LETTER TO THE EDITOR

Liver transplantation for the treatment of nonresectable metastatic duodenal paraganglioma

doi:10.1111/j.1432-2277.2006.00353.x

Paragangliomas are neoplasms that arise from primitive cells of the neural crest [1]. They are found scattered throughout the body associated with sympathetic and parasympathetic nerves. Paragangliomas have been found in virtually every location where normal paraganglia are known to occur [1,2]. Such tumours have been described in the orbit, nose, ear, carotid area, vagus nerve, larynx, mediastinum, retroperitoneum, urinary bladder, cauda equina and duodenum.

There are no reliable morphologic criteria to differentiate microscopically benign from malignant paraganglioma. Its malignant potential is defined after a metastatic lesion or direct invasion is found in a site with no residual embryonic paraganglionic tissue [3,4].

There are few articles reporting the use of liver transplantation (OLT) in the treatment of metastasic disease [5,6]. Most reports come from the European experience on the treatment of metastases from Neuroendocrine tumours (NET) [5,6].

Current methods to detect spread of the disease that were not readily available in the past, such as MRI, indium-111-pentetreotide (Octreoscan) and others, may expand the applications of transplantation allowing for better selection of candidates [7].

We evaluated a 68-year-old man with previous history of local resection of a Paraganglioma located in the fourth portion of the duodenum 11 years ago. In January 2005, he presented with right upper quadrant pain. A trifasic CT scan demonstrated an 11-cm lesion in the right lobe of the liver extending into the segment 4 of the left lobe. Liver function tests were completely normal. Upper and lower gastrointestinal endoscopies were also normal with no evidence of local tumour recurrence. An MRI of abdomen–pelvis and a CT scan of the chest were performed in addition to the CT of the abdomen and pelvis to complete the work-up for the presence of extrahepatic disease. The patient was explored for a possible extended right hepatectomy. Intra-operative ultrasound demonstrated presence of tumour in segments 4, 5, 6 and 7 with extension into segments 2 and 3. There was no evidence of local recurrence in the duodenum or extrahepatic disease. The lesion was deemed unresectable because of extension into the left lateral segment.

A multidisciplinary discussion was initiated in order to assess the role of OLT. The case was presented and approved at the Institutional Committee and at the Regional Review Board. After completion of the pretransplant evaluation protocol including a new MRI of abdomen–pelvis and CT of the chest to assess the presence of extrahepatic disease, a liver transplant was performed in June of 2005. The abdomen was explored through a bilateral subcostal incision with midline extension and no evidence of extrahepatic disease was observed. The decision was then made to proceed with a conventional OLT with excision of the native retrohepatic Inferior Vena Cava. Pathology reported an 11.4 cm (Fig. 1) metastatic paraganglioma without capsular invasion or regional lymph node involvement.

This case illustrates many of the features of this unusual nueroendocrine tumour. Paragangliomas are lesions thought to originate from the neural crest [1]. Neoplasms arising in the adrenal medullae are referred to as 'pheochromocytomas'; tumours arising in paraganglia are usually called paragangliomas. Recurrence may not be seen for many years after initial diagnosis and affected patients may live with recurring or persistent disease for many years [8].

Our patient presented with a single liver metastases from a duodenal paragangliona resected 11 years prior to the diagnosis of this metastases. Because of the impossibility of resecting the tumour obtaining clear surgical margins, the patient was proposed for OLT evaluation. There are only a small number of articles on the use of transplantation for the treatment of metastasic NET. The sample size and follow-up after OLT have been limited in these series [5,6]. The Hannover group published their results in 12 patients who underwent OLT for metastases from NET [4]. They had one operative mortality and two patients developed recurrent disease and died secondary to their malignancy. The remaining 75% of their patients were alive with an overall median survival of 55 months. Unfortunately, seven of their initial 12 patients had recurrence or residual tumour. They published a follow-up report showing 1, 5 and 10-year survival rates of 89%,

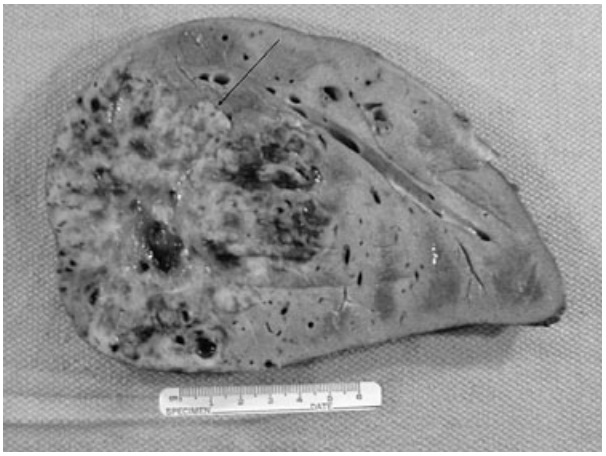

Figure 1 Gross photograph of resected liver with paraganglioma. The tumour measured 11.4 cm in greatest dimension (arrow).

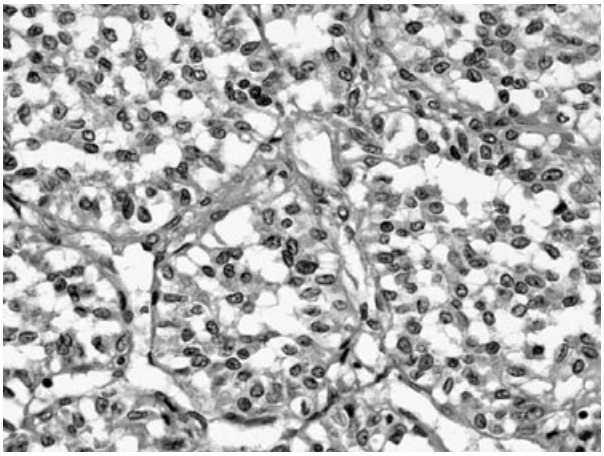

Figure 2 High-power view of paraganglioma (H&E stain). The neoplasm is composed of fairly homogeneous cells with oval to round nuclei. The tumour cells have an organoid arrangement with 'zellballen' or cell nests separated by delicate fibrous connective tissue stroma, characteristic of paraganglioma.

80% and 50% respectively [9]. Another very significant study was published by Le Treut *et al.* [10] who collected the French experience in a multicentric trial evaluating 31 patients with metastatic NET treated with OLT. The perioperative mortality was 19%, the remaining 25 patients were followed to determine the incidence and pattern of tumour recurrence, cause of death and survival. The primary tumour was removed at the time of OLT in 10 cases by upper abdominal exenteration in seven cases and pancreatoduodenectomy in three cases. Actuarial survival rate after OLT at 1, 3 and 5 years was 59%, 47% and 36% respectively. However, in the subgroup of patients with metastatic carcinoid tumours, a 5-year survival rate as high as 69% was observed. In 2004, the Mount Sinai Hospital group published their experience in 11 patients [11]. The 1- and 5-year survival among transplanted patients was 73% and 36%, respectively, with mean follow-up of 34 months.

Survival rates like those obtained by the Hannover group and the outcomes presented by the French multicentric trial on patients with metastatic carcinoid tumours demonstrates that excellent results can be obtained in highly selected patients. OLT has been used in most series in patients with advanced disease. The development and utilization of diagnostic techniques like MRI, indium-111-pentetreotide, ^{131}I-labelled-metaiodobenzylguanidine (MIBG) and positron emission tomography (PET) using (18)F-labelled deoxyglucose (FDG) or fluorinated dihydroxyphenylalanine [(18)F-DOPA] will enable us to determine the presence of advanced lesions not suitable for surgical treatment including liver transplantation [12–14]. This will improve outcomes by improving patient selection.

Our patient was approved for transplantation on the basis of good outcomes reported in the treatment of metastatic NET in selected patients, absence of extrahepatic disease, unsuitability for surgical resection and excellent cardiopulmonary status. Histology of the explanted liver demonstrated cell nests or 'zellballen' separated by delicate fibrous connective tissue stroma, characteristic of Paraganglioma (Fig. 2). Our patient is still alive and disease free eleven months after OLT.

Roberto Gedaly, Hosein Shoukouh-Amiri,
Atsushi Shimizu, A. Osama Gaber,
Pamela B. Sylvestre and Santiago Vera
Transplantation Institute, Methodist Hospital,
University of Tennessee Medical School,
Memphis, TN, USA

References

1. Patel SR, Winchester DJ, Benjamin RS. A 15-year experience with chemotherapy of patients with paraganglioma. *Cancer* 1995; **76**: 1476.
2. Kumaki N, Kajiwara H, Kameyama K, *et al.* Prediction of malignant behavior of pheochromocytomas and paragangliomas using immunohistochemical techniques. *Endocr Pathol* 2002 Summer; **13**: 149.
3. Proye C, Vix M, Goropoulos A, Kerlo P, Lecomte-Houcke M. High incidence of malignant pheochromocytoma in a surgical unit: 26 cases out of 100 patients operated from 1971 to 1991. *J Endocrinol Invest* 1992; **15**: 651.
4. Vassilopoulou-Sellin R. Clinical outcome of 50 patients with malignant abdominal paragangliomas and malignant pheochromocytomas. *Endocr Relat Cancer* 1998; **5**: 59.

5. Somasundar P, Krouse R, Hostetter R, Vaughan R, Covey T. Paragangliomas – a decade of clinical experience. *J Surg Oncol* 2000; **74**: 286.
6. Pascher A, Klupp J, Neuhaus P. Transplantation in the management of metastatic endocrine tumours. *Best Pract Res Clin Gastroenterol* 2005; **19**: 637.
7. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma: an analysis of 103 patients. *Transplantation* 1998; **66**: 1307.
8. Bucher P, Mathe Z, Buhler L, *et al.* Paraganglioma of the ampulla of Vater: a potentially malignant neoplasm. *Scand J Gastroenterol* 2004; **39**: 291.
9. Lang H, Oldhafer KJ, Weimann A, *et al.* Liver transplantation for metastatic neuroendocrine tumors. *Ann Surg* 1997; **225**: 347.
10. Rosenau J, Bahr MJ, von Wasielewski R, *et al.* Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. *Transplantation* 2002; **73**: 386.
11. Le Treut YP, Delpero JR, Dousset B, *et al.* Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997; **225**: 355.
12. Florman S, Toure B, Kim L, *et al.* Liver transplantation for neuroendocrine tumors. *J Gastrointest Surg* 2004; **8**: 208.
13. Li S, Beheshti M. The radionuclide molecular imaging and therapy of neuroendocrine tumors. *Curr Cancer Drug Targets* 2005; **5**: 139.
14. Brink I, Hoegerle S, Klisch J, Bley TA. Imaging of pheochromocytoma and paraganglioma. *Fam Cancer* 2005; **4**: 61.

