TRANSPLANTATION OF THE LIVER FOR METASTATIC ENDOCRINE TUMORS OF THE INTESTINE AND PANCREAS

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In the Pittsburgh series of 1,000 orthotopic liver transplants (OLTx), from January 1981 to July 1987, the indication for transplantation in five patients consisted of unresectable hepatic metastases arising from endocrine tumors of gastrointestinal origin: glucagonoma, two patients; carcinoid, two, and gastrinoma, one patient. Three patients underwent resection of the primary tumor (two distal pancreatectomies and one ileal resection) at the time of the hepatic transplantation. All patients underwent extensive nodal dissection. Three of the five patients are alive with no evidence of residual disease after a median follow-up study of 12 months. Hepatic transplantation broadens the concept of radical excision of tumor and may be considered as a potential therapeutic approach for some highly selected instances of unresectable hepatic metastases arising from endocrine tumors of the intestine and pancreas.

ENDOCRINE TUMORS of the intestine and pancreas are rare. In a large review of gastrointestinal neoplasms conducted at autopsy, the incidence of these tumors was 1.5 per cent (1). The main histologic types consisted of carcinoids (greater than 90 per cent), insulinomas and gastrinomas (2, 3).

The diagnosis of these tumors is quite commonly delayed and, thus, often associated with metastatic disease; the liver is the most commonly involved metastatic site (2). Because of the slow growth and less aggressive biologic nature of these tumors and because of their decreased tendency to metastasize to other organs besides the liver, hepatic resection should always be considered to achieve, at least, palliation of symptoms and to prolong survival time (4). In theory, 95 per cent of the involved liver should be removed to achieve such results.

In those patients in whom this type of subtotal hepatic resection is impossible (for example, bilateral disease or large central lesions), antihormonal therapy (5), cytotoxic chemotherapy (6) and ligation of the hepatic artery (7) have been attempted. These methods have provided poor long term control and palliation of the disease. In this report, we describe our experience with orthotopic liver transplantation (OLTx) in five patients with unresectable hepatic metastases originating from endocrine tumors of the gastrointestinal tract. The selection criteria for OLTx, as well as a comparison with other conventional nonsurgical approaches to this problem, are presented.

PATIENTS AND METHODS

We have recently reviewed the records of the first 1,000 patients who underwent OLTx under immunosuppression with cyclosporine at the University of Pittsburgh from January 1981 to July 1987 (8). Five of these patients had histologically proved endocrine tumors of gastrointestinal origin with metastases to the liver. The clinical characteristics and histologic diagnoses are summarized in Table I.

In all but one of these patients (No. 1), the diagnosis of metastatic endocrine tumor was established before transplantation. Patient No. 1 underwent OLTx for a presumed diagnosis of hepatocellular carcinoma, which was reclassified as metastatic glucagonoma 27 months later, after re-examination of the histologic slides. The definitive diagnosis was established in all patients after a complete immunoperoxidase work-up study for enolase, glucagon, chromogranin, somatostatin and insulin on samples of tumor taken from the removed native liver, resection margins,
lymph nodes and, whenever present, from the primary tumor. Electron microscopic evaluation was also performed to confirm the ultrastructural characteristics of the cells.

RESULTS

The demographics of the five patients studied are presented in Table I. The ileum was the primary site of origin for the two metastatic carcinoid lesions, while the two glucagonomas and the one gastrinoma originated in the pancreas.

Four of the five patients had synchronous metastases, and three (Patient Nos. 3, 4 and 5) underwent simultaneous resection of the primary tumor at the time of transplantation. This necessitated two distal pancreatectomies and splenectomies and one ileal resection. Patient No. 1 had a final diagnosis of glucagonoma made almost two years after OLTx, and although his blood level of glucagon is presently suspicious at a fasting value of 157 picograms per milliliter (normal value of 20 to 100 picograms per milliliter), the appearance on computed tomographic scan of the pancreas has been stable for 34 months and, at the moment, there is no other evidence of disease (by nuclear magnetic resonance scan). The patient is in excellent health, and the possibility of undergoing a pancreatectomy is still under evaluation.

All patients underwent extensive dissection of the lymph nodes of the hilar hepatic, periceliac and peri pancreatic areas as part of the transplant procedure. The presence of enlarged lymph nodes during the evaluation before transplantation was not considered to be a contraindication for OLTx. The radical surgical procedure was considered to be complete when no tumor was grossly detectable in the surgical field at the end of the procedure and when the resection margins were free of disease for at least 0.5 centimeter from the tumor. Using these criteria, potentially curative resections were achieved in four patients; however, in Patient No. 4, a focus of cholangiocarcinoma was detected at the resection margin of the bile duct. This patient died nine months after OLTx of recurrent cholangiocarcinoma. Only one patient (No. 4) with a full blown carcinoid syndrome underwent extensive preoperative chemotherapy. Two of the patients (Nos. 4 and 5) demonstrated symptoms classical for the hormone-producing cells of the tumor (6). No postoperative adjuvant treatment protocol was used. One patient (No. 1) received Adriamycin® (doxorubicin hydrochloride) (100 milligrams per square meter for seven cycles) mainly for the original misdiagnosis of hepatocellular carcinoma. Patient No. 4 received an incomplete cycle of radiotherapy (interrupted because of severe radiation enteritis), followed by ten cycles of 5-fluorouracil given orally. Serial monitoring of blood levels of the specific hormones produced by each tumor has been used for follow-up study to detect possible recurrence of the disease.

The more extensive surgical approach in these patients, especially Patient Nos. 3, 4 and 5, did not appreciably contribute to increased postoperative morbidity when compared with conventional OLTx. The one patient who died two months postoperatively had required retransplantation for irreversible rejection, and the second graft failed because of primary nonfunction. The other three patients are alive with no evidence of disease at 34, 16 and seven months after OLTx. In Patient No. 4, levels of 5-hydroxyindoleacetic acid in the urine remained normal for the nine months that the patient was alive, and furthermore, there was no evidence of the carcinoid component of the tumor at exploratory laparotomy four months after OLTx. There are no complaints of any endocrine-related symptoms, and in two of the three patients still alive, the levels of hormones are normal.

DISCUSSION

Classically, metastatic tumors of the liver have been considered to be a poor indication for OLTx, and the results have been disappointing, even after sophisticated postoperative treatment, such as high-dose chemotherapy, irradiation of the total body and autologous bone marrow reconstitution (9); however, these previously reported instances of hepatic replacement have been for metastatic carcinoma of the breast, carcinoma of the colon and rectum, adenocarcinoma of unknown origin, teratoma and melanoma (10-13). These types of tumors obviously have a much more biologically aggressive behavior, and therefore, the poor results with OLTx and immunosuppression are not surprising. One instance of metastatic carcinoid without detailed description or follow-up study is cited in the Hannover series (12), and two instances of endocrine neoplasia were published recently in the Cambridge-King's College experience (14); both patients are alive two and seven months after transplantation.

The present report represents the first detailed evaluation of OLTx for metastatic endocrine tumors. The biologically less aggressive nature of these tumors suggests a more favorable prognosis. In addition to the histopathologic criteria, confirmed by immunoperoxidase staining, several
TABLE I—ORTHOPTIC TRANSPLANTATION OF THE LIVER FOR METASTATIC ENDOCRINE TUMOR OF THE SMALL INTESTINE AND PANCREAS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis on the liver specimen</td>
<td>Glucagonoma</td>
<td>Carcinoid</td>
<td>Glucagonoma</td>
<td>Carcinoid plus cholangiocarcinoma</td>
<td>Gastrinoma</td>
</tr>
<tr>
<td>Age, yrs./Sex</td>
<td>41/M</td>
<td>52/F</td>
<td>41/F</td>
<td>39/M</td>
<td>45/M</td>
</tr>
<tr>
<td>Endocrine-related symptoms</td>
<td>No</td>
<td>No</td>
<td>Partial, glossitis</td>
<td>Yes, full syndrome</td>
<td>Yes, severe gastric ulcers</td>
</tr>
<tr>
<td>Preoperative hormone levels</td>
<td>Glucagon, 300 pgm./ml.</td>
<td>Glucagon, 157 pgm./ml.</td>
<td>Glucagon, 217 mgm./24 hrs.</td>
<td>Glucagon, 36 pgm./ml.</td>
<td>Glucagon, normal*</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>Pancreas?</td>
<td>Ileum, appendectomy</td>
<td>Pancreas</td>
<td>Ileum</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Per cent of metastatic hepatic involvement</td>
<td>&gt;70</td>
<td>&gt;80</td>
<td>80</td>
<td>70</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Extrahepatic metastases at OLTx</td>
<td>Peripancreatic lymph nodes</td>
<td>Peripancreatic lymph nodes</td>
<td>OLTx plus node dissection</td>
<td>OLTx plus node dissection</td>
<td>OLTx plus ileal resection</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>OLTx plus node dissection</td>
<td>OLTx plus node dissection</td>
<td>OLTx plus ileal resection</td>
<td>OLTx plus distal pancreatectomy, splenectomy plus node dissection</td>
<td>OLTx plus distal pancreatectomy, splenectomy plus node dissection</td>
</tr>
<tr>
<td>Radical surgical procedure, potential for cure</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Postoperative treatment</td>
<td>Adriamycin®</td>
<td>—</td>
<td>No</td>
<td>Radiotherapy plus 5FU</td>
<td>No</td>
</tr>
<tr>
<td>Recurrence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Survival</td>
<td>Alive 34 mos., disease free(?); glucagon, 157 pgm./ml.; pancreas without changes by NMR and CT scan for 34 mos.</td>
<td>Died 2 mos. post-operation; irreversible rejection, 1st graft and primary non-function 2nd graft</td>
<td>Alive 16 mos., disease free; glucagon, 21 pgm./ml.</td>
<td>Died 9 mos., recurrence of cholangiocarcinoma; 5HIAA, normal*</td>
<td>Alive 7 mos., disease free; gastrin, 36 pgm./ml.</td>
</tr>
</tbody>
</table>

*As of June 1988, six months after the submission of this report, patient treated for metastatic gastrinoma had multiple metastases of the lung and bone develop (eight months after hepatic transplantation). He died two months later. Disseminated metastatic gastrinoma was noted at autopsy (lungs, bone, liver, pancreas, duodenum, celiac mesentery and right adrenal gland). The two other surviving patients (Nos. 1 and 3) remain disease-free at 41 and 23 months after hepatic transplantation, respectively.

| N | Normal level of 5HIAA in urine, 1 to 7 mgm./24 hr. |
| N | Normal level of gastrin, less than 100 pgm./ml. |

Generally, when considering the natural history of the spread of the tumor, the probability that a tumor arising in an organ drained exclusively by the portal system will give rise to hepatic metastases without metastases elsewhere is much higher than in tumors drained by systemic circulation, with a ratio of ten to one (1). Moreover,
intestinal-related endocrine neoplasia have an even greater proclivity for metastasizing to the liver (16), with minimal or absent extrahepatic spread. In the instance of carcinoids, origin from the small intestine or pancreas, or both, is correlated with a better prognosis and longer survival time than for carcinoids arising in other primary sites (4). In most occurrences of advanced carcinoid tumors metastatic to the liver, death results from cardiac or hepatic failure secondary to the tumor replacement, usually without extrahepatic spread.

The primary tumor in all of the patients presented in this series of metastatic endocrine tumors originated in the more biologically favorable location, that is, drained by the portal system. Surgical treatment has always been considered the primary and potentially curative approach to hepatic metastases from intestinal-related endocrine tumors (2, 17). Hepatic transplantation broadens the concept of a radical approach in those situations in which a subtotal hepatic resection cannot eradicate the majority of the disease. Extensive nodal dissection was performed upon all of the patients in this series. It is important to note that this aggressive approach should and can successfully be extended to the simultaneous removal of the primary lesion.

The results of the present series are extremely encouraging thus far, in terms of survival time, disease-free interval and control of endocrine-related syndromes. One patient died early of causes entirely related to the transplant procedure itself; one patient died of recurrence of cholangiocarcinoma, which was found incidentally at the time of OLTx for a carcinoid tumor. The prognosis of OLTx for cholangiocarcinoma is known to be extremely poor (14, 18). It should be emphasized that this patient had no evidence of recurrence of carcinoid for nine months. Three of the five patients are alive with no apparent evidence of residual disease. The immunosuppressive protocol used in these patients, consisting of cyclosporine and steroids (19), has not as yet appeared to influence the behavior and course of the tumor significantly, particularly, because there has been no proved recurrence.

The follow-up study (seven to 34 months) is still too short for these tumors to express their ultimate natural history, but the over-all results obtained to date are certainly encouraging. Moreover, our results for this disease compare favorably with other reported approaches to management. In patients treated with chemotherapy, the mean five year survival rate for unresectable metastatic gastrinoma is about 20 per cent (20), whereas the median survival time for carcinoid tumors originating in the small intestine and pancreas with unresectable hepatic involvement ranges from 21 to 29 months (21). The mean response with hepatic arterial ligation for metastatic carcinoid is only five months (8, 18).

Although postoperative adjuvant treatment was not actually evaluated in the group of patients we studied, there is some suggestion from the two patients in the series who did receive such treatment that this approach may be beneficial and certainly warrants further study. Blood levels of tumor-related hormones can be used postoperatively to study recurrence of tumor, and the rapid decline of the levels of these hormones after OLTx can be considered to be an indirect index of successful resection (Table I).

In conclusion, OLTx appears to be a therapeutic approach, which should be considered for a limited number of highly selected patients with unresectable metastatic hepatic disease originating from endocrine tumors of the small intestine and pancreas. With careful selection criteria for patients and with careful adherence to the principles of surgical oncology, OLTx can successfully control this disease and its associated endocrine syndromes for prolonged periods.

SUMMARY

Five patients who underwent OLTx for unresectable hepatic metastases originating from gastrointestinal endocrine tumors are presented. Careful selection criteria for patients, the unique biologic behavior of these tumors and strict adherence to the principles of surgical oncology have resulted in extremely encouraging results. Four of the five patients are alive with no apparent evidence of residual disease after a median follow-up study of 12 months. Three patients have maintained normal levels of tumor-related hormones, and none complain of any endocrine-related symptoms. Hepatic transplantation conceptually broadens the principles of radical oncologic surgery in selected instances of otherwise unresectable metastatic hepatic involvement from endocrine tumors arising in the intestine and pancreas.

REFERENCES


