



Original Contribution

Partial hepatic resections for metastatic neuroendocrine tumors: perioperative outcomes[☆]



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ABSTRACT

Study objective: Partial hepatic resection reduces tumor burden in patients with metastatic neuroendocrine tumors, thereby improving quality and length of life. These procedures can be challenging as well as life-threatening. Our aim was to evaluate our patients' perioperative outcomes and propose a definition for an intraoperative carcinoid crisis relevant to this surgery, given its unique surgical considerations.

Design: Retrospective study.

Setting: Mayo Clinic, Rochester, Minnesota.

Patients: One hundred sixty-nine patients undergoing partial hepatic resection for metastatic neuroendocrine tumors between 1997 and 2015 were identified retrospectively from a surgical database at Mayo Clinic Rochester.

Interventions: None.

Measurements: Intraoperative carcinoid crisis for patients undergoing hepatic resection of neuroendocrine tumors was defined. Patients' medical records were reviewed and data were abstracted describing patient and procedural characteristics and perioperative outcomes.

Main results: There were no documented cases of carcinoid crisis (0.0%, 95% C.I. 0.0% to 2.2%). One patient developed clinical findings of an emerging carcinoid crisis, but was successfully treated with doses of octreotide and findings resolved in < 10 min. Prophylactically 500 µg octreotide was given subcutaneously in 77% (130/169) of patients preoperatively.

Conclusions: There were no documented cases of carcinoid crisis (0.0%, 95% C.I. 0.0% to 2.2%). Adverse events were infrequent.

1. Introduction

Despite rapid advances made in cancer treatment with chemotherapy, immunotherapy and emerging radiologic techniques, partial hepatic resection remains a primary treatment for patients with metastatic neuroendocrine tumors [1–4]. Hepatic resection removes functioning tumor and consequently the systemic release of serotonin and other vasoactive substances, thereby, alleviating the ‘carcinoid

syndrome’ [5]. These operations can improve patients' quality of life and prolong length of life as well [2,3]. Partial hepatic resection can be complex for both surgeons and anesthesia providers. Surgical manipulation of the liver, compression of the vena cava, intraoperative hemorrhage, hepatic inflow vascular clamping, and pharmacological agents can lead to hemodynamic perturbations that can be exacerbated by vasoactive substances released by neuroendocrine tumor metastases. Intraoperatively a life-threatening ‘carcinoid crisis’ can occur with

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Synopsis for Table of Contents: One hundred sixty-nine patients underwent partial hepatic resection for metastatic neuroendocrine tumors at Mayo Clinic Rochester by one surgeon between 1997 and 2015, and their medical records were retrospectively reviewed. Perioperative outcomes, octreotide administration, and a proposed definition of intraoperative carcinoid crisis specifically applicable for patients undergoing partial hepatic resection are described.

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profound flushing, bronchospasm, tachycardia, and widely fluctuating blood pressure [5,6]. The presence of concurrent carcinoid heart disease or other comorbidities can further adversely affect their intraoperative and postoperative outcomes.

Octreotide has improved the quality of life for many patients with metastatic neuroendocrine tumors. Octreotide blocks some somatostatin receptors which prevents hormone release from some neuroendocrine tumors. Efficacy depends on the type and prevalence of somatostatin receptors harbored by tumor cells. Perioperatively, octreotide has been administered to patients with neuroendocrine tumors utilizing varying protocols and with varying results [7–12]. Previously we reported our experience with patients undergoing a variety of liver-directed operations for metastatic carcinoid tumors both before (1983–1987) and after (1988–1996) the availability of short acting (SA) octreotide. In our previous study, only 31 patients (26%) received octreotide preoperatively, and 45 patients (38%) received octreotide intraoperatively [9]. Long-acting release (LAR) octreotide became available after that study [13,14].

Various perioperative short-acting octreotide protocols have been described in an attempt to minimize the occurrence of neuroendocrine-related cardiopulmonary perturbations during anesthesia, broadly termed ‘carcinoid crisis’, and potentially decrease the incidence of postoperative complications [8,10,15,16]. The variation in octreotide protocols likely reflects the specific indication for operation, primary carcinoid stage and extent of distant metastases, and the degree of carcinoid heart disease [17]. For example, a patient’s hemodynamic perturbations will likely be worse during a cardiac valve replacement surgery than during a partial small bowel neuroendocrine tumor resection without metastases and the perioperative octreotide protocol may reflect these differences. Because the carcinoid syndrome and the potential for a carcinoid crisis are most often observed in the setting of hepatic metastases, we focused our current study on patients undergoing partial hepatic resection for metastatic neuroendocrine tumors. We described our current octreotide management protocol for these patients and aimed to determine their perioperative outcomes including a specifically defined “carcinoid crisis.”

2. Materials and methods

Our study was approved by the Mayo Clinic Institutional Review Board (IRB). Our study was a single-center, retrospective study using the surgical database at Mayo Clinic Rochester that contains the names and clinic numbers of all patients who have undergone a partial hepatic resection for metastatic neuroendocrine tumors by one surgeon (DN). All patients who consented and who underwent a partial hepatic resection inclusive of right or left lobectomy, extended lobectomy, segmental resection, and/or subsegmental (wedge) resection for metastatic neuroendocrine tumors at Mayo Clinic Rochester between January 1, 1997 and June 30, 2015 were included in our study.

Patients’ medical records were reviewed according to a prepared data abstraction form. Categories of data abstracted included demographic data, comorbid disease, intraoperative data, and perioperative outcomes, generally classified as occurring during the intraoperative and postoperative periods during hospitalization and within 30 days of discharge from the index hospitalization. Data abstraction was performed by coinvestigators. We used an extensive, well-accepted set of definitions for each data entry.

We defined intraoperative carcinoid crisis in patients undergoing partial hepatic resection as the sudden or abrupt onset of at least two of the following: flushing or urticaria that is not explained by an allergic reaction, bronchospasm or bronchodilator administration, hypotension (systolic blood pressure < 80 mm Hg > 10 min and treated with pressors) not explained by volume status or hemorrhage, dysrhythmia not explained by volume status or hemorrhage, tachycardia of 120 bpm or greater (Fig. 1). The definition of ‘carcinoid crisis’ in patients undergoing partial hepatic resection was established prior to data

abstraction and analysis. The creation of this new definition arose with the specific intent of not misrepresenting expected hemodynamic perturbations commonly observed in hepatic surgery as a “carcinoid crisis.” We also sought to account for other confounders of hemodynamic changes such as intraoperative hemorrhage, hepatic vascular inflow occlusion, and CVP regulation that could affect components of the carcinoid crisis. Components of the carcinoid crisis were abstracted from anesthetic and operative records.

2.1. Statistical analysis

Data are summarized using median (25th, 75th) for continuous variables and frequency counts and percentages for categorical variables. The percentage of patients experiencing intraoperative events and postoperative complications are summarized using point estimates and exact binomial confidence intervals. Due to the low number of intraoperative and postoperative events observed, meaningful analyses to assess characteristics potentially associated with these events could not be performed.

3. Results

Patient demographics as well as patient and procedural characteristics of our research are shown below (Table 1). There were 169 total patients in the study. Discrepancy of patients and procedures (196) reflects the fact that some patients had multiple resections of the liver. The location of the primary carcinoid occurred predominantly in the small bowel, which is consistent with classical carcinoid tumors; other sites of origin were lungs and other areas of the digestive tract. Tumor markers, 5-HIAA and chromogranin A (CgA) were obtained at the discretion of the primary care physician [15]. Urinary 5-HIAA and serum CgA levels were available for 94 patients and 45 patients respectively. Operations undertaken included small bowel resection, hepatic arterial ligation, metastatic ablation, major or minor hepatic resection, cholecystectomy or any combination.

One hundred and sixty-nine patients underwent partial hepatic resection for metastatic neuroendocrine tumors during the study period. The median age at the time of surgery was 60 years (IQR, 51–68 years). The percentages of male and female patients were similar (49.1 and 50.9%, respectively). The average duration of anesthesia was $4:9 \pm 1.3$ h.

Long-acting release (LAR) octreotide usage was used in only 28% (48/169) of patients. The duration of monthly injections of LAR octreotide varied but was initiated preoperatively to control significant symptoms of the carcinoid syndrome. Regardless of monthly injections of LAR octreotide, 77% (130/169) of patients received 500 µg SA octreotide preoperatively subcutaneously. The use of SA and LAR octreotide changed over the duration of the study. After the clinical efficacy of LAR octreotide was established, it was employed to control the carcinoid syndrome before elective hepatic resection. SA octreotide was used on call to operation preoperatively in patients in whom the carcinoid syndrome was inadequately controlled with LAR octreotide or before LAR octreotide became clinically available. Currently LAR octreotide treatment is initiated to control carcinoid syndrome from hepatic metastases preoperatively. SA octreotide is used preoperatively or intraoperatively adjunctively in patients with incompletely controlled carcinoid syndrome. Intraoperatively, 23% (39/169) of patients received additional intravenous SA octreotide, with a median total dose of 500 µg (IQR 250, 650).

Intraoperative complications are listed below (Table 2). Flushing was noted in one patient but did not meet additional criteria for carcinoid crisis. One patient developed atrial fibrillation with rapid ventricular response intraoperatively and was treated with esmolol. Hypotension, defined as SBP < 80 mm Hg for > 10 min and treated with a vasopressor, occurred in 5.3% of patients. The majority of these hypotensive episodes correlated with concurrent opioid administration or

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