Outcomes of surgical resection and loco-regional therapy in patients with stage 3A hepatocellular carcinoma: a retrospective review from the national cancer database

Ramanathan M. Seshadri, Erin H. Baker, Megan Templin, Ryan Z. Swan, John B. Martinie, Dionisios Vrochides & David A. Iannitti

1Hepato-Pancreato-Biliary Surgery, Department of Surgery, Carolinas Medical Center, Charlotte, NC, USA, and 2Dickson Advanced Analytics Group, Carolinas Medical Center, Charlotte, NC, USA

Abstract
Objectives: In advanced stages, hepatocellular carcinoma (HCC) is often associated with major vascular involvement (cava, portal vein). The aim of the present study was to analyse the role of surgical resection (SR) and loco-regional therapy (LRT) in these advanced stage patients to determine if there was a survival benefit.

Methods: The study is a retrospective analysis from the Commission on Cancer’s National Cancer Data Base (NCDB) from 1998 to 2011. In total, 148 882 patients with liver cancer were identified, of which 126 984 had HCC. Of these, 64 264 patients (1998–2006) had 5-year survival data available and 8825 patients had Stage 3A disease based on AJCC classification. Of these patients, 884 had SR, 771 had LRT and 7170 patients had neither intervention. Kaplan-Meier curves and log-rank tests were used for statistical analysis.

Results: Eight thousand eight hundred and twenty-five patients met analysis criteria. The mean age (years) in the SR, LRT and no intervention group were 62.5, 64.3 and 64.2, respectively. Most patients were males in all three groups (77.5%, 74.5% and 68.1%). The mean tumour size (cm) in the three groups was 9.8, 6.4 and 8.4, respectively. SR and LRT were primarily performed in major academic and comprehensive cancer programmes compared with community cancer programmes and other centres (SR: 93% versus 7%; LRT: 94.6% versus 5.4%). The median 5-year survival (months) was 26.6 in SR, 16.5 in LRT and 4.8 in the no intervention group ($P < 0.0001$).

Conclusion: A SR and LRT offer a survival benefit in select patients diagnosed with Stage 3A HCC.

Introduction
Hepatocellular carcinoma (HCC) is the most common primary malignant tumour in the adult liver. 30 640 new cases and 21 670 deaths were recorded in 2014 by the National Cancer Institute in the US. It is the 5th most frequently diagnosed cancer in men and the 2nd leading cause of cancer-related death in the world. The primary modality of treatment for HCC has been a surgical resection (SR) or transplantation when feasible. Unfortunately, most patients at the time of initial presentation and evaluation have advanced disease, which is not amenable to a SR. Over the past decade, this ideology has been challenged by many surgeons across the world and there has been an increased propensity towards a more aggressive surgical approach in patients with locally advanced disease with vascular involvement.

The oncological principles towards cancer surgery still apply to this group of patients. The tumour has to be resected with negative margins to achieve the best outcomes. In the...
advanced stages of HCC, this would include resection of the major vascular structures with complex reconstruction also to the primary tumour resection. These procedures require the highest degree of expertise in hepatobiliary and transplant surgery; therefore, the access to healthcare offering high-quality expertise to all is very important to consider when discussing the outcomes. Not every patient diagnosed with tumours in these advanced stages has access to centres of excellence performing these procedures.

Hence, it was chosen to perform a retrospective analysis of patients with Stage 3A HCC (AJCC Staging 5th and 6th edn) from the National Cancer Database. The primary endpoint was to determine if a SR had an overall survival benefit compared with no treatment in advanced stage HCC patients. Our secondary endpoint was to define the socioeconomic factors that could potentially play a significant role with respect to the modality of treatment one would receive and their overall survival.

**Patients and methods**

**Data acquisition and patient selection**

Instituted in 1989, The National Cancer Data Base (NCDB) is a nationwide oncology outcomes database from more than 1500 commission-accredited cancer programmes in the United States and Puerto Rico. It is a joint programme of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. Approximately 70% of all newly diagnosed cases are captured at the centre and submitted to the NCDB. The database has approximately 29 million records from hospital cancer registries across the United States. The key components of the database include patient demographics, cancer diagnostics, clinical and pathological staging, treatment details (surgery, radiation, chemotherapy and palliative) and survival. Also, socioeconomic information and insurance information are also captured.

Using the NCDB, patients with HPC were identified according to the *International Classification of Diseases for Oncology* (3rd edn). There were 126 984 patients diagnosed with HCC between the years 1998 and 2011. For the purpose of the study, the cohort was restricted to the years 1998–2006 (64 264) to obtain 5-year survival data. Eight thousand eight hundred twenty-five patients had stage 3A disease at the time of diagnosis (Fig. 1). Subgroup analyses were also performed with the following variables: tumour size, race, facility type, median income by zipcode and insurance status at the time of evaluation.

**Statistical analysis**

Descriptive statistics, including counts, percentages, means and standard deviations, were calculated for patient specific demographics. Survival was calculated in months from the date of diagnosis to the date of death or last contact. The overall survival was estimated using Kaplan–Meier estimates. The log-rank test was used to analyse the statistical significance of the Kaplan–Meier estimates. Cox’s proportional hazard models were used for univariate and multivariate analyses of the time-to-event data. Multivariate Cox’s proportional hazard models adjusted for the procedure, tumour size, race, age, gender, insurance status, facility type and the median household income. SAS Enterprise Guide®, version 5.1, was used for all analyses. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

**Results**

**Patient demographics**

Seventy-seven thousand four hundred and sixty patients diagnosed with liver cancer from 1998 to 2006 were included in the NCDB of which 64 264 (83%) had HCC as the primary diagnosis. The group of interest was the patients with Stage 3 A HCC (8825). Eight hundred and eighty-four (10.0%) patients underwent a SR, 771 (8.7%) had loco-regional therapy (LRT) in the form of radio-frequency ablation, cryosurgery and alcohol injection. Seven thousand one hundred seventy (81.3%) patients had no intervention (Fig. 1). The mean age (years) in the SR, LRT and no intervention groups were 62.5, 64.3 and 64.2, respectively. Most patients were males in all three groups (67.4%, 73.4% and 76.3%).

**Survival data**

Patients with Stage 3A HCC undergoing a SR had the best overall median survival (26.6 months) followed by those who underwent LRT (16.4 months) The patients who had no treatment had the worst prognosis (4.8 months). Females had a better overall survival across all three groups compared with males (Fig. 2).
Our primary aim was to use the National Cancer Database and identify the group of patients with stage 3A HCC and determine if there was a long-term survival benefit in patients who under SR. We were also interested in determining the factors that influenced the type of treatment if any that the patient got when they presented to the hospital. Our results types of insurance included private, Medicare, Medicaid and uninsured. Patients with private insurance had the best outcomes overall in both the resection and locoregional therapy groups (Table 1).

**Discussion**

The surgical treatment of advanced stage HCC involving major vascular structures is tedious and complex. It usually involves extended resections with major vascular reconstruction. Over the last decade, there has been convincing evidence in the published literature that the overall survival after SR in advanced stage HCC is better than LRT.3–5 Liu et al. recently published on the outcomes of surgical resection for BCLC Stage C HCC (BCLC – Barcelona Clinic Liver Cancer). They were able to show that a resection provided significantly better long-term survival than transcatheter chemoembolization (TACE) in patients with BCLC stage C HCC.7 Peng et al., in their case review comparing a hepatic resection to TACE for the treatment of HCC with portal vein tumour thrombus, were able to show that a resection provided survival benefits for patients with HCC and tumour thrombus involving the right or left portal vein or their segmental branches.9 There are certain factors that definitely should be taken into consideration when deciding to operate on these patients to be able to provide the best possible outcomes. The degree of fibrosis and the presence or absence of cirrhosis would be of utmost importance. The synthetic function of the liver in addition to the other comorbidities of the patient including performance status will need to be taken into account.10

Major SR (lobectomy and trisectionectomy) has traditionally been reserved for patients with preserved liver function and in non-cirrhotic patients. In order to perform resections involving vascular reconstruction, one will need to perform a hepatic venous occlusion (partial or complete) depending on the primary tumour location and portal vein occlusion when needed.11 The techniques of ex vivo resection and in situ cold perfusion have also been described.12–15 Patients with advanced stage HCC in the setting of a non-cirrhotic liver have the ability to tolerate these procedures.16 In contrast, patients with Stage 3A HCC in the setting of background cirrhosis have a limited synthetic reserve and are not ideal candidates for major resections.17 These patients either receive LRT in the form of transarterial chemoembolization or thermal ablation (done percutaneously or laparoscopically) in the palliative setting.18 Chemotherapy in the form of Sorafenib has also been used in patients with advanced stage HCC with equivocal results.19,20

Our primary aim was to use the National Cancer Database and identify the group of patients with stage 3A HCC and determine if there was a long-term survival benefit in patients who under SR. We were also interested in determining the factors that influenced the type of treatment if any that the patient got when they presented to the hospital. Our results...
indicate that patients who underwent SR had a better overall survival than the group who had no therapy (26.6 versus 4.8 months). The group that underwent LRT had a median survival of 16.4 months. Patients with tumours < 5 cm had a better survival with both forms of treatment (SR and LRT).

Our analysis also revealed that the best outcomes after surgery were achieved at Academic/Research NCI-designated centres (27.7 months) followed by Comprehensive Community Cancer Programmes (26.48 months). We believe this to be consistent with the fact that most of the resections were performed at these centres (Table 1) and hence the better survival owing to the level of expert care available. From a socioeconomic standpoint, patients with private insurance had the best survival but surprisingly a median income did not affect median survival. We believe the reason for this observation is as a result of the fact the US healthcare system makes it mandatory to provide the best care available to a patient when they present to a facility irrespective of their income status.

The primary limitations of our study are to do with the staging system used to identify the patients in the database and inherent deficiencies that accompany a retrospective study. The AJCC staging system is a very comprehensive and detail-oriented system used widely in cancer staging; yet it does not include enough information to compute the model of end-stage liver disease scores for the group of patients included in the study and there is limited information on liver function. The database does not include information on disease recurrence. Most of the therapy for HCC these days are multi-modality based but this information is also lacking in the database. Last, but not the least, is the details on patient comorbidities and lack of data on timing of locoregional chemotherapy. Radioembolization using Yttrium-90 is a modality used these days in patients with advanced stage HCC. Unfortunately, there is no data captured for this form of LRT. We also believe there is a certain degree of selection bias introduced with the mode of therapy offered to patients based on their disease burden and overall functional status.

As the database has information on patients until 2011 but has clear instructions not to use data for survival analysis unless the patients have been followed up for 5 years, we restricted our patient cohort accordingly for the purpose of the study. Nonetheless, the information on the presence or absence of cirrhosis and its relationship with surgical intervention and LRT for advanced stage HCC was recorded in more detail in subsequent years and we did a basic analysis to look at the effects of cirrhosis on survival in patients who were treated surgically. One hundred and eighty-nine patients with stage 3A HCC were identified with data on the degree of fibrosis and cirrhosis. The median survival for Stage 3A HCC patients with a none-to-moderate degree of fibrosis (n = 123) was 35.8

### Table 1 Subgroup analyses

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<th>Subgroups</th>
<th>N</th>
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<th>SR (months.)</th>
<th>LRT (months.)</th>
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SR, surgical resection; LRT, locoregional therapy.
compared with 15.7 months in the severe fibrosis-to-cirrhosis group ($n = 66; P = 0.09$). When compared with LRT, the group with severe fibrosis or cirrhosis who underwent a SR had a similar median survival (15.3 for LRT versus 15.7 for SR). In the none-to-moderate fibrosis group, the median survival for the LRT group ($n = 22$) was 13.4 months compared with 35.8 months in the resection group ($n = 123$, $P = 0.09$). These data are purely for reference purpose and not to be taken as part of our results but it does show that the survival of patients with cirrhosis after a resection is not different from LRT and, hence, can be offered as a treatment option when indicated.

The National Cancer Database provides a wealth of information with regards to patients with liver-associated malignancies. The detail of information could be significantly improved by including vital information including the synthetic function of the liver, MELD score, the inclusion of TACE as part of the LRT and patient comorbidities. Some of this information is available in the more recent data as mentioned above and in time; most of the limitations in this study could be addressed suitably.

To our knowledge, this is the largest retrospective analysis to determine the survival benefit of a resection in patients with advanced HCC in the United States. Patients with advanced stage HCC involving the major vasculature do have a survival benefit with SR when performed in the right setting. Our analyses revealed that SR and LRT were primarily performed in major academic and comprehensive cancer programmes compared with community programmes and other centres. Socioeconomic factors had a significant impact on survival most probably owing to accessibility to healthcare, the effect of the timely intervention and the extent of adequate post-operative care and follow-up.

**Conflicts of interest**

None to declare.

**References**


