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Improved Survival for Hepatocellular Cancer With Combination Surgery and Multimodality Treatment

James V. Sitzmann, M.D.,* and Ross Abrams, M.D.†

From the Departments of Surgery and Radiation Oncology,† the Johns Hopkins Medical Institutions, Baltimore, Maryland*

Forty-one hepatic resections for malignant hepatomas were done in 35 consecutive patients from August 1985 to 1990. Twenty-one patients presented initially with resectable lesions and underwent resection for curative intent. Fourteen patients initially presented with unresectable intrahepatic disease. These patients underwent combined radiation and chemotherapy. Radiation consisted of external beam in all patients and ^{131}I-antiferritin in 10 patients. Greater than 50% tumor reduction was noted in all patients, and resection then was performed. Six patients recurred and were re-resected. Complications occurred in 15 patients (36%), with no difference between groups. There were no perioperative deaths. Five-year actuarial survival was 45% and 48% for resection and multimodality. The authors conclude that some patients with unresectable intrahepatic hepatoma may successfully be converted to resectable by multimodality radiation/chemotherapy. The survival of these patients is similar to that of primary resected patients. Further, multiple, sequential resections appear to significantly prolong survival and can be performed with an acceptable morbidity and mortality rates.

Hepatocellular cancer represents a major therapeutic challenge to the radiation or medical or surgical oncologist. As a common cancer worldwide, it is a highly lethal tumor with only an estimated 10% of patient eligible for resection, and with long-term 5-year survival achieved only in 25% to 30% of patients resected.[1,2] These results have prompted an aggressive evaluation of various alternative therapies for hepatocellular cancer, including systemic and regional chemotherapy, and radiotherapy with external beam or radiolabeled antiferritin immunoglobin.

The utility of developing effective chemotherapeutic or radiotherapeutic treatments for hepatoma cannot be overemphasized. Fully 90% of patients are unresectable at presentation because of tumor size, location, or underlying parenchymal disease, and recurrence of tumor after resection accounts for nearly 50% to 90% of postoperative death.[3–5] In theory, treatment could dramatically improve surgical results by either increasing the number of patients that could be resected, or by decreasing or delaying incidence of recurrence.

We previously reported that resectional therapies could be used safely in the context of multimodality chemo and radiation therapies.[6] Most of those initial 11 patients were all judged unresectable by laparotomy, and subsequently underwent resection after significant partial remissions induced by either radiolabeled antibody treatment, or external beam radiation in combination with chemotherapy. Encouraged by these findings, we continued to offer these patients resection after multimodality therapy.

This report summarizes the clinical pathologic features and long-term survival of two groups of patients

Address reprint requests to James V. Sitzmann, M.D., Johns Hopkins Medical Institutions, Blalock 665, 600 North Wolfe Street, Baltimore, MD 21205.
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with hepatocellular cancer undergoing resection: patients presenting with initially technically unresectable disease who received multimodality chemotherapy and radiation therapy, and subsequently remitted substantially to allow resection; and another group, patients who presented with initially resectable lesions.

METHODS

Patient Population

All adult patients undergoing hepatic resection for hepatocellular cancer by the author (JVS) from August 1985 until August 1990 were included for review. All patients underwent similar preoperative staging, consisting of hepatic arteriography and arteriographically enhanced computed axial tomography (T-ART), magnetic resonance imaging (MRI), and thoracic computed tomography (CT) scan, as previously described.[7]

Diagnosis in all patients was established by biopsy, either at operation or with percutaneous biopsy. Patients were deemed nonresectable by exploratory laparotomy or based on MRI and CT evaluation of venacaval, or common portal vein occlusion.

Unresectable disease included metastatic disease involving regional lymph nodes (biopsy proven at operation) or evidence of pulmonary metastasis on CT or chest x-ray; or from four segment hepatic parenchymal disease; or portal vein, or venal caval tumor thrombus or direct involvement by adjacent tumor. No patient was deemed unresectable in this group because of liver failure, or portal hypertension alone.

Tumor markers, alpha-fetoprotein (AFP), and ferritin were assessed in all patients. Initially unresectable patients had tumor volumes reconstructed by a complex computer program previously reported in which each pixel of an 8-mm slice of a CT scan of the entire liver were evaluated for tumor, and then added to a composite sum.[8] Tumor volumetrics were repeated at various treatment intervals to determine progression, stability, and remission as previously described. After treatment, when patients were deemed candidates for resection, arteriographic enhanced CT was performed. If metastasis were present initially, complete resolution for at least 3 months was required as determined by CT before consideration of resection.

Chemotherapy and Radiation Therapy

In patients with resectable disease, none received preoperative chemotherapy or radiation therapy. In patients with unresectable disease, treatment consisted of a variety of combinations of radiation and chemotherapy. Induction treatment for all patients included 2100 cGy (300 cGy functions), and 15 mg doxorubicin with 500 mg 5-fluorouracil on days 1, 3, 5, and 7 as previously reported.[9] Ten patients received radiolabeled polyclonal anti-ferritin immunoglobin conjugated with ^{131}I in nine cases,[9] and conjugated with 90 yttrium in one case.[10] Four patients received intra-arterial cisplatin 50 mg/m^2 into the hepatic artery.

Operative Procedure

The operations performed were classed as either anatomic or nonanatomic resections. Nonanatomic resections did not include single wedge excisions. Anatomic resections were classed as segmentectomies (left lateral or left medial segments), lobectomies (right, left, or caudate) or trisegmentectomies (left lobe and right anterior segment, right lobe and left medial segment, or left lobe and caudate lobe). Synchronous diaphragmatic resections, and venal caval or portal venous resections and reconstructions were performed as needed.

All resections were performed using an ultrasonic dissector (Cavitron surgical system, Stamford, CT). Preliminary margins of resection were determined by frozen section pathologic examination at the time of operation, and, if doubtful, extended.

A standard subcostal incision carried to the xiphoid was used for all patients. Sternal extension was required for patients with supracaval/hepatic or pericardial involvement.

Recurrence was documented by radiographic appearance of intra-abdominal, intrahepatic, or pulmonary tumor (typically on CT), or by rise in AFP levels. Either radiographic evidence, or tumor marker evaluation were considered presumptive evidence of recurrence, and biopsy was not required. Any patient death with any evidence of tumor recurrence was judged secondary to tumor. Any death within 30 days of resection or during hospitalization was deemed as an operative death.

STATISTICAL ANALYSIS

Kaplan-Meier survival curves were constructed on all patients (BMDP Statistical Software, California). Intergroup variables were compared by Student t tests from unpaired data, or chi squared analysis.[11]

RESULTS

Patient Population

Forty-one operations to resect hepatoma were performed on 35 patients; 23 male and 11 female, with a mean age of 51 (range, 14–78). Fourteen patients were

Table 1. PATIENT POPULATION

Initially resectable	
Age (yr) (mean)	60 ± 0.64
Sex	
M	17
F	7
Bilirubin (mg/dL)	0.8 ± 0.5
Alkaline phospatase (mg/dL)	131 ± 43
Albumin (mg/dL)	3.1 ± 0.2
Alphafetal protein (ng/mL)	128 ± 17.6
Initially unresectable	
Age (yr) (mean)	42 ± 0.94
Sex	
M	10
F	4
Bilirubin (mg/dL)	0.7 ± 0.1
Alkaline phosphatase (mg/dL)	152 ± 50
Albumin (mg/dL)	4.1 ± 1.0
Alpha fetal protein (ng/mL)	25 ± 5.6

initially considered unresectable as determined at laparotomy, and one was considered unresectable due to portal vein thrombosis. The mean age of this group was 42 years (range, 14–78). Ten were males and four were females (Table 1). The underlying liver disease associated with hepatoma included alcoholic cirrhosis in five, hepatitis in nine, and primary biliary cirrhosis in one.

OPERATIVE PROCEDURES

Twenty-one patients were initially resectable. Eighteen patients underwent formal lobectomy and three had trisegmentectomies. Five had concurrent diaphragmatic resections. Average operative time was 4 ± 0.7 hours, and average blood loss was 2.9 ± 0.1 liters. The mean weight of resected tissue was 893 ± 32 mL (Table 2).

Fourteen patients presenting with initially unresectable disease received chemotherapy or radiotherapy as summarized in Table 3. In these 14 patients, 4 were initially referred with recurrent unresectable disease after previous partial hepatectomies. After multimodality treatment, 11 underwent lobectomy and 3 underwent trisegmentectomy. Six patients subsequently recurred, and were re-resected (segmentectomy, 3; and nonanatomic resection, 3). Three patients had concurrent diaphragmatic resections, one had a portal vein resection, and two had hepatic vein or inferior vena caval resection and reconstruction. The average operative time for all resections in the initially unresectable group, was 5 ± .09 hours (5.24 for first resection, 3.4 hours for second resection), and average blood loss was 4.5 ± 0.29 liters. Complications occurred in 35% of patients (40% from the first and 20% from the second resection). Complications included perihepatic sepsis, pneumonia, wound infection, or gastrointestinal bleeding.

Operative data are summarized in Table 2. There were no significant differences between groups for any variable. Average blood loss and operative time were increased with patients treated with chemotherapy or radiation therapy, but this was not statistically significant.

SURVIVAL

There were no perioperative deaths. Actuarial survival at 24 months after diagnosis was 72% for patients with primary resection, and 75% for patients converted from unresectable to resectable; with 44.2% of patients initially resected alive at 5 years and 50.1% of patients initially deemed unresectable alive at 5 years. Median survival was 41.9 months for patients initially resectable, and 57.4 months for patients initially deemed unresectable (Figs. 1 and 2). Survival after resection was similar in both groups, with initially resectable patients achieving a 44% survival at 4 years and the initially unresectable patients achieving a 52% survival at 4 years. The liver was the commonest site of recurrent disease in both resected group (70%) and initially unresected (68%). There were no differences between groups in pattern of recurrence (Table 4). There were no significant differences in survival time between groups.

Table 2. OPERATIVE PROCEDURES

Procedure	
Initially resectable	21 patients
Lobectomy	18 patients
Trisegmentectomy	3 patients
Operative time	4 ± 0.7 hr
Blood loss	2.9 ± 0.1 L
Complication rate	35%
Initially unresectable	14 patients
Lobectomy	11 patients
Trisegmentectomy	3 patients
Operative time	5.24 hr
Blood loss	4.5 ± 0.29 L
Complication rate	40%
Second resection	6 patients
Segmentectomy	3 patients
Nonanatomic	3 patients
Operative time	3.4 hr
Blood loss	2.1 ± 0.8 L
Complication rate	20%

Table 3. CHEMOTHERAPY AND RADIOTHERAPY

Patient	External beam	RIT	Chemotherapy
1	2100	None	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
2	2880	30 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
3	2100	50 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
4	2100	50 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
5	900	50 MCI	None
6	2100	50 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
7	2100	30 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
8	2800	60 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
9	2100	85 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
10	2100	120 MCI	2000 mg 5-FU, 288/mg/m^2 Adriamycin IV
11	2100	100 MCI	970 mg 5-FU, 46/mg/m^2 Adriamycin IV
12	2100	120 MCI	2000 mg 5-FU, 60/mg/m^2 Adriamycin IV
13	2100	120 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV
14	2100	30 MCI	500 mg 5-FU, 15/mg/m^2 Adriamycin IV

Adriamycin (doxorubicin).

DISCUSSION

Resectional therapies have always been the only curative mode of therapy for hepatocellular carcinomas. Unfortunately, it is estimated that only 10% of hepatocellular cancers are resectable at the time of diagnosis.[3–5] Thus, most patients with hepatocellular cancer are treated with oncologic or radiologic forms of therapy rather than operation. Interest in the radiation therapy and chemotherapy of these tumors has been heightened by the advent of isotopic immunoglobulin therapy, and by the recent success rate of intra-arterial cisplatin therapy into the hepatic artery. At our institution, we have been particularly interested in combined modality treatment of hepatocellular cancer.[6]

The major contraindications to resectional therapy in patients with hepatocellular carcinoma include (1) pathologic stage of the tumor in the liver, (2) presence of distant metastasis, (3) presence of associated hepatic parenchymal disease or active hepatitis, (4) presence of medical contraindications such as significant coronary artery disease or pulmonary disease precluding major operative therapy.[2]

For the surgeon, there are two common major restrictions to resectional therapy. The first is anatomic: typically, only fibrolamellar tumors are routinely localized and amenable to surgical resection. Both diffuse and nodular forms of hepatoma are usually not suitable for resection due to bilobar involvement. The second is the high incidence of concurrent, non-nephrotic parenchymal

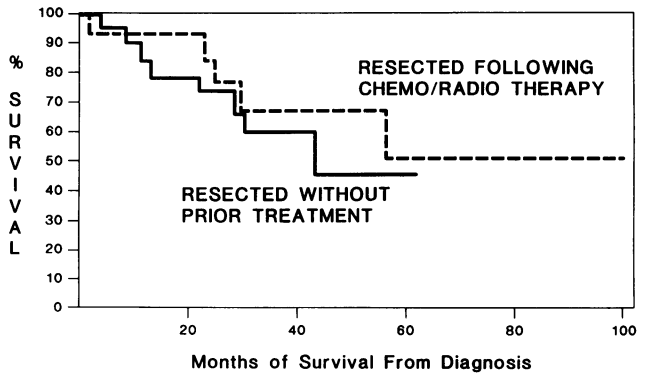

Figure 1. Months of survival from diagnosis. Patients undergoing resectional therapy from 1986 to 1990 at The Johns Hopkins Hospital; survival from the time of diagnosis. The two groups are patients who were initially unresectable and received combined chemotherapy and radiation therapies (resected after chemotherapy/radiation therapy) and those who presented initially with resectable disease (resected without prior treatment).

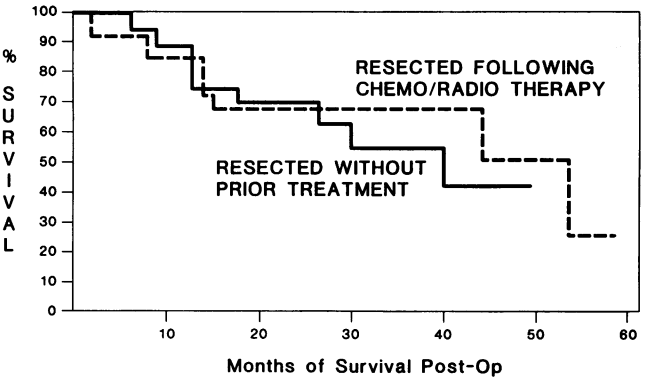

Figure 2. Months of survival after operation. Patients undergoing resectional therapy from 1986 to 1990 at The Johns Hopkins Hospital; survival from the time of diagnosis. The two groups are patients who were initially unresectable and received combined chemotherapy and radiation therapies (resected after chemotherapy/radiation therapy) and those who presented initially with resectable disease (resected without prior treatment).

Table 4. PATTERN OF RECURRENCE

	Site of Recurrence		
	Liver	Lung	Abdominal
Initially Resectable	7	1	2
Treated/unresectable	8	3	1
Total patients	15	4	3

disease, which limits the ability to do standard formal lobectomies. This has given rise to a more widespread use of the nonanatomic forms of resection, where the dissection across hepatic parenchyma is independent of lobar or segmental anatomies.[2] This technique allows the surgeon to do multiple resections while conserving parenchymal mass. In theory, this should increase the number of candidates for resection and diminish mortality rate by minimizing hepatic failure as a complication of operation.

Another contraindication to resectional therapy in the patient with hepatocellular carcinoma is the presence of associated major medical problems. These are infrequent as this tumor occurs across all age groups and is not concentrated in the elderly. Contraindications due to metastatic disease occur rarely with hepatocellular carcinoma.

Despite improvement in resectional techniques such as the ultrasonic dissector and the argon gas coagulator, most patients with hepatocellular carcinoma remain unresectable, usually due to the extent of intrahepatic disease. It is in these patients that multimodality treatment offers hope for survival by reducing intrahepatic disease and increasing opportunity for resection. The anatomic contraindications to resection include vena caval or portal involvement, or bilobar or four segment hepatic involvement.

The toxicities of external beam radiation therapy, isotopic radioimmunotherapy, or chemotherapy such as intra-arterial cisplatin or sensitizing doses of agents such as adriamycin and 5-fluorouracil are generally minimal.[5,12] The major toxicity of external beam radiation is dose-related hepatic parenchymal dysfunction. The major toxicity of isotopic immunoglobulin is myelosuppression, particularly thrombocytopenia.[9]

The data on our patients who received chemotherapy and radiation therapies indicates that the overall toxicity is low. Although some patients exhibited hematologic toxicity, this did not preclude successful subsequent resection in any patient.

Perhaps the most surprising outcome in these patients is that the patients who received radiation and chemotherapy had similar long-term survival as the patients who were primarily resected. Furthermore, both these groups had a survival higher than that previously reported in the literature.[1,4–6] Most trials report long-term survival in the range of 30% at 5 years rather than the 50% 5-year survival in our series. The median 57-month survival for those who were unresectable initially and 41.9% months for patients initially resectable represent a major increment in survival.

Speculatively, we would suggest that the low incidence of concurrent advanced parenchymal disease in the patients that we resect in the United States may improve our long-term survival rates. Most hepatocellular carcinomas occur in the Orient or Africa, and their resectability rates, particularly from Japan, are similar to ours; however, the incidence of associated severe parenchymal disease is much higher in those patients than in ours.

Although there was no statistical difference between the survival in patients who were treated with radiation or chemotherapy, and those who were initially resected, it is interesting that the survival in the treated group was higher than in those in the resected-only group. It could be that the chemotherapy or radiation therapy suppresses new hepatocellular cancer formation within the remaining liver. Indeed, most recurrences in our patient population occurred in the contralateral lobe in a diffused or nodular fashion. There were no marginal recurrences, and distant metastatic disease, while it occurred, was not as frequent as the recurrent intrahepatic disease.

These results imply a role for either radiation therapy or chemotherapy in the adjuvant setting to sterilize the remaining hepatic parenchyma and to suppress future hepatocellular cancer formation. The tumor biology of this particular cancer is not understood and the appearance of diffused or nodular disease in the remaining liver months to years after the successful resection could be due to new hepatoma formation or intrahepatic lymphatic spread and reactivation of the disease. Regardless of the cause, it would appear that chemotherapeutic modalities or radiotherapeutic modalities could be successfully employed in this particular group of patients.

In summary, these results show that an aggressive surgical approach combined with radiation therapy and chemotherapy is of benefit in patients with hepatoma. Patients who initially were deemed unresectable received high doses of radiation (both external beam and isotopic) as well as significant chemotherapy and then subsequently underwent resection. This is encouraging for the future of multimodality therapies. We conclude from this series of patients that further improvements in survival for patients with hepatocellular cancer could be achieved possibly by the use of multimodality therapy in the adjuvant setting.

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