

Long-Term Survival with Long-Acting Somatostatin Analogues Plus Aggressive Cytoreductive Surgery in Patients with Metastatic Neuroendocrine Carcinoma

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BACKGROUND: Long-acting somatostatin analogues (S-LAR) improve recurrence-free survival in patients with metastatic neuroendocrine tumor (NET) from gastrointestinal (GI) primary, but their impact on overall survival when combined with aggressive cytoreductive surgery is unclear.

STUDY DESIGN: We reviewed our institutional cancer database to identify patients who underwent cytoreductive surgery for metastatic NET from GI primary between December 1997 and June 2013. Additionally, a cohort selected from 3,384 metastatic neuroendocrine cases in the SEER-Medicare database (January 2003 to December 2009) was used to verify and expand on our results.

RESULTS: Most of the 49 patients from our institution had primary lesions in the small intestine (22 of 49 [44.9%]) or pancreas (14 of 49 [28.6%]); 37 patients (75.5%) had metastatic disease at initial diagnosis. These patients underwent 1 (32 of 49 [65.3%]), 2 (11 of 49 [22.4%]), or at least 3 (6 of 49 [12.3%]) surgical procedures; 33 patients (67.3%) underwent resection plus ablation, 19 (38.7%) underwent major hepatectomy, and 34 (69.4%) received S-LAR (29.4% administered preoperatively). Median follow-up was 112 months. Rates of 1-, 5-, 10-, and 15-year disease-specific survival (DSS) were 94%, 78%, 64%, and 31%, respectively, in the 34 patients undergoing aggressive cytoreductive surgery plus S-LAR. Of the SEER-Medicare population, 1,741 patients met inclusion criteria. The DSS for the 104 patients treated with combination therapy was 68.3% at 5 years and 60.6% at 10 years, as compared with 54.7% and 51.8%, respectively, for the 202 patients receiving surgery alone, and 50.0% and 36.0%, respectively, for the 342 patients receiving S-LAR alone ($p < 0.0001$). The group receiving neither treatment ($n = 1,093$) had 5-year and 10-year DSS of 34.3% and 26.3%, respectively.

CONCLUSIONS: Long-acting somatostatin analogues combined with aggressive cytoreductive surgery improves the long-term survival of select patients with metastatic NET from GI primary. (J Am Coll Surg 2015;221:26–36. © 2015 by the American College of Surgeons)

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The incidence of neuroendocrine or carcinoid tumors has increased markedly over several decades, likely due to improvements in diagnosis and surveillance.¹ Data from the SEER registry demonstrates a similar trend in metastatic cases, with a greater than 8-fold increased incidence since 1974.² Although these tumors can arise in almost every organ, neuroendocrine tumors (NET) from a gastrointestinal (GI) primary have a greater likelihood of metastatic disease at presentation.³ Unlike other types of disseminated cancer, metastatic NET from GI primary is often asymptomatic due to its indolent nature. When disease spreads to the liver, the most common site of metastases, there can be significant and debilitating morbidity

Abbreviations and Acronyms

DSS	= disease-specific survival
GI	= gastrointestinal
HR	= hazard ratio
NET	= neuroendocrine tumor
OS	= overall survival
S-LAR	= long-acting somatostatin analogue

(carcinoid syndrome). Even though improved options for the treatment of metastatic NET from GI primary have allowed long-term survival, there is still much controversy and lack of standardization.

Resection and/or ablation for cytoreduction of metastatic NET from GI primary have been associated with a survival benefit in several studies.⁴⁻⁶ In one of the largest multi-institutional series to date, Mayo and colleagues⁷ demonstrated 5- and 10-year survivals of 74% and 51%, respectively, in 339 patients undergoing liver-directed surgery for metastatic neuroendocrine tumors. Although most patients (94%) had recurrence by 5 years after surgery, median survival was 125 months, and several patients underwent multiple procedures. Taner and associates⁸ also used surgical resection plus radiofrequency ablation to increase the rate of complete cytoreduction; overall survivals were 80% and 59% at 5 and 10 years, respectively, and the need for ablation was not associated with inferior survival.

Recent studies evaluating the role of long-acting somatostatin analogues (S-LAR) have been comprehensively summarized in the literature.⁹ Although there appear to be significant antiproliferative effects, no clear survival benefit has been demonstrated to date. Furthermore, there are few data on the combination of cytoreductive surgery and S-LAR in the treatment of metastatic NET from GI primary. In 2001, we reported our initial experience in 10 patients who received adjuvant S-LAR, with encouraging results, but limited follow-up (median 26 months).¹⁰ An analysis of our institutional experience, with an approximate 10-year median follow-up, and concurrent assessment of the SEER-Medicare population, is the first to evaluate the long-term benefits of combination therapy in patients with metastatic NET from GI primary.

METHODS**Institutional cohort**

We identified adult patients with metastatic NET from GI primary seen at the John Wayne Cancer Institute (JWCI) at Providence Saint John's Health Center between December 1, 1997 and June 1, 2013. Only surgically resected patients with pathology-proven

Table 1. Patient, Tumor, and Treatment Information for the Entire Study Population

Variables	Institutional cohort		SEER-Medicare cohort	
	n	%	n	%
Age at diagnosis, y				
≤64	37	75.5	0	0
65–69	6	12.2	463	26.6
70–74	6	12.2	478	27.5
75–79	0	0	385	22.1
80+	0	0	415	23.8
Sex				
Male	25	51	939	53.9
Female	24	49	802	46.1
Race				
White	42	85.7	1,452	83.4
Black	1	2.0	184	10.6
Other	6	12.3	105	6.0
Primary tumor location				
Upper GI	22	44.9	740	42.5
Colon/rectum	7	14.3	467	26.8
Pancreas	14	28.6	534	30.7
No primary/unknown	6	12.3	0	0
Primary tumor grade				
Well differentiated	22	44.9	246	14.1
Moderately differentiated	5	10.2	119	6.8
Poorly differentiated	5	10.2	307	17.6
Undifferentiated	0	0	73	4.2
Unknown	17	34.7	996	57.2
Primary tumor size, cm				
<1	1	2.0	29	1.7
1–2	5	10.2	232	13.3
>2	30	61.2	736	42.3
No primary/unknown	13	26.5	744	42.7
Nodal involvement				
Positive	28	57.1	620	35.6
Negative	2	4.1	125	6.7
Unknown	19	38.8	1,052	57.7
Cytoreductive surgery				
Yes	49	100	306	17.6
No	0	0	1,435	82.4
Sandostatin-LAR				
Yes	34	69.4	446	25.6
No	15	30.6	1,295	74.4

GI, gastrointestinal; Sandostatin-LAR, long-acting somatostatin analogue.

neuroendocrine histology of the gastrointestinal tract or pancreas were included. Patient (sex, age), tumor (stage, grade, location), and procedure-specific (number, type, approach) variables were also assessed; lack of complete information for these variables was not an exclusion

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