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Surgical treatment of neuroendocrine metastases

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Neuroendocrine tumors of the intestinal tract have low malignant potential but can result in decreased survival if they spread to the liver. The estimated 5-year survival of patients with liver metastases from neuroendocrine tumor is only 20%. Further, morbidity related to the Carcinoid Syndrome and other endocrine symptoms may also greatly reduce the quality of life. Treatment options for liver neuroendocrine tumor include long-acting somatostatin receptor antagonists (LAR), inteferon-α, chemotherapy and hepatic artery embolisation with and without chemotherapy. Surgical resection is feasible in select patients, but it may result in major morbidity and even mortality. In our series of 18 patients with liver neuroendocrine tumors, there was no operative mortality and acceptable morbidity. All 10 patients with the Carcinoid syndrome had complete amelioration of symptoms and the 5-year actuarial survival was 80%. Aggressive major surgery for liver neuroendocrine tumor metastases can be performed safely with acceptable mortality by experienced surgeons. Results have been similar for patients with gastrinoma and pancreatic neuroendocrine tumors. Surgical resection appears to result in outstanding long-term survival and amelioration of symptoms. It should be the first-line therapy for patients with liver neuroendocrine tumors in whom the tumor can be completely removed.

Key words: liver neuroendocrine tumor; surgery; Carcinoid syndrome; survival; gastrinoma.

LIVER METASTASES

The most important predictor of poor survival in patients with neuroendocrine tumours is hepatic metatases[1–10], the extent of liver metastases correlating with subsequent survival.[4] Figure 1 shows survival data from 212 patients with gastrinoma followed for at least 10 years. Patients without any liver metastases had a 95% 20-year survival, whereas patients with diffuse bilobar liver metastases had a 10-year survival of only 15%.[2] Patients who had a solitary liver metastasis or fewer than five discrete metastases in both liver lobes had an intermediate survival (60% at 15 years).[2] The extent of liver neuroendocrine tumour is therefore the most important predictor of survival.

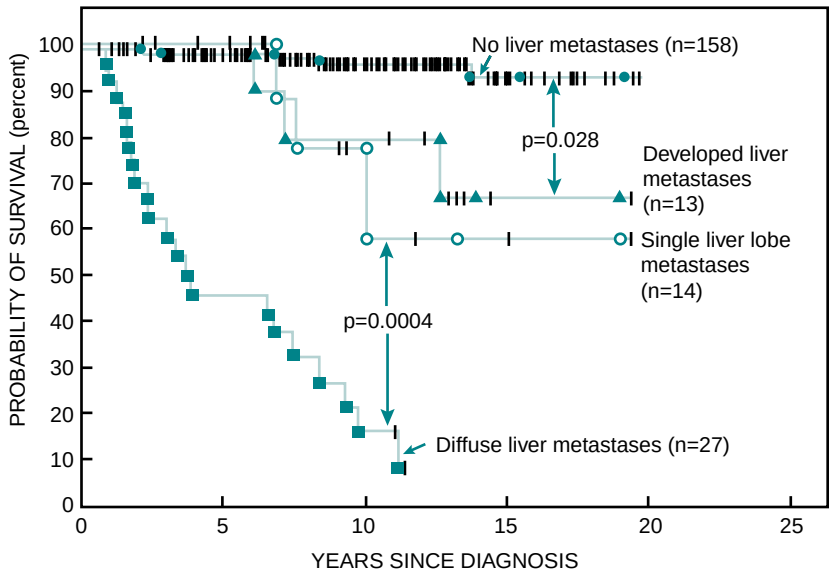

Figure 1. Survival of patients with liver metastases from gastrinoma. (Reproduced from Ref. 2, with permission.)

Medical therapy for metastatic neuroendocrine tumours is poor as no drugs have clearly been shown to cause tumour regression and improve survival; even chemoembolisation has not been shown to improve the latter. Modern surgery can effectively remove liver metastases arising from colon cancer and other tumours, and all these methods have been applied to metastatic neuroendocrine tumours. Surgery can be carried out safely with acceptable morbidity and mortality in experienced hands. The major issues concern whether or not it is beneficial and whether it improves survival.

SURGERY FOR LIVER NEUROENDOCRINE TUMOURS

The question remains of whether surgically resecting liver metastases will improve survival, but there are no prospective randomised studies to answer this. Some investigators believe that the removal of liver metastases can improve the survival and symptoms of patients with metastatic neuroendocrine tumours. Therefore, in gastrinoma[1,11–14], and in other malignant liver metastatic neuroendocrine tumours such as carcinoid[15–21], resection, cryoablation and radiofrequency ablation for liver metastases have all been attempted. Most studies have chosen only patients with a small liver tumour burden who can have all their tumour effectively removed or ablated but may already have a good prognosis. Patients with minimal localised liver metastases from neuroendocrine tumours are relatively few as only 5–15% of patients with metastatic liver neuroendocrine tumours have tumour localised to one lobe, or a discrete, limited number of (fewer than five) metastases in two lobes that would be fully

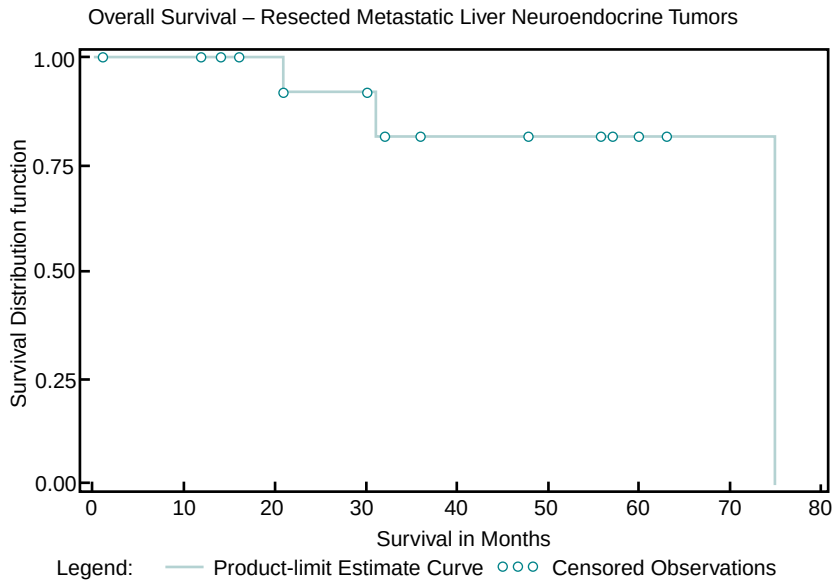

Figure 2. Survival of patients with resected liver metastases from neuroendocrine tumours. From Figure 4, Norton et al. (2003 *Surgery* **134**: 1057–1065) with permission.

resectable.[4,9,11,12,14,15,20,22] Surgery thus appears to be an option for a only a small fraction of these patients.

In various published studies, surgery has resulted in benefit for those who can undergo it. Surgery for liver metastatic neuroendocrine tumour has occasionally resulted in cure[12,21,23,24], and patients who can be resected surgically have 5-year survival rates of 71–85%[12,15,16,21,23,24], which is believed to increase survival over those who have not undergone surgical resection (Figure 2).[15,19,24] We have taken an aggressive approach and tried to extend these beneficial effects of surgery to more patients by removing liver and other tumours if all the tumour can be removed.

Aggressive surgery for metastatic liver neuroendocrine tumours is, however, controversial and difficult to prove effective, for a number of reasons. First, there are no controlled trials in which patients with resectable liver metastases from neuroendocrine tumours have been randomised to appropriately matched control groups without liver surgery. Therefore, in current studies, the improved survival with surgical resection may be explained by more advanced disease in the non-surgical group.

Second, patients with functional liver neuroendocrine tumours are often considered together with those with non-functional neuroendocrine tumours when evaluating the value of liver and debulking surgery. Patients with advanced functional liver neuroendocrine tumours in whom the symptoms of the state of hormone excess are not well controlled medically, for example insulinoma, may benefit from enhanced symptom control after resection, whereas in patients with non-functional tumours or gastrinomas (which are well controlled with proton pump inhibitors), who are usually asymptomatic, the value of surgery can be assessed only by its effect on survival.

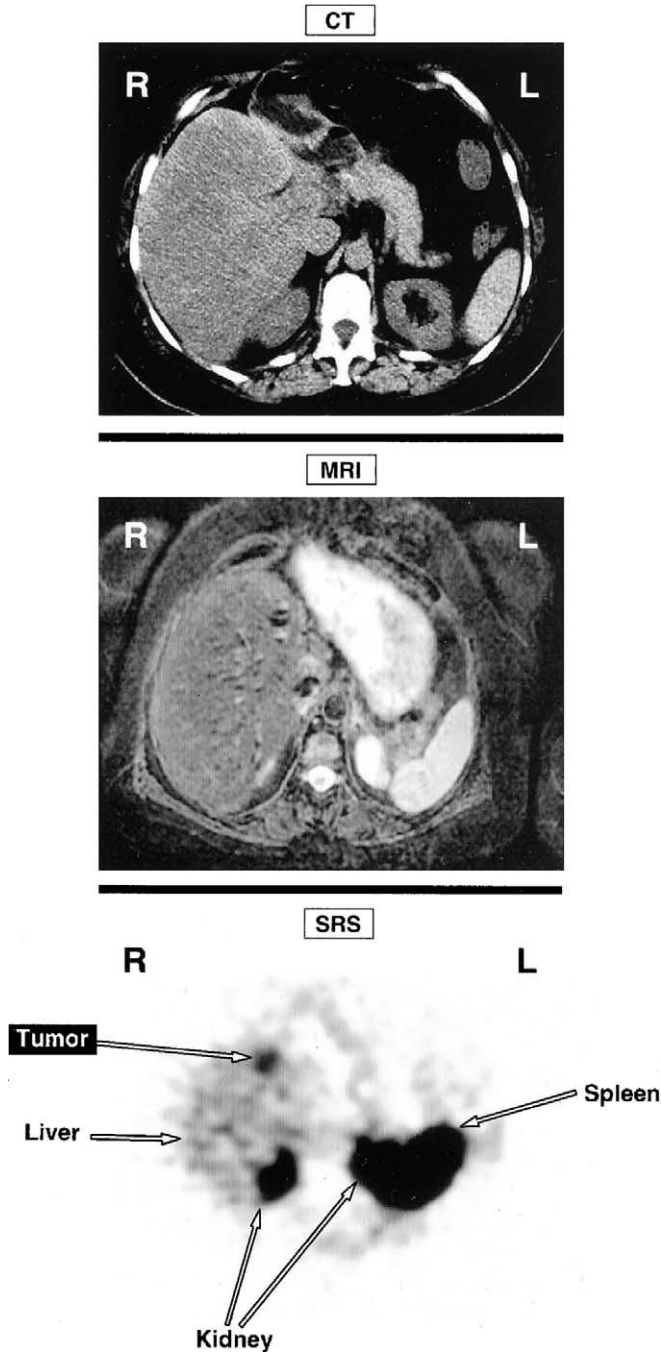

Figure 3. Computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SRS) of a patient with metastatic gastrinoma to the liver. SRS images the tumour (arrow) while both CT and MRI are negative. (Reproduced from Ref. 2, with permission.)

Third, because of the relatively slow growth of these malignant liver neuroendocrine tumours compared with more virulent malignancies such as sarcoma or adenocarcinoma, studies need to incorporate long-term follow-up to demonstrate differences in survival with significant numbers of patients. This is further exacerbated by the rarity of pancreatic and gastrointestinal neuroendocrine tumours because few institutions have a sufficient experience with these patients. Because of these issues and insufficiencies, there are currently no data from which to determine unequivocally which, if any, patients should undergo liver surgery and/or tumour debulking surgery. Most of the surgical studies demonstrate that these resections can be performed with acceptable morbidity and low mortality, and suggest that life may be prolonged.

Because the medical antitumour treatment of advanced liver disease in patients with liver neuroendocrine tumours[6,8] is generally unsatisfactory, our approach at present is

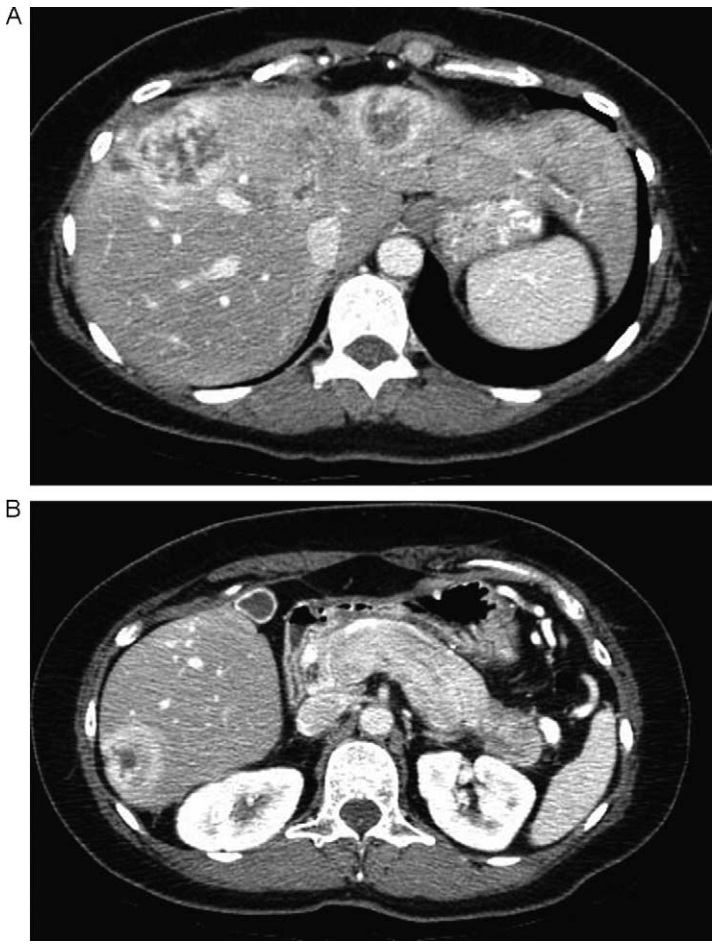

Figure 4. Representative patient with liver metastases from neuroendocrine tumour. A large tumour in the left lobe (A) requires left hepatic lobectomy, whereas a smaller, more peripheral tumour in the right lobe (B) is wedge-resected. The patient also had a primary ileal carcinoid tumour that was removed by right hemicolectomy. She was treated with a long-acting somatostatin analogue postoperatively.

to perform surgical resection in any patient with advanced liver neuroendocrine tumour in whom, based on imaging studies, all or at least 90% of the gross tumour can be removed. We use somatostatin receptor scintigraphy to rule out significant extrahepatic tumour and to be certain that the liver neuroendocrine tumour is well differentiated (Figure 3). We believe that tumours that are somatostatin receptor scintigraphy positive are more highly differentiated. This means that the tumour is less virulent and that any residual tumour after surgery may be controlled with somatostatin analogues, which will further inhibit tumour growth.

We have extended surgery to include as many patients as possible with well-differentiated somatostatin receptor-positive metastatic neuroendocrine tumours, such as the patient who presented with bilobar metastases and an unknown primary tumour (Figure 4). The removal of this tumour required a left hepatic lobectomy (Figure 4A) and the wedge resection of a large peripheral metastasis in the right lobe (Figure 4B). The primary tumour was not visualised on preoperative imaging studies, including computed tomography and somatostatin receptor scintigraphy, but was found at surgery to be a small ileal carcinoid tumour with lymph node metastases. This was removed by a right hemicolectomy that included the terminal ileum. If the liver neuroendocrine tumour is negative on somatostatin receptor scintigraphy (only about 10–20% of cases), we would not perform this aggressive cytoreductive surgery but would ask oncology team to treat with chemotherapy. Furthermore, during this aggressive surgery we perform a cholecystectomy because long-acting somatostatin analogues cause gallstones. Following surgical resection, we use long-acting somatostatin (sandostatin-LAR) 30 mg intramuscularly every 3 weeks to suppress residual tumour growth. This therapy is well tolerated and appears to decrease tumour recurrence and progression as we have had a 5-year survival rate of 80% (see Figure 2 above).

This aggressive surgical approach is used recognising that additional studies are needed to establish its value clearly in both patients with liver neuroendocrine tumours and those with other advanced neuroendocrine tumours. However, without the benefit of proof by well-designed prospective randomised trial, the value of liver resection has been well documented by multiple studies in multiple patients from multiple independent institutions, suggesting that this approach is appropriate and valid. The prognosis of those who can have most tumour removed is excellent, and the complication rate has been small.

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