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Laparoscopic Radiofrequency Ablation of Neuroendocrine Liver Metastases

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Abstract. We previously reported on the safety and efficacy of laparoscopic radiofrequency thermal ablation (RFA) for treating hepatic neuroendocrine metastases. The aim of this study is to report our 5-year RFA experience in the treatment of these challenging group of patients. Of the 222 patients with 803 liver primary and secondary tumors undergoing laparoscopic RFA between January 1996 and August 2001, a total of 34 patients with 234 tumors had neuroendocrine liver metastases. There were 25 men and 9 women with a mean ± SEM age of 52 ± 2 years who underwent 42 ablations. Primary tumor types included carcinoid tumor in 18 patients, medullary thyroid cancer in 7, secreting islet cell tumor in 5, and nonsecreting islet cell tumor in 4. There was no mortality, and the morbidity was 5%. The mean hospital stay was 1.1 days. Symptoms were ameliorated in 95%, with significant or complete symptom control in 80% of the patients for a mean of 10+ months (range 6–24 months). All patients were followed for a mean ± SEM of 1.6 ± 0.2 years (range 1.0–5.4 years). During this period new liver lesions developed in 28% of patients, new extrahepatic disease in 25%, and local liver recurrence in 13%; existing liver lesions progressed in 13%. Overall 41% of patients showed no progression of their cancer. Nine patients (27%) died. Mean ± SEM survivals after diagnosis of primary disease, detection of liver metastases, and performance of RFA were 5.5 ± 0.8 years, 3.0 ± 0.3 years, and 1.6 ± 0.2 years, respectively. Sixty-five percent of the patients demonstrated a partial or significant decrease in their tumor markers during follow-up. In conclusion, RFA provides excellent local tumor control with overnight hospitalization and low morbidity in the treatment of liver metastases from neuroendocrine tumors. It is a useful modality in the management of these challenging group of patients.

Since their initial descriptions by Paul Langerhans in 1869 in the pancreatic islets and by Heidanhain in 1870 and Kultschizky in 1897 in the gut mucosa, neuroendocrine cells have been a constant focus of interest due to their unique histologic and cytochemical features and the complex nature of the pathologies to which they give rise [1–3]. Liver metastases from neuroendocrine tumors, in the same sense, have distinct biologic and clinical features that render their management challenging.

Liver metastases develop in fewer than 5% of patients with a carcinoid tumor, in 5% to 10% of patients with insulinoma, in 23% to 90% of patients with gastrinoma, and in 70% to 75% of those with glucagonoma [3]. In contrast to most metastatic adenocarcinomas, neuroendocrine malignancies can have an indolent course with prolonged patient survival. Moreover, the clinical course may be dominated by hormonal secretion. Although these tumors run a rather indolent course, the 5-year survival of patients with neuroendocrine tumors and liver metastases is 11% to 40%. The 5-year survival rate of the largest group of patients, those with carcinoid tumors, is only 21% [4].

Although surgical removal is the gold standard, curative surgical resection is not possible in more than 90% of the patients, and chemotherapy has limited value [3]. The long indolent course and the importance of palliation in these patients have encouraged the application of regional treatment methods to the liver. Our group reported the first laparoscopic experience with radiofrequency thermal ablation (RFA) for treating hepatic neuroendocrine metastases in 6 patients with 13 tumors [5]. The aim of this study is to report our 5-year RFA experience in the treatment of this challenging group of patients.

Materials and Methods

Technique

Our technique for performing laparoscopic RFA of liver tumors has been described in detail elsewhere [6, 7]. In brief, the procedure is performed under general anesthesia. The patient is positioned supine on the operating table except for selected patients with disease limited to the right lobe of the liver or the posterior segments; these patients are treated in the left decubitis position with the table slightly flexed. An optical access trocar (Optiview; Ethicon Endo Surgery) is used for the initial abdominal entry. Two 11 mm trocars are placed underneath the right costal margin. Diagnostic laparoscopy is first performed with biopsy of any suspicious extrahepatic disease, followed by laparoscopic ultrasonography of the liver to map out all metastatic foci.

Ultrasonography is performed using a 7.5 MHz Aloka (Aloka, Wallingford, CT, USA) rigid, linear, side-viewing 10 mm laparoscopic transducer and the Aloka 2000 or 5500 ultrasound machine. Color flow studies of the lesions are done to assess their vascularity. Under ultrasound guidance, 18-gauge core biopsies of the suspected metastatic foci are performed for histologic confirmation using a spring-loaded biopsy gun. During the procedure

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one port is utilized for the laparoscope and one for the ultrasound transducer. An additional port may be required if extensive adhesions require dissection. Adhesions between the liver and the abdominal wall and viscera are taken down, although it is not necessary to divide the falciform ligament. The use of a picture-in-picture box to superimpose a quarter-size laparoscopic image over the full-size ultrasonographic image is convenient to coordinate the movement of the laparoscopic ultrasound transducer with the laparoscopic image and to have both images on one screen. After the lesions have been identified and measured, the RFA catheter is placed percutaneously in the lesion, and the prongs are deployed.

In the first part of the study (December 1996 to January 2001) the ablations were performed using the first-generation RFA technology, which consisted of the RITA Medical Systems (Mountainview, CA, USA) model 500 generator and the model 30 (four-prong) or model 70 (seven-prong) 3 cm diameter thermal ablation catheters with thermocopules at the tip of the prongs. This technology allowed ablation of 3.5 to 4.0 cm diameter spherical tumor tissue per cycle by running the RF generator in a temperature-controlled mode with an average target temperature of 105°C and maximum power of 50 watts. With this setup, each cycle of ablation was maintained for a period of 5 minutes, with the overall ablation cycle taking 7 to 10 minutes. A single ablation cycle was adequate for tumors < 3 cm in diameter to achieve an adequate tissue margin. However, for tumors > 3 cm in diameter, multiple overlapping thermal ablation zones were required to ensure an adequate volume of ablation. The ablation cycle itself is monitored by both the thermocouples at the tips of the catheter and the microbubble formation detected by ultrasonography. A laptop computer connected to the electrical generator allows accurate records to be kept of each ablation cycle. At the completion of an ablation, the temperatures continue to be monitored for 1 to 2 minutes to ensure adequate heating even at the periphery of the lesion. Ultrasound color flow examination of the lesion is then performed to document lack of blood flow within the tumor.

Since January 2001 we have been using second-generation RFA technology, which consists of the RITA Medical Systems Starburst XL (9 array, 5 cm) thermal ablation catheter and the model 1500 generator. The catheter consists of a 14-gauge needle, 25 cm in length with nine curved prongs. The one prong at the center and the four prongs going to the equator have thermocouples at the tips for monitoring temperature during ablation. The prongs are deployed to a maximum diameter of 5 cm by pushing the piston down the shaft of the catheter. The 3-, 4-, and 5-cm marks just distal to the piston inform the surgeon about the deployment diameter in any given position. The generator has a maximum power of 150 W and was run at the "average temperature" mode with the target temperature set to 105°C. Various algorithms were used for ablations. Tumors < 3 cm were ablated with a single 3 cm ablation and those between 3 and 4 cm with a single 4 cm ablation cycle. Tumors < 5 cm were treated with one cycle of a 5 cm ablation, and larger tumors required two to four cycles of ablation to obtain adequate margins. During the ablation procedure two grounding pads are placed on the anterosuperior aspect of the right and left thighs, respectively. The new 7 cm RITA Medical Systems Starburst XLI 7-cm catheter was also used in one of the recent patients.

Postoperatively, patients require only routine care. Most patients can be managed without narcotics, and intravenous lines were removed once the patient resumed oral intake.

Patients

Between January 1996 and August 2001 a series of 222 patients with 803 liver primary and secondary tumors underwent laparoscopic RFA by one surgeon (A.E.S.). Thirty-four (15%) of these patients with 234 neuroendocrine liver metastases underwent 42 ablations. All patients were enrolled in the study in accordance with a Phase II study protocol approved by the Institutional Review Board of the Cleveland Clinic Foundation. Indications for enrollment in this part of the study included the following.

1. Liver metastases from neuroendocrine tumors.
2. Predominance of disease in the liver. However, patients with additional minor extrahepatic disease were not excluded from the study.
3. Enlarging liver lesions, worsening of symptoms, or failure to respond to other treatment modalities.

Informed consent was obtained before the procedure. Laboratory studies consisted of a complete blood count (CBC), renal panel, liver function panel, serum albumin, prothrombin time (PT), partial thromboplastin time (PTT), and tumor markers obtained before ablation, on days 1 and 7, and every 3 months thereafter. The objective tumor response to treatment was assessed with triphasic (noncontrast, arterial, portal-venous) computed tomography (CT) scans obtained 1 week before ablation, 1 week after ablation, and every 3 months thereafter.

Results

Altogether, 25 men and 9 women with 234 liver metastases underwent 42 ablations. The mean ± SEM age was 52 ± 2 years. Primary tumor types included carcinoid tumor in 18 patients, medullary thyroid cancer in 7, secreting islet cell tumor in 5, and nonsecreting islet cell tumor in 4 (Figs. 1, 2). The mean number of lesions treated per patient was 5.6 (range 1–16). Mean ± SEM tumor size was 2.3 ± 0.1 cm (range 0.5–10.0 cm). A total of 53 lesions were located in segment IV of the liver, 52 in segment VII, 37 in segment VI, 36 in segment VIII, 22 in segment II, 17 in segment III, 16 in segment V, and 1 in segment I. There were 20 lesions (9%) in 11 ablations (26%) that were not seen on preoperative CT scans but were visualized by laparoscopic ultrasonography. Altogether, 120 lesions (51%) were ablated using the 3 cm ablation catheters, 113 lesions (49%) with the 5 cm ablation catheter, and 1 lesion with the 7 cm ablation catheter.

Nineteen patients (56%) had significant symptoms before the RFA procedure. These presenting symptoms included flushing (11 patients), diarrhea (10 patients), abdominal pain (5 patients), hypoglycemia (2 patients), and bronchospasm, anxiety, diabetes, skin rash, hypercalcemia, emesis, or back pain (1 patient each). After ablation, complete resolution of the presenting symptoms was observed in 12 patients (63%), significant relief in 3 patients (16%), some relief in 3 patients (16%), and no change in 1 patient. The symptomatic response to RFA lasted for a mean ± SEM of 10.1 ± 1.5 months (range 6–24 months).

At the time of the RFA, 15 patients (44%) had extrahepatic disease including pancreatic primary tumors ($n = 3$), lung metastases ($n = 3$), lung primary tumors ($n = 2$), colonic primary