UNIVERSITY OF MANITOBA | MAX RADY COLLEGE OF MEDICINE
Rady Faculty of Health Sciences

Bachelor of Science in Medicine Degree Program
End of Term Final Report

Office of Graduate and Advanced Degrees
Education in Medicine Max Rady College of Medicine
Rady Faculty of Health Sciences
University of Manitoba

Student Name: Amelia Baker

Date: 03/08/22

Project Title: Survival of Patients with Hepatocellular Carcinoma in Manitoba after the introduction of Transarterial Chemoembolization

Primary Supervisor Name: Dr. Cassano-Bailey
Department: Interventional Radiology

Co-Supervisor Name: Dr. Maged Nashed
Department: Radiation Oncology

Summary (250 words max single spaced):
Hepatocellular carcinoma (HCC) is the most common type of primary liver tumor. It is the second fastest growing cancer in incidence. The 5 year survival in Manitoba for those diagnosed between 2011 and 2015 was 14%. This poor outcome was thought to be due to lack of treatment options. The aims of this study were to look at changes in survival after the introduction of Transarterial Chemoembolization (TACE) and to study the characteristics of three groups; those who received curative treatment, those who received noncurative treatment, and those who received supportive care. This was a retrospective study of patients diagnosed between 2011 and 2019 and included 572 patients. There has been a significant improvement in survival from 2011 to 2019. The 5 year OS has increased from 14% to 21% between the 2011 to 2015 and the 2011 to 2019 cohorts. Patients with ascites, portal vein thrombosis or multiple focal disease are significantly more likely to get supportive care only. Therefore, early identification and maintenance of liver function are paramount to providing curative and noncurative treatments. Cirrhosis and portal hypertension do not affect treatment options. Consequently, primary care providers should be aware that cirrhosis and portal hypertension do not exclude their patients from treatment. In conclusion, our study indicates that adopting new proven treatments has a positive effect on survival of patients. Additionally, developing provincial guidelines that include clear criteria for use of local therapies is likely to continue the trend of improving survival.

Student Signature [redacted]

Primary Supervisor Signature [redacted]

Acknowledgments: I gratefully acknowledge the sole or partial funding support from the following sponsors;

H.T. Thorlakson Foundation
Dean, College of Medicine
Research Manitoba

Manitoba Medical Service Foundation (MMSF)
Vice-Dean, Research Rady FHS
Health Sciences Centre Research Foundation
Heart and Stroke Foundation

Sponsorship if different than above;

MD/PHD MD/MSc. BSc. (MED) MED II Summer Research Program
Joe Doupe Annual Event Undergraduate Medical Student Research Symposium

Introduction and Background

Hepatocellular carcinoma (HCC) is the most common primary liver cancer[1]. Liver cancer is the third most common cause of cancer deaths and the sixth most common cancer worldwide[2]. It is the second fastest growing cancer in incidence [2]. It is estimated in 2022 that 3,500 Canadians will be diagnosed with liver cancer, and 1650 will die from the disease[3]. Although there have been considerable advancements in treatments offered for HCC, the overall prognosis is still disheartening, especially in Manitoba where the 5 year survival rate is 14% compared to the Canadian average of 19%[4,5].

Risk factors play a significant role in the development of HCC. Cirrhosis is the most common risk factor being present in 80% of patients at time of diagnosis[6]. In high Human Development Index (HDI) countries chronic alcoholism and non-alcoholic steatohepatitis (NASH) are currently the most common causes of HCC with nonalcoholic fatty liver disease and NASH becoming an increasingly more frequent cause[1].

Currently those with risk factors such as, but not limited to, hepatitis, Non-Alcoholic Fatty Liver Disease (NAFLD) and alcoholic cirrhosis, are screened with ultrasound (US) every 6 months[6,7]. If a lesion is identified, it will be further characterized with cross sectional imaging[8]. HCC may be diagnosed based on imaging criteria according to the Liver Reporting and Data System (LI-RADS). These criteria include arterial enhancement, washout and signal characteristics [7]. For lesions that do not meet these criteria, correlation with serum Alpha Fetal Protein (AFP) along with a biopsy will be performed to confirm the diagnosis[7,9,10].

Treatment in Manitoba currently follows the Canadian Guidelines published in 2011[7]. The Canadian consensus summarizes multiple studies and provides recommendation for treatments based on disease stage. For HCC, multiple variables affect disease stage and these include the Barcelona Liver Clinic (BCLC) stage, Child-Pugh scores and patients Eastern Cooperative Oncology Group (ECOG) score[7]. The BCLC considers patients' tumor stage, liver function and physical status to determine the best course of treatment[11]. In Manitoba, Multidisciplinary Liver Tumor Board Meetings (LTBM) were established in (year) to ensure all patients with HCC received the optimal treatment for their disease. Since then, the number of referred patients has steadily increase. LTBM consists of interdisciplinary teams which include Interventional Radiologists, Radiation Oncologists, Hepatobiliary Surgeons, Hepatologists and Transplant Physicians. Currently, a proposal for a study to determine the effect of these meetings on treatment plan and overall survival is being revised.

Treatment of HCC ranges from curative to palliative depending on how early the cancer is diagnosed as well as the overall liver function of the patient. Curative treatments include surgical resection, radiofrequency ablation (RFA) and transplant[7]. HCC most often occurs when a liver is damaged, and cirrhosis is present. A liver transplant replaces the tumor and all the damaged liver and therefor removes liver that is prone to developing into HCC[12]. When transplanted, the patient is also effectively cured from future sequalae of their liver disease. Transplants are limited by the number of donor livers available. The second curative option is surgery, which is the best treatment option when there is mild to no cirrhosis[13]. However, only 10-37% of patients are potential candidates for resection at diagnosis[13]. To undergo a surgical resection the patient's general health, residual liver volume post-surgery, and liver function must be considered. In some cases, if the residual liver volume is too small, portal vein embolization of the side containing the tumor can be performed to induce compensatory hypertrophy of the future liver remnant[14]. Surgery has a 5 year survival rate around 70% in patients with single tumors and preserved liver function[6]. Finally, RFA is a good choice for those who have a tumor

radius smaller than 2 cm and BCLC stage of 0 as curative treatment in unresectable situations[11]. Surgical resection appears to be superior to RFA in both overall survival and disease-free period[15], and is therefore preferable especially as the size of the tumor increases.

Non-curative treatments can be stratified into local and systemic treatments. Currently, local noncurative treatments in Manitoba include trans arterial chemoembolization (TACE) and stereotactic body radiation (SBRT). TACE is performed by Interventional Radiology and was introduced to Manitoba in 2015. Arteries that supply the tumor are selectively entered and a concentrated dose of chemotherapy, typically doxorubicin, is administered. Once the doxorubicin has been administered the artery is embolized with Poly Vinyl alcohol (PVA), blocking further blood flow. The tumor response is then characterized by MRI 4-6 weeks post procedure. TACE has a 5 year overall survival (OS) of 32.4%[16]. SBRT is a newer local therapy, which was introduced to Manitoba in 2016, that has promising outcomes with a three-year survival of 70.4%[17]. SBRT delivers radiation, usually between 3 to 5 fractions, to the tumor which is marked with fiducial markers[18]. SBRT and TACE are not curative themselves but can be part of curative treatment by bridging patients to transplant. Lastly, chemotherapy is a systemic treatment that improves OS. The patient must have preserved liver function and be healthy enough to endure the side effects of various agents. Historically, the most common agent was Sorafenib which has been proven in clinical studies to prolong survival in the time frame of months, however with significant side effects[19–21]. One phase 3 Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial showed an overall survival (OS) of 10.7 months with treatment vs 7.9 in the placebo group[21]. Currently the National Comprehensive Cancer Network (NCCN) guideline recommends atezolizumab and bevacizumab as its superior to sorafenib in overall survival with a mean OS of 19.2 months vs 13.4 on sorafenib[22–24].

HCC is a relatively common cancer with increasing incidence. If detected early, treatment can be curative. However, globally over half of newly diagnosed patients can only be offered supportive care, with a 5 year survival of 10%[25]. Although the prognosis is poor in comparison to other cancers, advancement and new treatments are now available.

The aims of this study are as follows

1. To identify factors that determine the type of treatment a patient might receive: curative, noncurative, or supportive.
2. To study if the overall survival has improved with the introduction of new local treatments

Methods

Cohort and data collection:

This is a retrospective study of Manitoban patients who were diagnosed with HCC between January 1, 2011 and December 31, 2019. I performed data collection on patient diagnosed with HCC between 2016-2019. These patients were added to the previous cohort of patients diagnosed between 2011 and 2015. Some previously missed patients were also added to the 2011-2015 data set. Patients were identified from the Manitoba Cancer Registry (MCR). The MCR is a data system that includes information on all patients in Manitoba diagnosed with a malignant neoplasm[26]. Patients coded as C22.0, liver cell carcinoma, between January 1, 2016 and Dec 13, 2019, had their chart reviewed by myself. Patients diagnosed between January 1, 2011 and December 31, 2015 were reviewed by a prior BSc student. Patients were removed from the study if the cancer was not HCC or if the diagnosis was unknown. Patients who had mixed cancer (HCC and another) were included, but a special note was made. Using MedOnc, RadOnc and IMPAX data was collected on patients. The study was approved by the Health Research Ethics Board (HREM) at the University of Manitoba.

Data extraction:

Patient charts were reviewed on electronic chart systems and radiology reports were accessed through IMPAX. When patient information wasn't available, a note was made, and then left as unknown. Demographic information including patient's birthday, age at diagnosis, sex and previous cancers were collected. Information on the patient's liver status such as cirrhosis, ascites, portal hypertension and Liver Function Tests (LFT's) aswell as cancer characteristics such as portal vein thrombus (PVT), number of foci were also collected. Etiology was collected and categorized as ETOH (alcoholic cirrhosis), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Non-Alcoholic Steatohepatitis (NASH), multiple, or unknown/none. Treatments followed in the study include transplant, surgery, RFA, chemotherapy, SBRT and TACE. Treatments were recorded along with the date the intervention was performed and if applicable, dosages, cycles and number of tumors treated. Treatment approach was categorized into curative which includes transplant, resection and RFA, non-curative which includes TACE, SBRT and chemotherapy, and supportive care only. Patient identifiers were then removed and the data was then cleaned for the statistician Pascal Lambert at Cancer Care Manitoba.

Data Analysis:

Data analysis was performed with the help of a Cancer Care Manitoba (CCMB) statistician Pascal Lambert. Descriptive statistics were produced for the entire cohort, 2011-2019, in order to describe patient characteristics, cancer and treatment details that were collected from the CCMB Registry database. Descriptive statistics included demographic, radiological and clinical data including delivered treatment.

The cohort was split according to the goals of treatment; curative, non-curative and supportive care. Analysis of Variance, Chi-square tests, Fisher's exact tests were used for comparing variables (such as age and cancer details) between groups of treatments (curative, non-curative, and supportive care). The Kaplan-Meier method was used to estimate overall survival rates by diagnosis year and Cox regression was used to detect any potential trend in survival by diagnosis year. When the amount of missing data exceeded 10%, multiple imputation was used for rectifying this problem.

Results

Please refer to the end of the paper to see Figures and Tables.

Characteristics of the population

Referring to Table 1 the mean age at diagnosis was 66.8 years old. The sex of the patients were 73.3% male and 26.7% female. Looking at Table 2 the most common etiology was alcohol without viral infection followed by mixed etiology, Hepatitis C virus (HCV) infection, Hepatitis B Virus (HBV) infection, NASH and lastly hemochromatosis. Metastasis were present in 14.7% of patients, while 75% had no metastasis. The most common type of treatment was supportive care with 59.1% of patients receiving it. The next most common type was curative with 24.1% of patients receiving curative care. Finally, non-curative treatment was offered 16.8% of the time. Biochemical data was collected but was poorly recorded in charts, therefore labs such as bilirubin, albumin, international normalized ratio (INR) and liver enzymes were not included in the analysis.

Description by Cancer and Treatment Details

Treatment intent was broken up into curative, noncurative and supportive. Looking at Table 2, characteristics of the patient's cancer such as etiology, number of foci, PVT, portal hypertension, ascites and cirrhosis, metastasis and tumor size were all compared between different treatment groups for the complete data set of 2011-2019. A significant difference was noted in age between curative and supportive care, with a mean age of 63.8 vs 68.3. Patients were more likely to have curative treatments if they had a single lesion as well as no portal vein thrombosis. Patients were more likely to have supportive care if they had ascites. There was no statistical significance with portal hypertension, gender, original tumor size or cirrhosis.

Survival

Viewing Figure 1, the survival at 1, 2,3 4, and 5 years were 0.44, 0.31, 0.24, 0.22 and 0.21. There is a significant increase survival from 2011 to 2019 with a p value of 0.013.

Discussion

The main goal of this project which was to determine if the 2-year survival rate had changed since the previously published Manitoba study in 2019. Looking at figure 2, there is a general upwards trend of 2 year survival. Additionally, there is a statically significant increase in survival from 2011 to 2019 with a p value of 0.013. Survival of the complete data set from 2011-2019 at 2 and 5 years is 31% and 21% respectively. Survival of the 2011-2015 data set at 2 and 5 years was 27% and 14% respectively[4]. Therefor there has been a notable change in 2 and 5 year survival. Future iterations of this study will compare directly between the 2011-2015 cohort and the 2016-2019 cohort and their respective 2 and 5 year survival.

This increase in life expectancy is likely due to several factors. First, we believe that the main impact was the addition of two new treatment which became available in Manitoba in the noncurative category: SBRT and TACE. SBRT and TACE have both been shown to improve survival when compared to no treatment[16,17]. As seen in figure 3, there is a large change in the proportion of patients, starting in 2016, that received more than best supportive care. The proportion of patients that can be offered curative care is usually limited by at which stage they are diagnosed. There have been no changes in screening guidelines, as such we would not expect to see a change in the proportion of patients being diagnosed early enough to receive curative care. This matches our data as the curative proportion of patients remains relatively unchanged. However, since 2011 there has been an increasing number of treatment options available for noncurative care. As such we would expect to see an increase in the portion of patients receiving noncurative care. Graph 3 clearly demonstrates an increase in noncurative treatment. Non curative treatment consisted of 6.8-12.5% of treatments prior to 2016, and between 15.1-31.8% of treatments from 2016 onwards. Other factors that could have contributed to improved survival include the use of new immunotherapy drugs such as atezolizumab and bevacizumab, however these only became available in 2021[22–24].

We see a decrease in 2 year survival in years 2018-2019, we believe this could be due to tapering down of hospital service in the Coronavirus Disease (COVID) pandemic. Patients that were diagnosed in 2018-2019 would have likely received noncurative treatments in the years 2020-2021. COVID could have affected noncurative treatment in several ways. Firstly, as COVID regulations tightened, patients may have opted to stay out of hospitals and not receive noncurative treatment. Secondly, there was a large shortage of staff, which could have reduced procedural capacity. Finally, at times in the pandemic, there was an age limit on patients' procedures including TACE. To support this hypothesis there was a plateau and then decrease in TACE procedures performed between 2020 and 2021. To confirm if this hypothesis has merit, further investigations are needed. Additionally, there is a decrease in patients diagnosed in 2019 that received noncurative treatment. This could be due to missing data not given to cancer

care. There were several patients who had received TACE but were not included in the cancer care registry and therefore not included in our study.

Looking at the descriptive factors of the various treatment groups, a lot of the trends we see are expected. Table 1 shows a younger age in the curative treatment category makes sense as a part of determining whether a patient can undergo a major surgery is their overall health and comorbidities. Younger patients tend to be healthier, have less comorbidities and can undergo more aggressive treatments and operations. Additionally younger patients may be more likely to want aggressive treatment.

Comparing the etiology of the patients studied in, Table 2, we can see similar trends to what is reported in other literature. In the USA 10-16% of HCC is related to HBV infection[27]. Our data indicated that in Manitoba 6.6% of HCC was related to HBV alone, however that number is likely closer to 10% when including HBV from the mixed etiology category. In Canada alcohol and NASH are the most common causes of HCC. The most common etiology we had was alcohol with 19.6% of patients having alcohol as their sole risk factor. The prevalence of NASH was lower than expected, with only 5.8% of patients having just NASH. This is most likely due to NASH being under reported in patients notes. It would be expected that many of the patients in the unknown category had NASH. Cirrhosis was present in 74.5% of our patients. With approximately 80% of patients having cirrhosis in the literature[6,28]. This discrepancy may be due to under reporting of cirrhosis, error in reading the charts, or a large portion of our population having liver injury such as NAFLD or NASH, but no cirrhosis.

Many of the statistically significant findings in respect to type of treatment and liver characteristics make sense considering treatment criteria. For example, portal vein thrombosis places a patient at a BCLC stage of C, and there for likely to receive non curative treatment[11]. Multinodular disease means the patient is at stage B and more likely to receive non curative treatment, or possible transplant depending on tumor characteristics[11]. Ascites is a clinical indicator of poor liver function. Therefor it makes sense that the absence of PVT, multinodular disease and ascites is statistically related to curative treatment. Because factors such as PVT and multinodular disease become more common as the disease progresses, it is important that we diagnose HCC early with screening. Additionally, as ascites is a surrogate indicator of Liver Function Tests (LFTs) there should be added efforts by physicians to maintain LFTS as to not preclude their patients from curative/noncurative treatment. It is note worthy that portal hypertension and cirrhosis are not barriers to receiving active treatment. This should be conveyed to primary care providers, so they understand these factors do not preclude their patients from more aggressive care.

Manitoba, in comparison to other provinces, had lagged in adopting some cancer treatments. In the previous rendition of the study, our survival rates were lower than the Canadian average[4]. Now, with treatments such as TACE, and SBRT with Calypso beads, our 5 year survival is 21%. This serves as a reminder, that as new proven clinical treatments arrive, by investing in these treatments we can change and extend lives of the patients here in Manitoba. Therefore, in the future, by adopting further treatments that have been recommended such as Transarterial Radioembolization (TARE) we can expect to see an even larger improvement in survival. An additional way we can match our fellow provinces in standard of care for HCC is creating provincial guidelines for HCC treatment.

This research has set the foundations for further future studies to determine the effectiveness of TACE by dose. Data collected such as number of lesions, and dose of doxorubicin were not used in this study but can be used in further research, once all patients

who received TACE is available as well as funding to perform statistical analysis. This data is planned to be used to look at the relationship between doxorubicin dose and tumor response. A board-certified radiologist will look at the tumors individually before TACE treatment and 4 to 6 weeks after imaging, rating tumor response with Modified Response Evaluation Criteria in Solid Tumors (M-RESIST). The dose of doxorubicin will then be correlated with tumor response.

The problems encountered in this study also reflect other issues in the way patients with HCC move through the Manitoban health care system. Currently Manitoba does not have its own guidelines on how to treat patients with HCC. Additionally, not all patients go through the same process. Some patients are reviewed at Multidisciplinary Tumor Board Meetings (MTBM), others are not. Some patients go through cancer care, while others do not. Having a standardized process that includes a multidisciplinary team has been shown to improve out comes with other kinds of cancer[29]. Currently our team is revising an application to study the effectiveness of these LTBM as well as create Manitoban guidelines for the treatment of HCC.

Although Manitoba's 5 year survival is improving, there still is much to be desired in terms of OS. However, we have seen an improvement in survival as we adopt and utilize new treatment options.

Weaknesses

The main weakness of the study was missing patients information. Information for several patients was either not collected at time of diagnosis or not available on the databases used in this study. Standardizing what physicians write in their referrals may help with this problem in future research. While some characteristics were commonly mentioned such as cirrhosis, others such as encephalopathy were often not mentioned at all. An example of how this can be remedied is the forms filled out for Liver Tumor Board Meetings. For these forms referring physicians are supposed to include the patients diagnosis, liver function, cirrhosis, portal hypertension and more. This would help standardize data collection for future projects and allow for other physicians to have quick access to important information.

Secondly, after looking at patient data collection a few problems were encountered. Data that was collected by my predecessor had errors that needed to be fixed to ensure the best possible quality of data. Furthermore, I discovered that several patients who had been treated with TACE and had HCC were not included in the Cancer Care database. We are in the process of sending these patients information to Cancer Care so their database can be updated. Further presentations or additions to this data set will include these patients.

Our patient pool was moderately sized at 572 patients, however a larger sample size may have given us better insight. Additionally, as stated previously some patients who received TACE, a non-curative treatment, where not included in this data set. This would effect our data especially in terms of the percent of patients who received noncurative care, and in terms of survival as TACE prolongs survival.

Lastly, our data analysis was predetermined to be an addition of the previous data set. Analyzing the two data sets 2011-2015 and 2016-2019 separately may have given us better insight into how much treatment has changed in Manitoba over the past decade.

Changes to Plan

Due to the lack of data on some TACE patients, as well as lack of funding we could not perform all the analysis specific to TACE we desired. However, based on the improvement in survival we can infer treatments are improving and this is leading to an improvement in survival.

Conclusion

This study confirms the importance of providing new and proven treatment to our patients here in Manitoba and accordingly has resulted in improved survival which meets the national average.

Tables And Figures

Table 1: Patient Characteristics, Etiology and Treatment Type of 2011-2019 Cohort

		N	%
Age at diagnosis	mean (SD)	66.8	(10.9)
Sex	Female	153	26.7
	Male	419	73.3
Etiology	Alcohol (without viral infection)	112	19.6
	HBV infection only	38	6.6
	HCV infection only	68	11.9
	Other	46	8.0
	Mixed etiology	99	17.3
	Unknown	209	36.5
	Cirrhosis	426	74.5
Metastatis	Yes	84	14.7
	No	429	75.0
	Unknown	59	10.3
Most effective treatment	Curative treatment	138	24.1
	Liver transplantation	19	
	Surgery	64	
	RFA	48	
	Missing	7	
	Non-curative treatment	96	16.8
	TACE	50	
	SBRT	4	
	Chemotherapy	37	
	Missing	5	
	Supportive care	338	59.1

Table 2: Univariable analysis of Demographics, Etiology and Disease Characteristics at Diagnosis with Treatment Category

	Cohort (N = 572)	Curative (N = 138)	Non-curative (N = 96)	Supportive care (N = 338)	p	Significant pairwise comparisons
Age at diagnosis						
mean (SD)	66.8 (10.9)	63.8 (9.1)	65.9 (9.2)	68.3 (11.7)	<0.001	Curative vs supportive care
Gender						
Female	153 (26.9)	36 (26.1)	22 (22.9)	95 (28.1)	0.586	
Male	419 (73.3)	102 (73.9)	74 (77.1)	243 (71.9)		
Etiology						
EtOH	112 (19.6)	24 (17.4)	15 (15.6)	73 (21.6)		
HBV	38 (6.6)	15 (10.9)	8 (8.3)	15 (4.4)		
HCV	68 (11.9)	29 (21.0)	9 (9.4)	30 (8.9)		
Hemochromatosis	5 (0.9)	1 (0.7)	0 (0.0)	4 (1.2)		
NASH	33 (5.8)	14 (10.1)	9 (9.4)	10 (3.0)		
Other	8 (1.4)	2 (1.4)	2 (2.1)	4 (1.2)		
Mixed	99 (17.3)	23 (16.7)	29 (30.2)	47 (13.9)		
Unknown	209 (36.5)	30 (21.7)	24 (25.0)	155 (45.9)		
Number of foci						
Single	244 (42.7)	97 (70.3)	32 (33.3)	115 (34.0)	<0.001	Curative vs non-curative
Multiple	296 (51.7)	35 (25.4)	63 (65.6)	198 (58.6)		Curative vs supportive care
Unknown	32 (5.6)	6 (4.3)	1 (1.0)	25 (7.4)		
PVT						
Yes	115 (20.1)	7 (5.1)	26 (27.1)	82 (24.3)	<0.001	Curative vs non-curative
No	422 (73.8)	123 (89.1)	67 (69.8)	232 (68.6)		Curative vs supportive care
Unknown	35 (6.1)	8 (5.8)	3 (3.1)	24 (7.1)		
Portal hypertension						
Yes	327 (57.2)	73 (52.9)	52 (54.2)	202 (59.8)	0.164	
No	213 (37.2)	58 (42.0)	41 (42.7)	114 (33.7)		
Unknown	32 (5.6)	7 (5.1)	3 (3.1)	22 (6.5)		
Ascites						

Yes	233 (40.7)	29 (21.0)	24 (25.0)	180 (53.3)	<0.001	Curative vs supportive care
No	304 (53.1)	102 (73.9)	68 (70.8)	134 (39.6)		Non-curative vs supportive care
Unknown	35 (6.1)	7 (5.1)	4 (4.2)	24 (7.1)		
Cirrhosis						
Yes	426 (74.5)	105 (76.1)	75 (78.1)	246 (72.8)	0.911	
No	117 (20.5)	28 (20.3)	19 (19.8)	70 (20.7)		
Unknown	29 (5.1)	5 (3.6)	2 (2.1)	22 (6.5)		
Metastasis						
Yes	84 (14.7)	2 (1.4)	15 (15.6)	67 (19.8)		
No	429 (75.0)	129 (93.5)	77 (80.2)	223 (66.0)		
Unknown	59 (10.3)	7 (5.1)	4 (4.2)	48 (14.2)		
Tumour size, mm						
Median (Q1, Q3)	50 (30-85)	30 (22-46)	50 (37-72)	65 (38-113)		
Unknown	51 (8.9)	3 (2.2)	4 (4.2)	44 (13.0)		

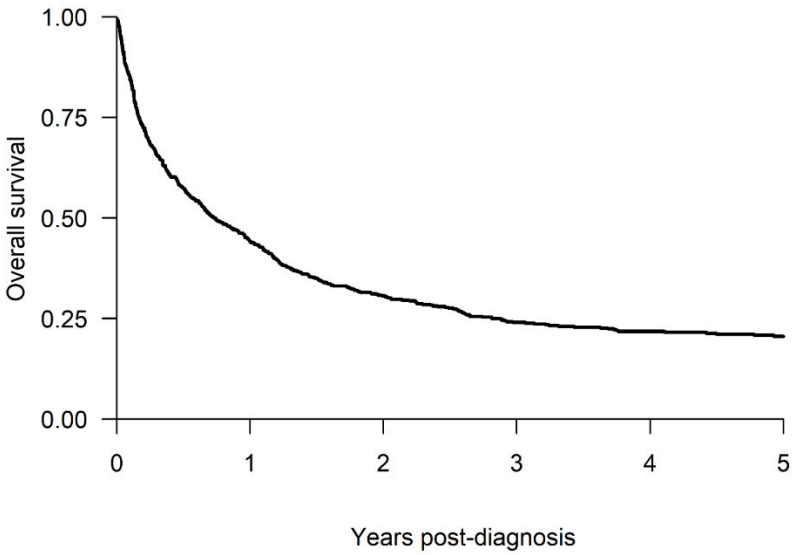

Figure 1 Overall Survival of Patients Diagnosed from 2011 to 2019

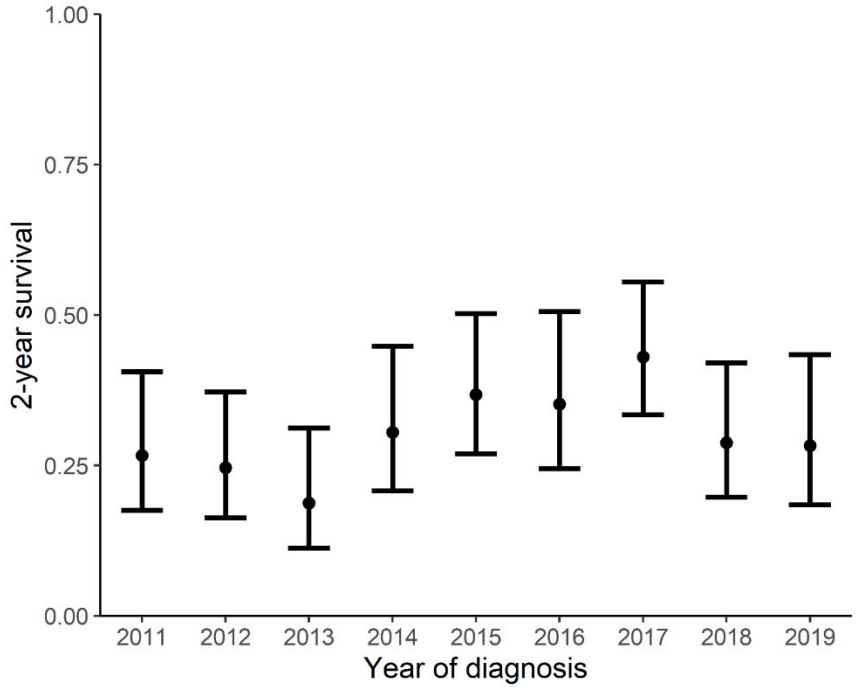

Figure 2- Two Year Survival of Patients Diagnosed in Each Year from 2011 to 2019

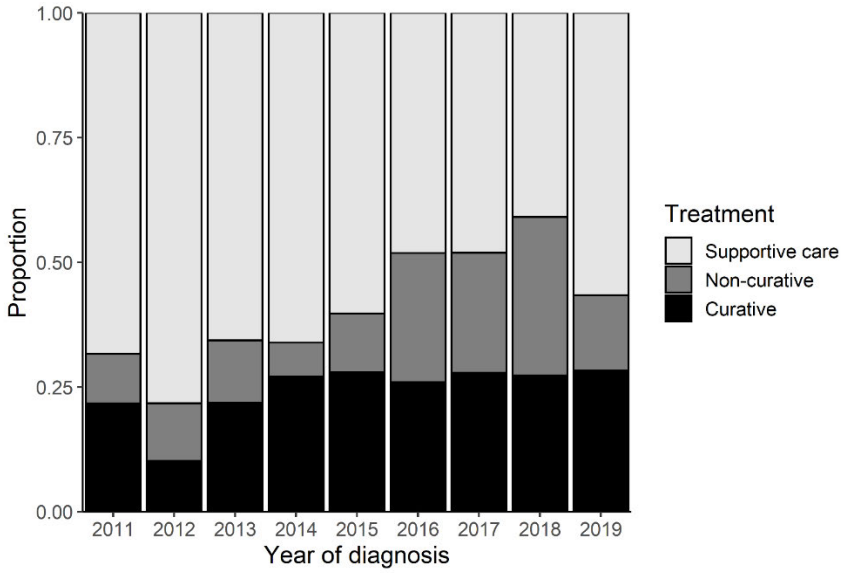

Figure 3- Proportion of Care Type Annually from 2011 to 2019

Citations

1. Philips CA, Rajesh S, Nair DC, Ahamed R, Abduljaleel JK, Augustine P. Hepatocellular Carcinoma in 2021: An Exhaustive Update. Published online 2021. doi:10.7759/cureus.19274

2. Brenner D, Poirier A, Smith L, et al. Members of the Canadian Cancer Statistics Advisory Committee Analytic leads Additional analysis Project management. Published online 2021.

3. Statistical analysis Ethics approval. doi:10.1503/cmaj.212097/tab-related-content

4. Hanumanthappa N, Cho BH, McKay A, et al. Epidemiology, clinical treatment patterns, and survival of hepatocellular carcinoma in Manitoba. *Canadian Liver Journal*. 2020;3(2):194-202. doi:10.3138/CANLIVJ.2019-0015

5. Survival statistics for liver cancer | Canadian Cancer Society. Accessed July 24, 2022. https://cancer.ca/en/cancer-information/cancer-types/liver/prognosis-and-survival/survival-statistics

6. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases Purpose and Scope. 2018;68(2). doi:10.1002/hep.29913

7. Sherman mb bch phd M, Burak md bsc msc K, Maroun md J, et al. *PRACTICE GUIDELINE SERIES Multidisciplinary Canadian Consensus Recommendations for the Management and Treatment of Hepatocellular Carcinoma*. Vol 18.; 2011.

8. Morgan TA, Maturen KE, Dahiya N, Sun MRM, Kamaya A. US LI-RADS: ultrasound liver imaging reporting and data system for screening and surveillance of hepatocellular carcinoma. *Abdominal Radiology 2017 43:1*. 2017;43(1):41-55. doi:10.1007/S00261-017-1317-Y

9. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130(7):417-422. doi:10.1007/S00432-004-0552-0

10. Bialecki ES, di Bisceglie AM. Diagnosis of hepatocellular carcinoma. *HPB*. 2005;7(1):26-34. doi:10.1080/13651820410024049

11. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *Journal of Hepatology*. 2022;76(3):681-693. doi:10.1016/J.JHEP.2021.11.018

12. Belghiti J, Kianmanesh R. Surgical treatment of hepatocellular carcinoma. *HPB*. 2005;7(1):42-49. doi:10.1080/13651820410024067

13. Ju MR, Yopp AC. Evolving thresholds for liver transplantation in hepatocellular carcinoma: A Western experience. *Annals of Gastroenterological Surgery*. 2020;4(3):208-215. doi:10.1002/AGS3.12316

14. Beppu T, Yamamura K, Okabe H, Imai K, Hayashi H. Oncological benefits of portal vein embolization for patients with hepatocellular carcinoma. *Annals of Gastroenterological Surgery*. 2021;5(3):287-295. doi:10.1002/AGS3.12414

15. Li JK, Liu XH, Cui H, Xie XH. Radiofrequency ablation vs. Surgical resection for resectable hepatocellular carcinoma: A systematic review and meta-analysis. *Molecular and Clinical Oncology*. 2020;12(1):15-22. doi:10.3892/mco.2019.1941

16. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JFH. Lipiodol Transarterial Chemoembolization for Hepatocellular Carcinoma: A Systematic Review of Efficacy and Safety Data HEPATOBILIARY MALIGNANCIES A HE STUDY OF LIVER D I S E ASES T MERICAN ASSOCIATION FOR. *HEPATOLOGY*. 2016;64(1). doi:10.1002/hep.28453/suppinfo

17. Hara K, Takeda A, Tsurugai Y, et al. Hepatobiliary Malignancies Radiotherapy for Hepatocellular Carcinoma Results in Comparable Survival to Radiofrequency Ablation: A Propensity Score Analysis. *2533 Hepatology*. 2019;69(6). doi:10.1002/hep.30591

18. Shampain KL, Hackett CE, Towfighi S, et al. SBRT for HCC: Overview of technique and treatment response assessment. *Abdominal Radiology*. 2021;46:3615-3624. doi:10.1007/s00261-021-03107-7

19. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. *Journal of Hepatology*. 2012;57(4):821-829. doi:10.1016/J.JHEP.2012.06.014

20. Sanoff HK, Chang Y, Lund JL, O'neil BH, Dusetzina SB. Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma. doi:10.1634/theoncologist.2015-0478

21. *Sorafenib in Advanced Hepatocellular Carcinoma*.; 2008. www.nejm.org

22. Finn RS, Qin S, Ikeda M, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *https://doi.org/101200/JCO2021393_suppl267*. 2021;39(3_suppl):267-267. doi:10.1200/JCO.2021.39.3_SUPPL.267

23. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine*. 2020;382(20):1894-1905. doi:10.1056/NEJMOA1915745/SUPPL_FILE/NEJMOA1915745_DATA-SHARING.PDF

24. Benson III AB, D MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021. *J Natl Compr Canc Netw*. 2021;19(5):541-565. doi:10.6004/jnccn.2021.0022

25. de Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol*. 2014;15(1):23-34. doi:10.1016/S1470-2045(13)70546-1

26. What is the Manitoba Cancer Registry? Accessed July 3, 2022. https://www.cancercare.mb.ca/Research/epidemiology-cancer-registry/what-is-the-manitoba-cancer-registry

27. Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *Journal of Carcinogenesis*. 2017;16(1):1-8. doi:10.4103/JCAR.JCAR_9_16

28. Tarao K, Nozaki A, Ikeda T, et al. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases—meta-analytic assessment. *Cancer Medicine*. 2019;8(3):1054. doi:10.1002/CAM4.1998

29. Lu J, Jiang Y, Qian M, Lv L, Ying X. The Improved Effects of a Multidisciplinary Team on the Survival of Breast Cancer Patients: Experiences from China. *International Journal of Environmental Research and Public Health*. 2020;17(1). doi:10.3390/IJERPH17010277