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Treatment of Lymph Node Recurrence in Patients with Hepatocellular Carcinoma

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Abstract: The clinicopathological features and results of lymph node dissection were investigated in four patients with hepatocellular carcinoma (HCC) who developed lymph node recurrence following hepatectomy. One patient was found to have metastasis in the periportal lymph nodes at the time of a second laparotomy, while the other three developed posterior pancreaticoduodenal lymph node metastasis. All four patients had concomitant cirrhosis of the liver and were negative for hepatitis B surface antigen. No relationship between the site of the primary lesion and the location of lymph node metastasis was found. Two of the four patients are alive and in good health 4 years and 3 months, and 7 years and 3 months after their first operation, respectively. Thus, we conclude that the posterior pancreaticoduodenal lymph nodes are the most common site of lymph node recurrence of HCC, and that dissection of the affected lymph nodes offers the best chance of long-term survival.

Key Words: hepatocellular carcinoma, hepatectomy, lymph node recurrence

Introduction

Hepatocellular carcinoma (HCC) is a highly malignant form of cancer which recurs frequently after hepatectomy,[1,2] and even after liver transplantation;[3] the most frequent site of recurrence is the residual liver.[4,5] Recent advances in the techniques used for imaging cancers in the abdominal cavity have enabled the early detection of small lesions in the liver, which has in turn resulted in an improved prognosis for patients with HCC.[6] Consequently, lymph node metastasis or recurrence is also being detected earlier.[7] However, although there have been many reports on the patterns and treatment of intrahepatic recurrence after hepatectomy,[8,9] the modality of treatment for HCC with lymph node metastasis or lymph node recurrence has not been discussed. We report herein on the clinical features of four patients who developed lymph node recurrence of HCC following resection, and the effects of lymph node dissection and multimodal treatment on such recurrent lesions.

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Patients and Methods

Between January, 1978, and December, 1991, a total of 254 patients with HCC underwent hepatectomy in our department. All patients were followed up postoperatively at the outpatient clinic by measurement of the tumor markers, ultrasonography (US), and computed tomography (CT) scanning. Of these 254 patients, 123 (48.2%) showed signs of recurrence, and another 8 developed recurrence in multiple organs simultaneously. Of the 131 patients with recurrence, the metastatic site was the residual liver in 109 patients (83.2%), the lungs in 12 (9.1%), the bone in 4 (3.1%), and the regional lymph nodes in 4 (1.6%). The four patients with regional lymph node recurrence were the subjects of this study which investigated the clinicopathological features and prognoses of all four patients, three of whom underwent repeat laparotomy for lymph node dissection. The pathological factors and locations of lymph nodes are described according to the general rules for the clinical and pathological study of primary liver cancer.[10]

Results

All four patients had concomitant cirrhosis of the liver, but were negative for hepatitis B surface antigen (HBsAg). A hepatitis C virus (HCV) antibody test

was done in only one patient which showed a negative result. The serum α-fetoprotein (AFP) levels ranged from 5.3 to 11,287 ng/ml, and the carcinoembryonic antigen (CEA) levels were within normal limits in all four patients. The tumor size ranged from 3.0 to 6.5 cm in diameter, and histopathologically, three out of the four patients were classified as Edmondson grade II, and one as grade III.

The first patient was diagnosed as having metastasis in a periportal lymph node (no. 12) at the time of a second laparotomy. Initially, he was suspected as having intrahepatic recurrence for which a repeat laparotomy was performed. The other three patients were diagnosed by US and CT as having posterior or pancreaticoduodenal lymph node (no. 13) metastasis. Cases 3 and 4 had associated intrahepatic recurrence, diagnosed at the same time as the lymph node recurrence. The primary tumor occupied more than one hepatic segment in all four patients, but no relationship was seen between the sites of the primary lesions and the location of lymph node metastasis (Table 1).

Two patients died 3 years and 4 months, and 4 years and 10 months after their first operation, respectively. The quality of life of the other two patients is good, although one has intrahepatic recurrence and the other has regional lymph node metastasis. We performed a reoperation on three patients, at which time the hepatic hilar, hepatoduodenal, perihepatic arterial, and posterior pancreaticoduodenal lymph nodes were dissected (Table 2).

Case Reports

Case 1 developed metastasis in the hepatoduodenal lymph nodes 1 year after undergoing a left hepatic lobectomy. He died of intrahepatic dissemination of the tumor 4 years and 10 months after his first operation.

Case 2 initially underwent a subsegmentectomy of S6, but 2 years and 8 months later, the serum AFP level again became elevated. Although US and CT imaging showed no intrahepatic recurrence, a solitary lymph node metastasis in the posterior pancreatic head region was suspected by magnetic resonance imaging (MRI), CT, and US findings. Angiography showed a hypervascular lesion, and dissection of the lymph nodes revealed metastasis of the trabecular type of HCC. Tissue AFP was confirmed by immunostaining, but the serum AFP returned to within normal limits immediately after the lymph node dissection. Intrahepatic recurrence developed 6 years after the first operation, which was treated by percutaneous ethanol injection (PEIT) into the tumor. The patient is alive and well at the present time.[11]

Case 3 developed intrahepatic recurrence and involvement of the posterior pancreatic lymph nodes which was confirmed 2 years and 9 months after he underwent a partial hepatic resection of S5 and S8. This patient had had periportal lymph node metastases in the hepatoduodenal ligament which were removed at the first operation. Because of decreased hepatic reserve, we chose to treat this patient conservatively.

Table 1. Clinicopathological findings of the primary hepatocellular carcinoma (HCC) lesions

Case	Age	Sex	Stage	Cirrhosis	Tumor size (cm)	Edmondson grade	Histology	fc-inf	vp	im	HBsAg	AFP (ng/ml)
1	63	M	II	Z_1	6.5	III	trabecular	+	0	0	–	11,287
2	59	M	II	Z_1	3.0	II	trabecular	–	1	1	–	162
3	62	M	IVA	Z_2	3.0	II	solid	+	0	1	–	36.3
4	60	M	III	Z_2	4.5	II	trabecular	+	0	0	–	5.3

fc-inf, capsular invasion; vp, portal vein invasion; im, intrahepatic metastasis; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein

Table 2. Outcome of patients with HCC associated with lymph node recurrence

Case	Primary site	Operation	Site of recurrence[a]	Interval of recurrence	Treatment of recurrence	Survival after initial operation
1	S2, 3, 4	Hr2	12	12 mo	dissection	4 yr 10 mo died
2	S6	HrS	13	10 mo	dissection	7 yr 3 mo alive
3	S8, 5	Hr0	13 S5, 8	33 mo	dissection Hr0	4 yr 3 mo alive
4	S6, 7	Hr0	13 S5, 7	19 mo	radiation PEIT	2 yr 4 mo died

[a] Sites of recurrence were designated by the number of lymph nodes and the hepatic segment (From ref. 10)
PEIT, percutaneous ethanal injection; yr, years; mo, months; Hr, area of hepatic resection (From ref. 10)

Thus, a new intrahepatic lesion was treated by PEIT and a posterior pancreatic lymph node recurrence was treated by irradiation of the linear accelerator. After completion of a total irradiation dose of 60 Gy, the metastatic lymph node showed marked regression (Fig. 1). The patient is alive without any signs of further recurrence 10 months after the irradiation.

Case 4 underwent a partial hepatic resection of S6 and S7, followed by a postoperative arterial infusion of Adriamycin, interleukin-2 (IL-2), and spleen derived lymphokine-activated killer (LAK) cells. However, 18 months after this operation, the serum AFP and CEA levels became elevated and CT revealed a recurrent tumor on S7 and the posterior pancreaticoduodenal lymph nodes (Fig. 2). Thus, dissection of the lymph node with a partial hepatic resection of S5 was performed 2 years after the initial operation. Another recurrent hepatic tumor on S6/7 was treated by ethanol injection due to poor liver function and the deeper location of the tumor. The lymph node metastasis was diagnosed as Edmondson III solid type HCC, and the resected intrahepatic tumor from S5 was confirmed to be a combined type of HCC and cholangiocarcinoma. The patient died of intrahepatic dissemination of the tumor 2 years and 9 months after his second operation.

Discussion

It has been reported that cholangiocarcinoma has a higher frequency of lymph node metastasis than HCC.[12] Edmondson and Steiner[13] and Anthony[14] reported finding lymph node metastases in 28.0% and 25.4% of autopsied cases of HCC, respectively.

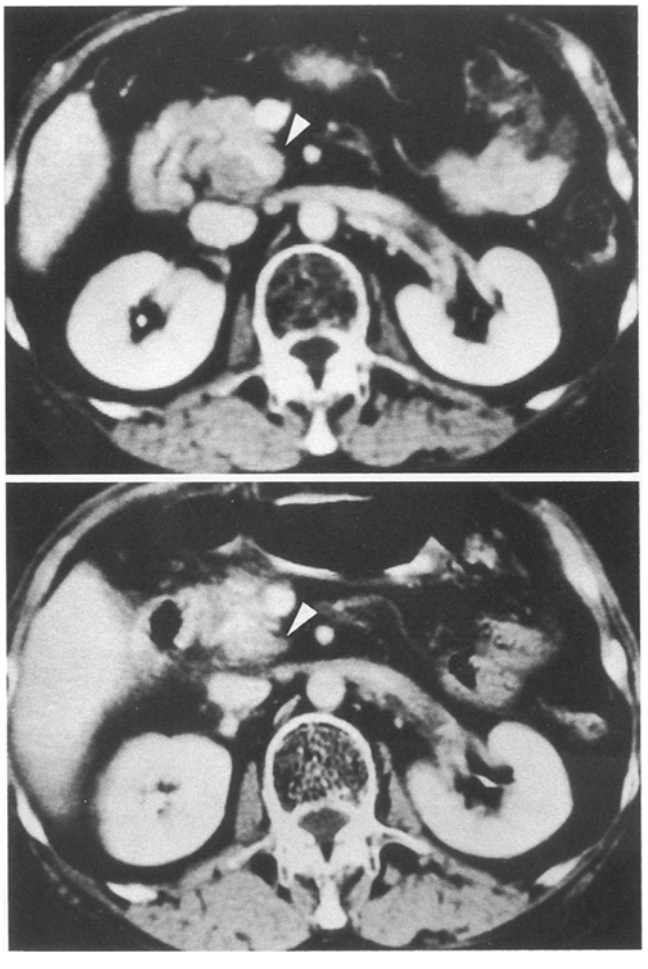

Fig. 1. Computed tomography (CT) findings of case 3. Swelling of the posterior pancreaticoduodenal lymph node can be see (*top*), which showed marked regression after the completion of irradiation therapy (*bottom*)

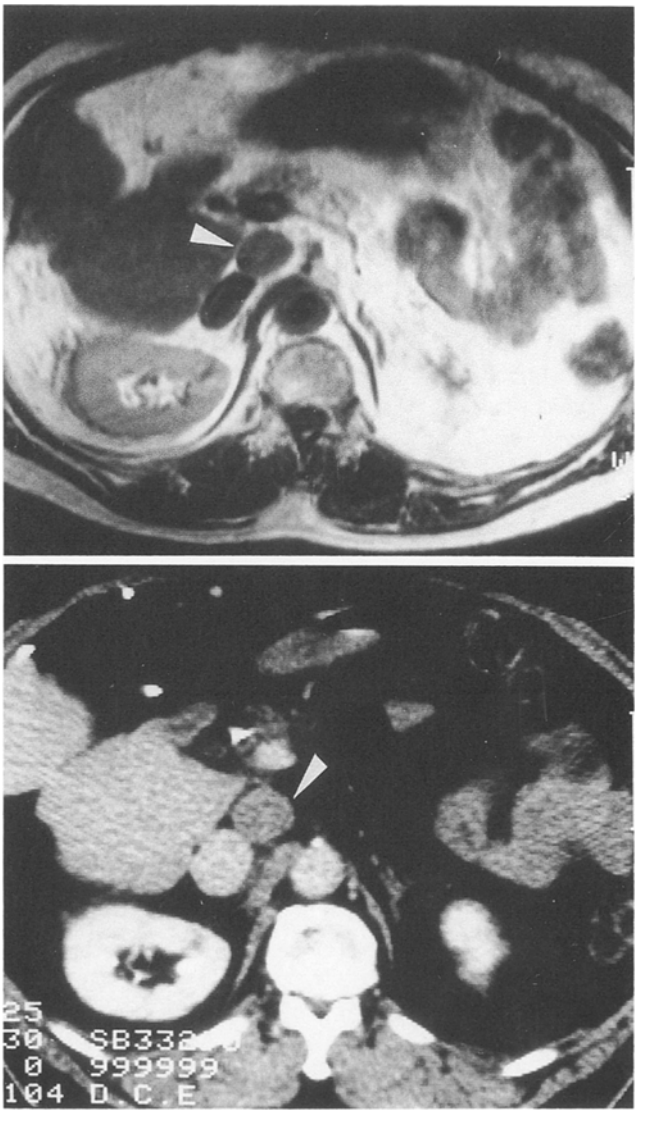

Fig. 2. CT (*top*) and T1-weighed magnetic resonance imaging (MRI) (*bottom*) findings of case 4. Swelling of the posterior pancreaticoduodenal lymph node can be seen

However, although there have been many reports on the patterns and treatment of intrahepatic recurrence after hepatectomy,[8,9] very few studies have been conducted on lymph node metastasis in surgical patients, despite the significance of lymph node dissection at the time of hepatectomy. We have performed lymph node dissection combined with hepatectomy for six patients with lymph node metastasis, one of whom has survived for a long period, although recurrence has been found in the posterior pancreaticoduodenal lymph nodes.

The most frequent site of recurrence of HCC after hepatectomy is the residual liver.[4] In fact, the Liver Cancer Study Group of Japan[5] reported that 80.3% of 1,803 patients with HCC treated by resection developed recurrence in the liver, with other extrahepatic recurrence sites being: the lungs in 7.4%, the bone in 5.8%, and the lymph nodes in 2.2%. In our series, lymph node recurrence was found in four patients (3.1%) and no relationship was found between the histopathological type or primary site in the liver and the location of metastatic lymph nodes. Anthony[14] reported that the invasive growth and portal invasion of hepatic tumors resulted in a tendency to cause metastasis to the regional lymph nodes. All four of our patients showed so-called jumping metastasis, which is described by Miyoshi et al.[15] as occurring more frequently in cirrhotic livers, the posterior pancreaticoduodenal lymph nodes being an important site of recurrence of HCC.

The treatment of choice for recurrent HCC with concomitant lymph node involvement has not yet been established. We performed dissection of the metastasized lymph nodes on four patients, two of whom had associated intrahepatic metastasis, and all of whom showed a solitary lymph node metastasis. All these patients survived for more than 3 years after their initial operation. It should also be considered that metastasized hepatoduodenal and posterior pancreaticoduodenal lymph nodes might cause obstructive jaundice through compression of the common bile duct.[16]

We previously reported that DNA ploidy pattern is a useful prognostic factor in HCC patients[17] as metastatic lymph nodes showed an aneuploid pattern with a higher DNA Index, while primary hepatic lesions tended to be diploid. This finding suggests the heterogeneity of HCC cells; however, a future study using a larger group of patients will offer more information about the biological characteristics of HCC recurrence.

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