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Metastasectomy of neuroendocrine tumors in patients with multiple endocrine neoplasia type 1

Benzon M. Dy, M.D.[a], Florencia G. Que, M.D.[a], Geoffrey B. Thompson, M.D.[a], William F. Young, M.D.[b], Phillip Rowse, M.D.[a], Veljko Strajina, M.D.[a], Melanie L. Richards, M.D.[a,*]

[a]*Department of Surgery;* [b]*Department of Endocrinology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*

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Abstract

BACKGROUND: Neuroendocrine (NE) tumors commonly afflict patients with multiple endocrine neoplasia type 1 (MEN1). It is thought that patients with MEN1 have improved survival compared with individuals with analogous lesions. The role of metastasectomy of NE tumors in MEN1 patients is not clearly defined.

METHODS: A review of MEN1 patients undergoing surgery for NE tumors from 1994 to 2010 at a single tertiary care center was performed. Tumor function, the extent of metastasis, R0 resection, and survival were analyzed.

RESULTS: We identified 30 patients who underwent resection including synchronous and metachronous metastasectomy. Synchronous metastases were identified in 19 patients (63%), whereas 11 (37%) had metachronous disease. R0 resection was achieved in 93% of patients. Estimated 10-year survival is 86.4% (95% confidence interval, 60% to 100%) with no factors predictive of overall survival. The disease-free interval at 1, 5, and 10 years was 89%, 50%, and 19%, respectively, with recurrence occurring at a median of 5.4 years (95% confidence interval, 77.7% to 100%). Synchronous metastasis ($P = .0072$; hazard ratio [HR], 3.4) and nonfunctioning tumors ($P = .014$; HR, 3.3) were more likely to recur, whereas age ($P = .09$; HR, 1.5), gender ($P = .49$; HR, 1.3), and the site of metastasis ($P = .81$; HR, 1.1) did not influence recurrence.

DISCUSSION: Patients with MEN1 benefit from resection of metastatic NE disease. Despite a high recurrence rate, survival and disease-free interval is favorable vs patients without MEN1.

Multiple endocrine neoplasia type 1 (MEN1) is an inherited endocrinopathy characterized by a predisposition for tumor development in various hormone-producing tissues. The combined occurrence of tumors in the anterior pituitary gland is found in 15% to 50%, parathyroid glands in 80% to 100%, and pancreas in 30% to 80% of MEN1 individuals.[1,2] The prevalence of MEN1 is estimated at 1 to

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* Corresponding author. Tel.: +1-507-284-2511; fax: +1-507-284-1693.

E-mail address: richards.melanie@mayo.edu

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10 per 100, 000 inhabitants.[3] Transmission occurs with high penetrance as the inherited tumor suppressor gene *MEN1*, located on chromosome 11q13, is autosomal dominant. Clinical manifestations of the syndrome are variable as the cell lineages affected can either be hormonally active or inactive.[4–6] In addition, other enterochromaffin-like neoplasms and carcinoids in MEN1 patients have been identified in several foregut structures including the thymus, bronchopulmonary region, stomach, and even the adrenal cortex.[7,8] Although multiglandular primary hyperparathyroidism remains the hallmark endocrinopathy of MEN1 with nearly 100% penetrance by the age of 50 years, the most common source of MEN1-related mortality is metastatic disease from neuroendocrine (NE) tumors originating from the duodenum and pancreas.[9–11]

Pancreaticoduodenal NE tumors (PNETs) generally have an earlier age of onset in patients with MEN1 as compared with non-MEN1 individuals. They also frequently occur multifocally throughout the pancreas and duodenum and possess an inherent risk of malignant transformation.[12] The operative role in treatment of PNETs remains controversial. Ongoing debate regarding PNET resection includes the extent of primary disease at the time of diagnosis including the presence or absence of metastasis, the timing of resection, and the management of small nonfunctioning asymptomatic lesions.[13] Although surgical resection focuses on reducing symptoms and preventing the development of malignancy in MEN1, the operative approach including the extent of resection remains controversial. This is especially evident as occult metastatic disease appears more prevalent in MEN1 patients with PNETs than in patients with sporadic endocrine tumors.[14] However, the course of disease in MEN1 patients with metastatic disease, as compared with non-MEN1, is regarded to be more indolent with most patients presenting with nonfunctioning islet cell tumors.[10,15,16]

Recommended treatment options for both primary and metastatic disease have ranged widely from observation to aggressive surgical resection, with the heterogeneous subtypes increasing the complexity of treatment decisions.[16,17] The guidelines for surgical treatment have evolved with time and differ among groups of experts.[18] Treatment for patients with MEN1-related PNETs has been similar to the treatment of related tumors in non-MEN1 patients, but the recurrence-free and overall survival (OS) may be altered secondary to larger tumors, more aggressive disease, and the presence of metastases.[14] It is well known that recurrence rates are high for PNET resection (20% to 60%) in these patients, and size criteria is often not a reliable indicator for resection. It is unknown in this cohort of patients whether metastasis at the time of resection indicates more aggressive and proliferative NE tumor biology that may consequently impact OS.

In this study, we examined disease-free interval, tumor recurrence, and survival outcomes in patients with MEN1 presenting with metastatic disease both locoregionally and distant occurring either synchronously or metachronously with resection of the primary tumor.

Methods

We examined patients undergoing surgical intervention for duodenal and pancreatic NE tumors with a diagnosis of MEN1 from January 1, 1994 to December 31, 2010. Patients who underwent surgical resection of their primary disease and metastasectomy of distant disease were examined for both disease-free interval and OS. Disease-free interval calculated from the time of resection of tumor in patients achieving an R0 resection to the time of recurrence detected biochemically or on imaging. OS was calculated from the time of resection of index tumor to the time of last follow-up or death. Metastasectomy was defined as resection of disease separate from the site of primary disease (pancreas and/or duodenum) including resection of lymph nodes and liver parenchyma involved with NE tumor.

Pathology data were reviewed and patients were included in the examination if they presented with enteric or pancreatic NE tumors confirmed by histologic examination and the presence of gross metastatic disease in either regional lymph nodes, liver parenchyma, or both.

Each patient underwent an evaluation by a comprehensive medical and surgical team including oncologists, endocrinologists, and surgeons. Follow-up was performed using biochemical analysis of appropriate tumor markers along with specific assays appropriate to individual patient's known disease. In addition, imaging studies, primarily involving endoscopic ultrasonography, pancreatic protocol multiphasic computed tomography scan, and/or somatostatin receptor scintigraphy (SRS; 111In-labeled diethylenetriaminopentaacetic [DTPA]-D-Phe1-octreotide), when warranted, were used to detect and localize recurrent disease every 6 to 12 months. Institutional review board approval was obtained for this study.

Statistical analysis was performed using SAS software (version 9.2; SAS Inc, Cary, NC). Survival curves were performed using the Kaplan-Meier method. The Wilcox rank sum test or the Fisher exact test was used for comparison of nominal data for baseline characteristics. Ordinal data were compared with the Spearman rank order correlation coefficient.

Results

We identified 30 patients with MEN1 who underwent resection of their primary tumor and either synchronous or metachronous metastasectomy at Mayo Clinic, Rochester from 1994 to 2010. The diagnosis of MEN I was performed by either the presence of 2 of 3 classic manifestations including PNET, primary hyperparathyroidism, and pituitary adenoma or mutation of the *MEN1* tumor suppressor gene after genetic assays became readily available in 1997.

Median age was 47 years (range, 20 to 64 years) at the time of surgery, with 18 men and 12 women. Median follow-up was 6.5 years (range, 3 months to 16 years). There were no perioperative deaths.