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Wait Time for Curative Intent Radio Frequency Ablation is Associated with Increased Mortality in Patients with Early Stage Hepatocellular Carcinoma

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ABSTRACT

Introduction. Radiofrequency ablation (RFA) is a recommended curative intent treatment option for patients with early stage hepatocellular carcinoma (HCC). We investigated if wait times for RFA were associated with residual tumor, tumor recurrence, need for liver transplantation, or death. **Material and methods.** We conducted a retrospective study of patients diagnosed with HCC between January 2010 and December 2013 presenting to University Health Network (UHN) in Toronto, Canada. All patients receiving curative intent RFA for HCC were included. Multivariable Cox regression was used to determine if wait times were associated with clinical outcomes. **Results.** 219 patients were included in the study. 72.6% were male and the median age was 62.7 years (IQR 55.6-71). Median tumor size at diagnosis was 21.5 mm (IQR 17-26); median MELD was 8.7 (IQR 7.2-11.4) and 57.1% were Barcelona stage 0. The cause of liver disease was viral hepatitis in 73.5% (Hepatitis B and C). The median time from HCC diagnosis to RFA treatment was 96 days (IQR 75-139). In multivariate analysis, wait time was not associated with requiring liver transplant or tumor recurrence, however, each incremental 30-day wait time was associated with an increased risk of residual tumor (HR = 1.09; 95% CI 1.01-1.19; p = 0.033) as well as death (HR = 1.23; 95% CI 1.11-1.36; p ≤ 0.001). **Conclusion.** Incremental 30-day wait times are associated with a 9% increased risk of residual tumor and a 23% increased risk of death. We have identified system gaps where quality improvement measures can be implemented to reduce wait times and allocate resources for future RFA treatment, which may improve both quality and efficiency of HCC care.

Key words. Wait times. Quality Improvement. Hepatocellular carcinoma. Radiofrequency ablation. Mortality.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide with incidence rates tripling in North America over the last three decades.[1,2] HCC develops in 5-30% of patients with cirrhosis depending on its etiology with chronic hepatitis B (CHB), chronic hepatitis C (CHC), alcoholic, and non-alcoholic fatty liver (NAFLD) disease carrying the highest risks.[1] Fortunately, curative intent treatment options are available, if HCC is identified at an early stage, according to the Barcelona Clinic Liver Cancer (BCLC) staging system which has been widely accepted in international guidelines for HCC management.[1,3]

Liver transplantation is currently the only treatment able to address the HCC and underlying liver disease, and in HCCs within the so-called Milan criteria, leads to a 5-year survival rate exceeding 70%.[4] However, the shortage of organs makes transplant an option for a highly selected and otherwise not treatable minority of patients.[5] Partial hepatectomy (i.e., HCC resection) is associated with 5-year survival rates up to 60%, however, in western countries where the majority of HCC occur in patients with

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cirrhosis less than 5% of patients are suitable candidates for resection due to the risk of postoperative liver decompensation.[6,7] Given these limitations of available surgical options, less invasive methods for achieving cure of HCC have been developed and patients with early HCCs are now considered for radiofrequency ablation (RFA) with a curative intent. Multiple studies have shown RFA for early stage HCC has similar survival to surgical management at 3 and 5 years around 90% and 70%, respectively.[8-11] However, effectiveness and success may depend on how quickly treatment is administered. Delays in access to RFA after an early stage HCC has been diagnosed may increase the risk of tumor progression beyond a stage that is curable by RFA, may lead to more invasive and expensive treatment modalities such as liver transplant or hepatectomy, and lastly, could potentially lead to death.

The University Health Network (UHN) and affiliated hospitals in Toronto, Ontario is the quaternary Hepatology referral center in the Greater Toronto Area (GTA) with a population of more than 6 million individuals. The majority of all RFA procedures in the GTA are performed at UHN to treat HCC, however, for several reasons, the time from diagnosis of early HCC to referral and administration of RFA is often longer than expected in many cases.

Currently, Cancer Care Ontario (CCO) have set systemic wait time targets of 28 days from diagnosis to treatment of common malignancies.[11] However, HCC has not been included in this target wait time despite being a malignancy with the fastest growing incidence.[12] In addition, no recommendations or target wait times currently exist in the literature for the management of HCC with RFA. The derivation of optimal time points for prevention of adverse events mentioned could lead to implementation of wait time guidelines, identification of patients requiring triage, and prediction of tumor growth characteristics. Thus, the aim of this study was to measure the diagnosis to treatment lag and its impact on patient outcomes, namely residual and recurrent HCC post-treatment, the need for liver transplant, and death. In doing so, we aimed to determine the barriers to RFA access and the threshold wait-time that would need to be achieved in order to minimize adverse patient outcomes.

MATERIAL AND METHODS

Study design, inclusion and exclusion criteria

A retrospective cohort study was performed of patients diagnosed with HCC and referred to our HCC Tumor Board for review between July 1, 2010 and December 31, 2013. Multidisciplinary HCC Tumor Board rounds convene weekly and are attended by Hepatologists, Hepatobiliary Surgeons, Diagnostic and Interventional Radiologists, Medical and Radiation Oncologists. The diagnosis and management of HCC is based on the respective AASLD guidelines.[3] We screened the entire database of patients discussed at HCC Tumor Board rounds during the study period. Patients with a newly diagnosed HCC and who were eligible to only receive RFA in a curative intent form the basis of this analysis. Patients were excluded if there were contraindications to RFA such as hepatic decompensation with a Child-Pugh Turcotte score of > 10 (CTP C). Additional exclusion criteria included the following: tumor size greater than 4 cm, more than three HCC lesions, previous HCC, extra-hepatic spread, listed for or previous liver transplant, or RFA performed in non-curative intent (e.g. for down staging/bridging to liver transplant).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice and is approved by the ethical review board of UHN, Toronto, Canada.

Data acquisition, definitions, and endpoints

Two investigators extracted demographic and clinical data from the HCC database. Diagnosis of HCC occurred when the Radiologist confirmed HCC by ultrasound (US), contrast enhanced ultrasound (CEUS), computed tomography (CT), or magnetic resonance imaging (MRI). Patient death due to HCC was the primary outcome. Residual or recurrent tumor and need for liver transplantation were secondary outcomes. Residual tumor was defined as HCC seen on the first cross sectional contrast enhanced imaging after RFA, which per our institution's protocol, is performed three months post RFA. Tumor recurrence was defined as reappearance of a visible HCC on cross sectional imaging (performed as per protocol every 3 months) in a patient who had at least one negative imaging study after RFA.

Statistical analysis.

Continuous variables were expressed as median values with interquartile ranges (IQR) and categorical variables were expressed as frequencies (percentages). Continuous variables were compared between groups using the Wilcoxon rank-sum test, and categorical variables were compared using Pearson's χ^2 test. Univariate and multivariate analysis of baseline risk factors was performed using Cox proportional hazards regression with death due to HCC as the primary outcome; death due to other causes was considered a competing risk in the analysis. The starting time point, or baseline, for the analysis was defined as the date a

patient received RFA treatment. Patients were followed until death or date of the last outpatient visit. In the multivariate analysis, wait time was a continuous covariate and the following confounders were adjusted for in the model: sex, age at diagnosis, MELD score, and Barcelona stage. As the event count was not high we did not include tumor size (however, in a separate univariate analysis tumor size was not associated with HCC death - data not shown). For the secondary outcomes, we adjusted for size of tumor at baseline, age at diagnosis, sex, MELD, and Barcelona stage, and all-cause death was considered to be a competing risk. In the case of transplant, where the event count was not high, we adjusted for age at diagnosis and Barcelona stage. All statistical tests were two-sided and evaluated at the 0.05 level of significance. Data was analyzed in the R statistical software (Version 3.2.2).

RESULTS

Patient characteristics

Three hundred and twenty two patients were eligible for RFA in curative intent during the study period as identified by screening our HCC database. Of these, a total of 103 patients (32%) were excluded for the following reasons: previous HCC (n = 77), contraindications that precluded RFA (n = 20; not related to wait time), and missing data (n = 6). Thus, a total of 219 patients were included in the study. Patient demographic, clinical and HCC characteristics are detailed in table 1. The majority of the patients were males (72.6%) with a median age of 62.7 years (IQR 55.6-71); the median tumour size at diagnosis was 21.5 mm (IQR: 17-26) with a maximum size of 40 mm; 125 (57.1%) patients had Barcelona stage 0 and 94 (42.9%) had Barcelona stage A; the median MELD score at diagnosis was 8.7 (IQR 7.2-11.4); 96 (43.8%) patients had chronic hepatitis C, 65 (29.7%) had chronic hepatitis B, while 40 (18.3%) had NASH/Alcohol related cirrhosis, and 18 (8.2%) had cirrhosis related to other disease entities (Primary Biliary Cholangitis, etc.).

Time from diagnosis to RFA

The median wait time from diagnosis to presentation to tumor board rounds was 21 days (IQR 11-49), from tumour board to Interventional radiology (IR) consultation

Table 1. Baseline characteristics of patients by death group*.

Variable	All (n = 219)	No death (n = 174)	HCC death (n = 30)	Other death** (n = 15)	p-value
Age	62.7 (55.6-71)	62.8 (55.6-70.9)	62.7 (59.3-72.6)	61.9 (54.9-72.1)	0.749
Gender, male	159 (72.6)	125 (71.8)	24 (80)	10 (66.7)	0.605
HCC size at diagnosis (mm)	21 (17-26)	20 (17-26)	22 (18-25)	25 (19-30.5)	0.153
Ethnicity					
Asian	104 (47.5)	86 (49.4)	13 (43.3)	5 (33.3)	0.127
Caucasian	86 (39.3)	64 (36.8)	16 (54.3)	6 (40)	
Other	29 (13.2)	24 (13.8)	1 (3.3)	4 (26.7)	
Etiology					
Hepatitis B	65 (29.7)	52 (29.9)	9 (30)	4 (26.7)	0.686
Hepatitis C	96 (43.8)	75 (43.1)	12 (40)	9 (60)	
NASH/Alcohol	40 (18.3)	31 (17.8)	8 (26.7)	1 (6.7)	
Other	18 (8.2)	16 (9.2)	1 (3.3)	1 (6.7)	
BCLC					
0	125 (57.1)	104 (59.8)	17 (56.7)	4 (26.7)	0.047
A	94 (42.9)	70 (40.2)	13 (43.3)	11 (73.3)	
ALP (IU/mL)	106 (77-136)	103 (76.3-133)	121.5 (78.8-171.5)	120 (91-144)	0.010
ALT (IU/mL)	43 (28-77)	41 (28-81.8)	49.5 (34.5-72.3)	50 (35-67)	0.772
AST (IU/mL)	51 (34.5-90)	48.5 (34-99.3)	64.5 (35.3-87.8)	55 (42.5-84.5)	0.777
Bilirubin (umol/L)	16 (10-26)	16 (11-27.8)	16 (9.3-20)	20 (11-26)	0.937
Creatinine (umol/L)	71 (65-87)	71 (65-87.8)	74 (65.3-90.5)	70 (65-74)	0.699
INR	1.12 (1.04-1.25)	1.13 (1.03-1.27)	1.09 (1.04-1.18)	1.14 (1.08-1.18)	0.466
MELD	8.7 (7.2-11.4)	8.8 (7.2-11.7)	8.1 (7.1-9.9)	8.3 (7.9-9.3)	0.592
Platelets ($x10^9$/L)	103 (71-147.5)	105 (71-144.8)	106 (79.3-183)	81 (59.5-135.5)	0.656

** Values are median (interquartile range) or n (%). ** Other death group comprised of patients with liver decompensation and non-liver related deaths.*

was 30 days (IQR 21-44), and from IR consultation to RFA was 35 days (IQR 25-48), respectively. Overall, the median wait time from diagnosis to RFA was 96 days (IQR 75-139) (Table 2).

Primary outcome

Forty-five (20.5%) patients died during a median follow-up of 799 days (IQR 542-1,182), with 41 (91.1%) deaths being attributed to liver related mortality. The 4 non-liver related deaths were due to respiratory failure, intracranial hemorrhage, primary spinal tumor not present prior to RFA, and esophageal adenocarcinoma not detected prior to RFA. Of the 41 liver related deaths, 30 (73.2%) were classified as deaths due to HCC and 11 (26.8%) were classified as deaths due to liver decompensation. The analysis was based on the 30 deaths due to HCC. In univariate Cox regression analysis, increased wait time was associated with an increased risk of death due to HCC (HR=1.22, per 30 days; 95% CI 1.10-1.36; $p \leq 0.001$) (Table 3). In multivariate analysis, increased wait time was also associated with an increased risk of death (HR = 1.23, per 30 days; 95% CI 1.11-1.36; $p \leq 0.001$) (Table 3). There were no significant baseline differences between those experiencing death and those who did not aside from ALP values (103 IU/mL in no death *vs.* 121.5 IU/mL in HCC death *vs.* 120 IU/mL in other death; $p = 0.010$) and Barcelona stage A (40.2% in no death vs. 43.3% in HCC death and 73.3% in other death; $p = 0.047$) (Table 1). Figure 1 shows worse HCC mortality for those waiting longer for RFA (Wait-time groups were defined according to median wait-time). Appendix 1 shows death rates by 30-day wait-time increments.

Table 2. Wait times for curative intent radiofrequency ablation treatment (days).

Clinical outcome	Median (IQR)
Time from Diagnosis to RFA	96 (75.0-139)
Time from Diagnosis to Tumor Board Rounds	21 (11.0-49.0)
Time from Tumor Board Rounds to Interventional Radiology Consult	30 (21.0-44.0)
Time from Interventional Radiology Consult to RFA	35 (25.0-48.0)

Secondary outcomes

Twenty-nine (13.2%) patients required a liver transplant after failure of RFA for curative intent. No patient undergoing liver transplant had tumor recurrence at the end of the study period. Fifty-eight (26.5%) patients had residual tumor and after excluding these 58 patients from the cohort of 219, 66 patients (41%) had tumor recurrence. In univariate Cox regression analysis, increased wait times were not associated with need for liver transplant (HR = 1.10, per 30 days; 95% CI 0.92-1.30; $p = 0.290$) or tumor recurrence (HR = 1.00; 95% CI 0.91-1.10; $p = 0.980$) but

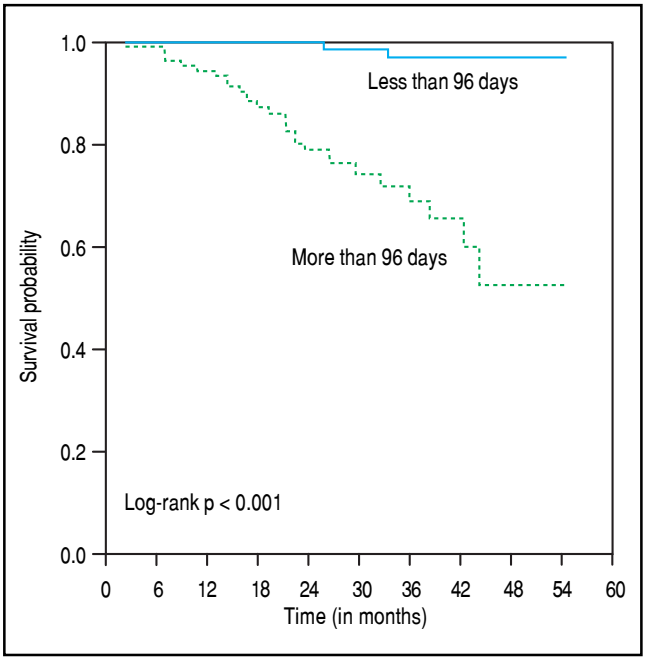

Figure 1. *Kaplan Meir survival curve of HCC based mortality by wait time group.*

Table 3. Cox regression analysis of primary and secondary outcomes adjusting for competing risks* with wait time as a covariate.**

Clinical Outcome	Univariate analysis Hazard ratio (95% CI); P value	Multivariate analysis Hazard ratio (95% CI); P value
Death (HCC)	1.22 (1.10-1.36); < 0.001	1.23 (1.11-1.36); < 0.001
Liver transplant	1.10 (0.92-1.30); 0.290	1.10 (0.92-1.29); 0.310
Tumor recurrence	1.00 (0.91-1.10); 0.980	1.00 (0.91-1.11); 0.930
Tumor residual	1.09 (1.00-1.18); 0.042	1.09 (1.01-1.19); 0.033

*Hazard ratios for wait time expressed per 30 days. * Competing risks for primary outcome were non-HCC death; for all secondary outcomes any death was a competing risk. ** Model adjusted for sex, age at diagnosis, MELD score, and Barcelona stage for the primary outcome (death) and tumor size, age, sex, MELD, and Barcelona stage for the secondary outcomes (liver transplantation, tumor residual, and tumor recurrence).*

was associated with residual tumor (HR = 1.09; 95% CI 1.00-1.18; p = 0.042). In multivariate Cox regression analysis, wait time was associated with increased risk of residual tumor (HR = 1.09; 95% CI 1.01-1.19; p = 0.033), while it did not show any association with the other secondary outcomes at the 5% level of statistical significance (Table 3).

DISCUSSION

Our study shows patients with newly diagnosed early HCC and who were candidates for curative intent RFA waited a median of 96 days from diagnosis to treatment. This vastly exceeds the 28-day wait time stipulated by Cancer Care Ontario for other malignancies. Additionally, incremental 30-day wait time for treatment was associated with a 9% increased risk of residual tumor and a 23% increased risk of death. We have previously shown a 2.5 fold increase in the proportion of new early stage (BCLC 0) HCC's detected at our center, and along with the continual annual rise in the incidence of HCC, this means the expected number of HCC cases requiring RFA outpaces the allocation of the resources to this treatment modality in the GTA.[12,13] Addressing these excessive wait times is urgently needed in the province of Ontario to mitigate poor patient outcomes related to HCC.

Understanding the important contributors to delayed access to HCC is paramount before instituting solutions. In our study, we identified three essential care points in the management of a patient with HCC treated with RFA at our institution, however, each care point also contributes to wait time delays (Table 2). Delays in presentation to multidisciplinary cancer conference rounds, scheduling consultations with Interventional radiologists and the resource constraints in performing RFA all lead to a "snowball" effect contributing to the current level of wait times. In addition, although physicians are the cornerstone of services provided they are only one aspect of a patient's care in a complex medical system involving many other personnel and bureaucracies which reflect the larger social and economic features of the hospital environment that also play an important determinant of variability in HCC wait times (Figure 2).

Wait time references for curative intent treatment of early HCCs have not been developed locally or internationally. In our study we report an initial attainable measure of a wait time target not to be greater than 60 days as

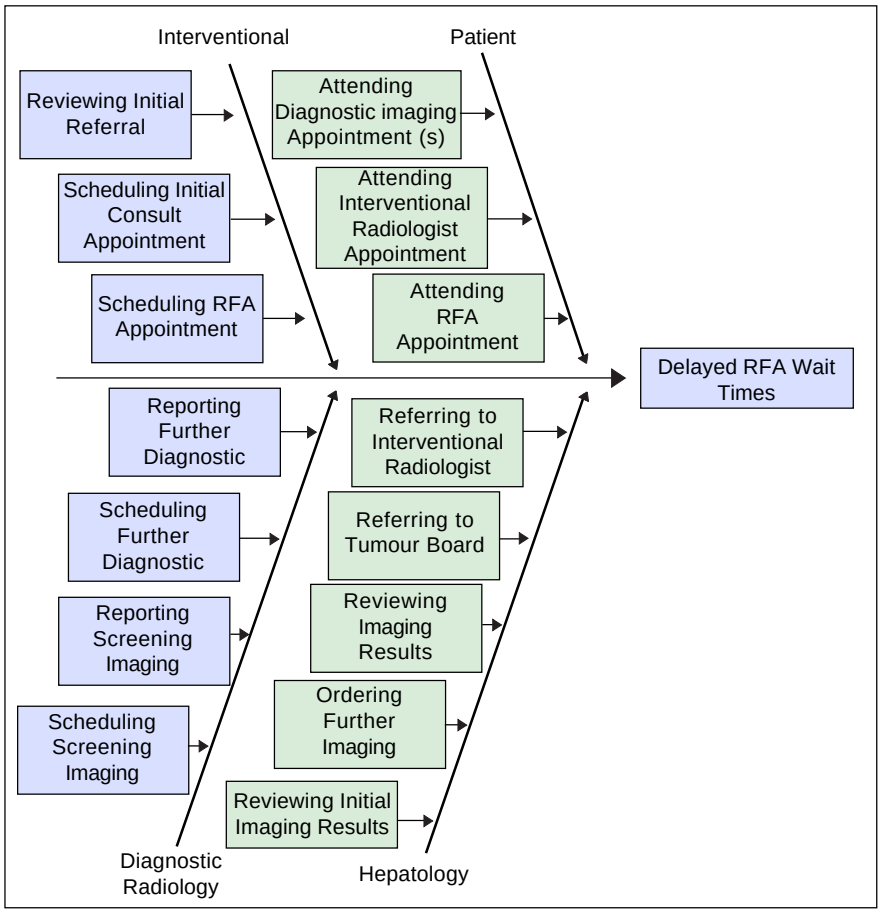

Figure 2. *Ishikawa Diagram (Cause and Effect Diagram).*

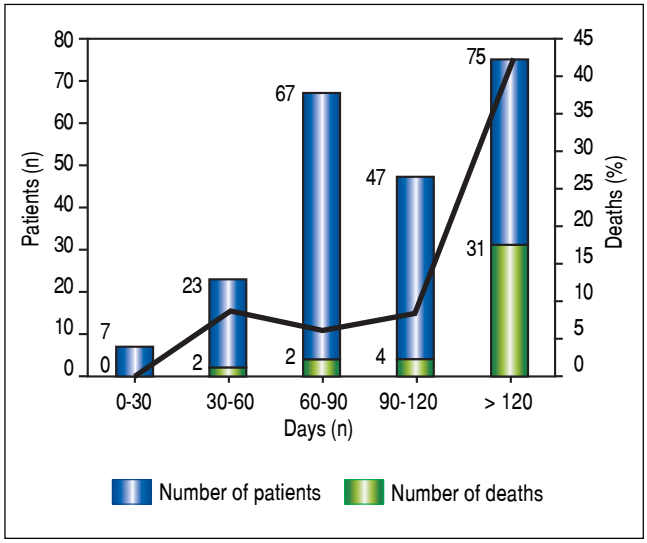

Figure 3. *Number of patients by time to radiofrequency ablation from HCC diagnosis.*

death rates increased from 6.7% to 28.1% after this period (Figure 3). Optimally, a 30-day wait time target would be achieved thereafter as no deaths were seen in this time period. To achieve improvements in performance, hospitals may need to focus on the key care points described above and also explore other factors such as triage practices, patient flow, physical environment, and (under) staffing. As these measures may be correlated with patient outcomes, improving performance in wait time could have a large impact on quality of care for all patients seen with curable HCC. However, a focus on shortening wait times should be balanced against unintended consequence such as increasing volume of procedures in a system not equipped or staffed for the burden which may lead to physicians prioritizing efficiency over accuracy, thoroughness and perhaps safety.

Our analysis has revealed three areas for actionable interventions that we believe could improve HCC wait times and patient outcomes. First, the development of criteria allowing certain cases to be referred directly for RFA treatment with no review or a less comprehensive/accelerated review at multidisciplinary cancer conference rounds. This change would eliminate the backlog created by the review of low-priority cases, and create time for complicated cases to be discussed in an adequate and timely manner. Second, development of a triaging system of patients referred for RFA would also ensure that higher risk of poor outcomes receive treatment earlier. Specifying consensus criteria using AFP, tumor biology and tumor size would help physicians/administrative staff triage more efficiently and without bias. Third, foregoing many steps in the care pathway such as eliminating Hepatology/Surgery consult and direct referral to multidisciplinary cancer conference rounds then to RFA procedure. This type of triaging enables early treatment and relevant diagnostic tests (e.g., blood work) to be completed even while patients are waiting. In addition, as process are put in place patient advocacy programs will need to be included in order to optimize patient satisfaction within this comprehensive care model.

Our study has several limitations. Our institution is a quaternary care referral center with a high volume of cases, which may not reflect other centres that offer RFA. Wait times in a center/city with a low incidence of viral hepatitis may differ as well as health systems with various providers and payers like in the United States. Additionally, our study only analyzed patients who were eligible for curative intent HCC treatment by RFA thus our results may not apply to those who are candidates for other forms of treatment such as trans arterial chemo-embolization (TACE).

CONCLUSION

Compared to other malignancies in the province of Ontario we found a relatively poor performance in treating curable HCC with wait times exceeding 90 days and incremental 30 day wait times to be significantly associated with a risk of residual tumor and death. We have identified this gap in care as a property of a system, in which the key barriers need to be addressed to prevent adverse patient outcomes. As these factors are better understood across institutions, best hospital practices could be developed to promote standardization of quality and efficiency of HCC care.

AUTHOR CONTRIBUTIONS

Brahmania had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

STUDY CONCEPT AND DESIGN

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ANALYSIS AND INTERPRETATION OF DATA

Brahmania, Kowgier.

DRAFTING OF THE MANUSCRIPT

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CRITICAL REVISION OF THE MANUSCRIPT FOR IMPORTANT INTELLECTUAL CONTENT

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STATISTICAL ANALYSIS

Kowgier.

FINANCIAL DISCLOSURES

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