises within two years after liver transplantation (Mazzaferro et al., 1996). The recurrence of the cancer does not necessarily return to the liver, but is commonly seen as metastatic cancer. This form of HCC spreads between multiple organs, commonly seen in the lungs and in bone (Roberts, 2005). The studies produced by Vagefi et al. (2015), Felga et al.(2012), and Varona et al. (2015) had similar findings, with recorded incidence of 6.5%, 6.9%, and 7%, respectively. Research performed by Fisher et al. (2007), Bonadio et al. (2015), and Kornberg et al. (2015) identified higher incidence, reported at 18%, 22%, and 23.3%, respectively. The third range of incidence was significantly higher, with Chaiteerakij et al. (2015) reporting 32%. No consensus is given for an exact range of incidence, but research suggests a common range of 6 to 20%, with outliers of 30% or more.

The data collected through the literature review identifies many possible risk factors of recurrence of HCC after liver transplantation. The risk factors can be attributed to the donor, the recipient, or even the surgical operation. Data collected through this literature review will allow for comparison of data from OHSU to nationally reported data. Analyzing risk factors and

incidence between OHSU and published literature will allow for hypotheses to be created for future points of research.

Results

The data collected from OHSU sampled 69 patients between the ages of 43 and 69, with an average age of 57.03 ± 5.45 years (Table 1 in Appendix A). When these patients received initial imaging, they had 1 to 3 tumors, ranging in size from 0.5 to 4.1 cm. The average number of tumors patients had was 1.33 ± 0.61 , while the average size was 2.31 ± 0.84 cm. Patients had a slightly higher average of explant tumors of 1.56 ± 0.99 , with the range extended from 1 to 7 tumors. The average size of the explant tumor was smaller, with a size of 2.16 ± 1.00 cm, but the explant size range expanded to 0.02 to 6.00 cm. AFP levels were examined at the initial stage and at the time of transplant. The initial AFP levels averaged 65.26 ± 202.42 μg , with a range of 1 to 1430 μg . AFP at time of transplant were lower, with an average level of 46.66 ± 101.04 μg and a range of 2 to 611.3 μg . Calculated MELD and MELD exception values were also collected. Calculated MELD at transplant averaged 13.94 ± 5.92 , with a range from 6 to 25. The MELD exception values were higher, with an expanded range of 12 to 39, and an average value of 23.94 ± 3.95 . The only donor demographic analyzed was the age of the liver donor. The average age of the donor was 41.68 ± 13.13 years, with the age ranging from 17 to 65 years (Table 2 in Appendix A).

Patients were further divided into two categories, depending on the presence of HCC recurrence after liver transplantation. There were 11 patients diagnosed with HCC recurrence and 58 patients that exhibited no recurrence after liver transplantation (Table 3 in Appendix A). The incidence of recurrence was calculated as 15.9%. The average age of recurrence patients was

57.6 ± 6.07 years, while the average age of patients without recurrence was slightly lower at 56.91 ± 5.37. Patient age had no statistical association with HCC recurrence (p=0.69). The four categories of ethnicity recorded in the EPIC system were white, Hispanic, Asian, and black. Of the total patients, 57 patients were of white ethnicity. Of this group, 10 patients exhibited recurrence (17.5%) and 47 patients had no recurrence (82.5%). Six patients were of Hispanic ethnicity, with one patient exhibiting recurrence (16.7%) and five patients having no recurrence (83.3%). Five patients were of Asian ethnicity, all having no recurrence (100%). One patient without recurrence was of black ethnicity (100%). Ethnicity did not have a statistically significant association to HCC recurrence (p=0.741). The study population was composed primarily of males, with 57 out of the 69 patients being male. Of those males, 9 patients had recurrence (15.8%) and 48 patients did not have recurrence (84.2%). The remaining 12 patients were female, with 2 patients having recurrence (16.7%) and 10 patients without recurrence (83.3%). Gender did not have a statistically significant association to HCC recurrence (p=0.940).

Initial imaging examined the average of number and size of tumors at the initial stage. The average number of tumors for patients with recurrence was 1.22 ± 0.44, while patients without recurrence had a higher average of 1.33 ± 0.66 (Table 3 in Appendix A). The average initial size of the tumors was 2.40 ± 1.08 cm for patients with recurrence, which was larger than the average of 2.30 ± 0.80 cm for patients without recurrence. Initial imaging methods did not have a statistically significant association to HCC recurrence, with a p-value of 0.647 for number of tumors and a p-value of 0.737 for the size of initial tumors. Explant pathology examined the same elements as initial imaging. The average number of explant tumors for patients with recurrence was 2.00 ± 1.84, while the average size of these tumors was 2.07 ± 0.88 cm. Patients without recurrence had an average of 1.47 ± 0.67 tumors, averaging 2.18 ± 1.03 cm in size.

There was not a statistically significant association between explant data and HCC recurrence, with a p-value of 0.107 for number of tumors and a p-value of 0.758 for tumor size. AFP levels were examined at initial diagnosis and at the time of operation. Milan pathology was determined from explant pathology. A total of 51 patients fit within the Milan criteria, with 6 patients exhibiting recurrence (11.8%) and 45 patients without recurrence (88.2%). A total of 10 patients were considered outside of Milan criteria, 5 patients having recurrence (50%) and 5 patients without recurrence (50%). The Milan criteria was a significant indicator of recurrence, with a p-value of 0.004. Initial AFP levels were 50.5 ± 55.4 μg for patients with recurrence. Average AFP levels were higher and more variable for patients without recurrence, with an average of 67.80 ± 218.2 μg . AFP levels were lower for both groups at the time of operation, with patients with recurrence having an average level of 33.89 ± 57.04 μg and patients without recurrence having an average level of 48.75 ± 106.76 μg . Initial AFP levels and the level at the time of transplant did not have a statistically significant association to HCC recurrence, with p-values of 0.805 and 0.686, respectively. Cold ischemia time for patients with recurrence was shorter than the cold ischemia time for patients without recurrence, with average times of 7.93 ± 2.49 hours and 8.32 ± 2.68 hours, respectively. The cold ischemia time did not have a statistically significant association to HCC recurrence ($p=0.651$).

MELD scores were analyzed from three different categories. Patients exhibiting recurrence had average initial MELD scores of 13.00 ± 6.63 , average calculated MELD scores of 15.45 ± 8.35 , and average exception scores of 23.13 ± 2.23 (Table 3 in Appendix A). The MELD scores for patients without recurrence were similar, with an average initial MELD of 14.71 ± 6.65 , average calculated MELD scores of 13.64 ± 5.36 , and average MELD exception score of 24.05 ± 4.14 . Each MELD risk factor did not have a statistically significant association to HCC

recurrence, with p-values of 0.597 for initial MELD, 0.356 for calculated MELD, and 0.539 for MELD exception. Diagnoses reflected the original diagnosis of the patient, which was split into five categories. Two patients without recurrence were diagnosed with Type C Cirrhosis (100%). One patient without recurrence was diagnosed with alcoholic cirrhosis and hepatitis C (100%). One patient without recurrence was diagnosed with hemochromatosis (100%). Ten patients were diagnosed with only HCC, with 1 patient having recurrence (10%) and 9 patients having no recurrence (90%). Fifty-five patients were diagnosed with HCC and cirrhosis, with 10 patients having recurrence (18.2%) and 45 patients having no recurrence (82.8%). Original diagnosis did not have a statistically significant association to HCC recurrence ($p=0.873$). The type of donor was primarily categorized as brain death donors, with 50 patients without recurrence (84.7%) and 9 patients with recurrence (15.3%) receiving this type of donor liver. The remaining patients received cardiac death donor livers. In this category, 2 patients with recurrence (20%) and 8 patients without recurrence (80%) received this type of donor liver. Type of donor did not have a statistically significant association to HCC recurrence ($p=0.705$).

Discussion and Conclusions

Significant Risk Factors

The analyzed data from OHSU revealed that whether a patient is within or outside of Milan criteria is an accurate predictor of HCC recurrence after liver transplantation ($p=0.004$). This risk factor has been accepted nationwide as an indicator of recurrence, and continues to underlie the MELD exception point system. Scholars propose additional factors to consider in staging that could enhance the effectiveness of the Milan criteria. The Milan criteria was the only

risk factor identified to have statistical significance with HCC recurrence from the OHSU data set.

Scholars proposing that Milan criteria is not an independent risk factor, argue that the criteria and biomarkers should be used in combination. The data from OHSU did not show a statistically significant relationship between biomarkers and HCC recurrence, so the data was unable to support this claim. Berry and Ioannou (2013) argue that AFP is an important indicator of recurrence and should be used for patients regardless of whether they are within the Milan criteria, suggesting that the Milan criteria is currently too narrow and therefore can undergo improvements. Berry and Ioannou (2013) emphasize the importance of finding a threshold AFP level before being able to revise the Milan criteria. The study completed by Bonadio et al. (2015) agrees that the Milan criteria is an accurate predictor of recurrence, but it currently has too strict of requirements. These researchers also suggest that of the current criteria methods (Milan, UCSF, and Asan), Milan is the weakest indicator of recurrence. Data from OHSU cannot support or disprove this idea, because data for the UCSF and Asan criteria were not available for data analysis.

Despite the general consensus that improvements need to be made to Milan criteria guidelines, the Milan criteria has been widely accepted as a predictor of recurrence. For example, in the study by Chaiteerakij et al. (2015), patients within the Milan criteria experienced a recurrence rate of 8%, while patients outside of this criteria experienced a recurrence rate of 41%. In another study by Felga et al. (2012), patients within the Milan criteria had a recurrence rate of 6.9%. While the Milan criteria is not a perfect indicator of recurrence, the accuracy has been significant enough to be used as one of the top predictors of HCC recurrence in liver transplantation patients.

Non-Significant Risk Factors

According to the data collected from OHSU, all variables but one did not have a statistically significant association to HCC recurrence. Articles collected during the research process touched on the following variables, but did not identify them as being major contributors to recurrence: Age, ethnicity, and diagnosis. Other articles focused on significant risk factors that were determined as non-significant in the data collected from OHSU: Initial imaging, explant pathology, AFP levels, MELD, Ischemia time, and donor type.

Scholarly articles, found during the literature review process, all emphasized patient age, ethnicity and original diagnosis. While these variables were examined in each study, none of them were identified as significant risk factors for HCC recurrence. For example, a study conducted by Sharma et al. (2012) found a connection between liver donor age and recurrence, but there was no statistically significant association between patient age and recurrence. The data from OHSU had a p-value of 0.69, giving support that patient age is not a significant risk factor. Another study by Mazzaferro et al. (1996) found that “Survival was not affected by the patient’s age or sex or by common markers of chronic liver disease.” While age, ethnicity and original diagnosis are not significant indicators of recurrence, they are important elements that can be used to study patient demographics.

Data regarding initial tumor imaging, explant pathology, and AFP biomarker levels from scholarly articles have similarities and differences in comparison to the results collected from OHSU. A study conducted by Sharma et al. (2012) concluded that initial imaging of size and number of lesions was a more accurate indicator of recurrence compared to the Milan criteria. The data from OHSU does not support this claim because there was not a statistically significant association between initial size or number of tumors and recurrence. Many scholarly articles did

not put an emphasis on the size and number of tumors of the explanted liver, but rather the differentiation and grade of the tumor. For example, a study by Pecchi et al. (2015) found that differentiation degree, enhancement patterns, and vascular invasion of tumors were risk factors associated with recurrence. The data from OHSU was not sufficient enough to analyze these risk factors, and therefore these risk factors cannot be supported. The explant elements from OHSU data were determined to have no statistical significance in relation to HCC recurrence. AFP levels are one of the more controversial risk factors suggested among the research community. Many scholars are in agreement that biochemical markers should be used in combination to Milan criteria, but the AFP level of concern is far from consensus. A study by Berry and Ioannou (2013) suggest an AFP lower limit of ≥ 15 ng/mL, while Varona et al. (2015) suggests a larger lower limit of ≥ 100 ng/mL. These studies argue that AFP levels are accurate indicators of recurrence when combined with Milan criteria, but scholars cannot agree upon the level of concern. This disagreement suggests that AFP levels should not be used as absolute cut-offs. The initial AFP data from OHSU had a large range of 1 to 1430 ng/mL, but there was not a statistical significant relationship found between the level of AFP and the incidence of recurrence.

No statistical significance was found between the MELD scores and recurrence according to the data collected from OHSU. Research articles did not identify MELD scores as an indicator of recurrence, but focus rather on the priority of MELD scores in regard to HCC patients. Patients with HCC are given exception scores, which are a prediction of the mortality of the patient (Heimbach et al., 2015). While the MELD exception score is a prediction of mortality, it is not identified as a recurrence risk factor among the research community. The data from OHSU supports these claims.

Some risk factors examined by scholars focused more on donor factors, although these articles are not as plenty as patient factors. Many scholars have examined the effect of ischemia time involved in organ transport. The data from OHSU only focused on cold ischemia time, which did not have a statistically significant association with incidence of recurrence. Literature articles have identified warm ischemia time as an independent factor of recurrence, with longer time correlating with recurrence (Kornberg et al., 2015). OHSU did not have sufficient enough data to analyze and support statistical significance between warm ischemia time and recurrence. Another donor characteristic that scholars focus on is the type of donor. The data from OHSU looked at deceased donors who were diagnosed with either cardiac or brain death, finding no statistically significant association between the type of donor and recurrence. Of the scholarly article analyzed, none mentioned the type of donor in regards to cardiac or brain death, but rather in terms of whether the donor was living or deceased. For example, a study by Fisher et al. (2007), found that patients who received a living donor transplant had a higher risk of developing recurrence than patients who had received deceased donor liver transplants. Deceased donors were the primary focus of the data from OHSU, so the data cannot support any claims by scholars regarding living versus deceased donors.

Incidence

The incidence of recurrence for the sample of OHSU patients was 15.9% from a study sample of 69 patients. This incidence is within the range identified in the literature review section, with literature suggesting common incidence from 6 to 20%. In terms of incidence, this study is most closely related to the studies by Bonadio et al., Kornberg et al. and Fisher et al.. Bonadio et al. (2015) had an incidence of 22% in a sample size of 76 patients, Kornberg et al.

(2015) had an incidence of 23.3% for a sample size of 63 patients, and Fisher et al. (2007) had an incidence of 18% for 92 patients.

Studies with larger sample sizes reported smaller incidences of recurrence. Three studies analyzed in the literature review followed this rule, with Vagefi et al. (2015) having an incidence of 6.5% for 324 patients, Varona et al. (2015) with an incidence of 7% for 480 patients, and Felga et al. (2012) with an incidence of 6.9% for 603 patients. These studies were larger in scope and sample size compared to the data collected from OHSU.

Comparison of the the smaller and larger sample sizes reveals an inverse trend of smaller incidence of recurrence for larger sample sizes. This trend is supported by the literature review, as well as the data collected from OHSU. A likely explanation for this trend is the difference in the origin of sample sets. Single center studies, like the data collected from OHSU, tend to report higher incidences of recurrence. Studies using multiple centers have larger sample sizes and smaller reported incidences of recurrence. The larger studies are susceptible to inconsistencies in data reporting, which could explain the lower reported incidences. Only a few articles found during the research process did not follow this trend, suggesting that reported incidences higher than 32% can be considered as outliers.

Limitations

Many limitations in the research process contribute to gaps in the research. The biggest limitation was the amount of data available for the study. The time frame chosen for analysis at OHSU was February 27, 2002 through December 31, 2011, which included the time frame in which OHSU switched to an electronic charting system for patient files. This meant that patients in the earlier years of the study did not have as much data in their electronic files as the patients from the more recent years did. In addition, the switch led to inconsistencies in which the

information was recorded, or to how much data could be obtained. In the original data collection, the scope of risk factors was more extensive, including treatments, resections, criteria, and time frames. The number of patients with all of the risk factor data available was minimal, which meant that many of the original categories had to be excluded during data analysis.

Another limitation to this study was regarding the sample size. This study used patient information from files that clearly designated HCC. Since information was transferred to the EPIC charting system during the study time period, it is possible that some eligible patients were excluded from the data analysis. Patients from the Veteran's Affairs (VA) hospital were in the EPIC system, but their transplant information was inaccessible. This means that the sample size analyzed in this study may not reflect the whole population of OHSU patients that received liver transplantations for HCC.

Future

Through collection and analysis of risk factors at OHSU, a few proposals can be suggested for future research. Data collection was difficult and limited due to the lack of information recorded in OHSU patient files. Unlike many aspects of healthcare, transplantation is one of the most regulated, with accurate reporting required by federal law. Recording, integrating, and recovering data in Epic is an ongoing improvement at OHSU. Patient data from the beginning of the study time period was difficult to access, while patient data from the end of the study time frame was more accessible. This suggests that continued accurate data recording may provide more opportunities for HCC recurrence risk factor analysis in the future.

Only a small portion of possible HCC recurrence risk factors were analyzed in this thesis. Published literature suggested possible risk factors that were not able to be analyzed from the OHSU data. These risk factors include, but were not limited to, treatment options, criteria

methods, and living donor liver transplantations. Future studies from OHSU will have the opportunity to examine these elements in comparison to data across the nation.

The study of possible of risk factors of HCC recurrence will continue to be an area of interest and concern for future researchers. Unfortunately, this topic is difficult to study due to the lack of knowledge of the biology of HCC. Diagnostic tools are unavailable to determine on a molecular level how each tumor will act in each patient. As the field of medicine progresses, the goal of accurate prediction of HCC recurrence after liver transplantation could be a possibility.

This thesis has identified the risk factors of HCC recurrence from the Oregon Health and Science University in comparison to scholarly literature already within the field. While the data examines only a small scope of HCC research, it does contribute to the research field, by presenting data from a teaching hospital that will promote more accurate treatment and diagnosis of HCC in the future.

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Appendix A

Table 1. General Recipient Demographics

Variable	Mean	Standard Deviation	Median	Range
Age (years)	57.03	5.45	57.00	43-69
Initial Number of Tumors	1.33	0.61	1.00	1-3
Initial Tumor Size (cm)	2.31	0.84	2.15	0.5-4.1
Explant Number of Tumors	1.56	0.99	1.00	1-7
Explant Tumor Size (cm)	2.16	1.00	2.00	0.02-6.00
Initial AFP (μg)	65.26	202.42	11.1	1-1430
AFP at Transplant (μg)	46.66	101.04	10	2-611.3
Calculated MELD	13.94	5.92	13	6-25
MELD Exception	23.94	3.95	22	12-39

Table 2. General Donor Demographics

Variable	Mean	SD	Median	Range
Age	41.68	13.13	45	17-65

Table 3. Statistical Analysis of Recipient Demographics

Variable		Recurrence (N=11)	No Recurrence (N=58)	P-value
Age	Average Age (SD)	57.6 (± 6.07)	56.91 (± 5.37)	0.69
Ethnicity	White (N,%)	10 (17.5)	47 (82.5)	0.741
	Hispanic (N,%)	1 (16.7)	5 (83.3)	
	Asian (N,%)	0 (0.0)	5 (100)	
	Black (N,%)	0 (0.0)	1 (100)	
Gender	Male (N,%)	9 (15.8)	48 (84.2)	0.940
	Female (N,%)	2 (16.7)	10 (83.3)	
Initial Imaging	Average Initial Number of Tumors (SD)	1.22 (± 0.44)	1.33 (± 0.66)	0.647
	Average Initial Size	2.40	2.30	

	of Tumor (SD)	(± 1.08)	(± 0.80)	0.737
Explant Pathology	Average Explant Number of Tumors (SD)	2.00 (± 1.84)	1.47 (± 0.67)	0.107
	Average Explant Tumor Size (SD)	2.07 (± 0.88)	2.18 (± 1.03)	0.758
Milan Pathology	Within Milan (%)	6 (11.8)	45 (88.2)	0.004
	Outside Milan (%)	5 (50.0)	5 (50.0)	
AFP Level	Average AFP Initial (SD)	50.5 (± 55.4)	67.80 (± 218.2)	0.805
	Average AFP at OLT (SD)	33.89 (± 57.04)	48.75 (± 106.76)	0.686
Ischemia	Cold Ischemia Time (SD)	7.93 (± 2.49)	8.32 (± 2.68)	0.651
MELD	Initial MELD (SD)	13.00 (± 6.63)	14.71 (± 6.65)	0.597
	Average Calculated MELD (SD)	15.45 (± 8.35)	13.64 (± 5.36)	0.356
	Average MELD Exception (SD)	23.13 (± 2.23)	24.05 (± 4.14)	0.539
Diagnosis	Cirrhosis: Type C (N,%)	0 (0.0)	2 (100)	0.873
	Alcoholic Cirrhosis with Hepatitis C (N,%)	0 (0.0)	1 (100)	
	Hemochromatosis- Hemosiderosis (N,%)	0 (0.0)	1 (100)	
	Hepatoma – Hepatocellular Carcinoma (N,%)	1 (10.0)	9 (90.0)	
	Hepatoma (HCC) and Cirrhosis (N,%)	10 (18.2)	45 (82.8)	
Donor Type	Brain Death (N,%)	9 (15.3)	50 (84.7)	0.705
	Cardiac Death (N,%)	2 (20.0)	8 (80.0)	