The American Journal of Surgery (2013) 205, 642-646

The American Journal of Surgery®

Clinical Surgery

Metastatic carcinoid tumors—are we making the cut?

Kathryn E. Coan, M.D., Richard J. Gray, M.D., Richard T. Schlinkert, M.D., Barbara A. Pockaj, M.D., Nabil Wasif, M.D.*

Department of Surgery, Mayo Clinic, 5777 E Mayo Boulevard, Phoenix, AZ 85054, USA

KEYWORDS:
Surgery;
Metastases;
Carcinoid tumors

Abstract

BACKGROUND: Although controversial, surgical resection for metastatic carcinoid tumors (MCTs) can potentially prolong survival.

METHODS: Patients with MCTs were identified from the Surveillance, Epidemiology and End Results database. Patients undergoing surgery were compared to unresected patients.

RESULTS: Surgery was performed in 33% of patients. Predictors of surgery included age <50 years (odds ratio [OR], 2.4), low grade (OR, 3.1), and the appendix (OR, 36.2) or small intestine (OR, 27.2) as the primary site. Predictors of adverse survival included high grade (hazard ratio, 2.4) and no surgery (hazard ratio, 2.5) or surgery on only primary or distant disease (hazard ratio, 1.5) compared with surgery for both. Survival at 5 years was 5% with no surgery, 28% with surgery on either site, and 46% with surgery at both sites ($P < .001$).

CONCLUSIONS: Surgery for MCTs is more common in younger patients, those with low-grade disease, and those with small bowel or appendiceal primary tumors. Although selection bias cannot be excluded, these data lend support to "debulking" for MCT.

© 2013 Elsevier Inc. All rights reserved.

Although carcinoid tumors are the most common neuroendocrine tumors, they are still considered rare. However, recent studies have indicated that the prevalence is increasing from 1 to 2 per 100,000 to 5.25 per 100,000.[1] In general, these tumors have an indolent course but may become severely debilitating, either because of hormonal hypersecretion, resulting in the classic carcinoid syndrome of cutaneous flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease,[2,3] or secondary to tumor bulk resulting in bowel obstruction and/or mesenteric vascular involvement, producing unremitting abdominal pain.[4]

Metastatic disease in patients with carcinoid tumors is generally incurable and requires a multidisciplinary approach focused on symptom control.[5] One of the management options is surgical "debulking" of disease sites without achieving complete removal of all tumor. Although a source of controversy, there are data to support improved quality of life[4–11] and the potential to prolong survival in select patients with this approach.[4–6,8,9,11–14]

Multiple studies have highlighted improved survival and a quality-of-life benefit from hepatic resection of metastatic neuroendocrine tumors[6,9,11,14–17]; the largest study from the Mayo Clinic demonstrated control of carcinoid symptoms in 96% of patients and overall survival of 61% compared with historical control of 30% to 40%.[9] Boudreaux et al[8] examined a series of 82 patients who underwent debulking, with 91.5% experiencing symptom reduction and median survival of 51.2 months. Gulec et al[4] demonstrated symptom relief in 83% of patients.

Because of the rarity of the disease, it is unlikely that a randomized control trial will be conducted to assess the impact of surgical resection in metastatic carcinoid tumors. Current clinical recommendations are based on small,

The authors declare no conflicts of interest.

* Corresponding author. Tel.: +1-480-342-2849; fax: +1-480-342-2866.
E-mail address: wasif.nabil@mayo.edu

Manuscript received March 30, 2012

0002-9610/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2012.05.036

specialized single-institution retrospective series. Consequently, our goal for this study was to use data from a national cancer registry to study the impact of surgical resection in the largest sample size of patients with metastatic carcinoid tumors reported in the literature to date. This also allows analysis of "real-world" use across multiple institutions in both community and academic settings.

Methods

The Surveillance, Epidemiology and End Results database

The National Cancer Institute's SEER tumor registry was used for this study. SEER contains >3 million cases from 17 geographic sites, covering approximately 26% of the United States population. The database is designed to reflect the overall characteristics of the US population and is regarded as a model population-based cancer database. Quality control is an important component of the SEER program; the current standard for accuracy of data is an error rate of <5%.[18] Registries that are part of SEER routinely collect data on patient demographics (eg, age, sex), tumor characteristics (eg, primary site, stage, grade), surgical intervention (eg, biopsy only, cancer-directed surgery of the primary site, surgery of distant sites), vital status, and survival. The 2011 update was used for this study, providing information from 1975 to 2008.[19] As a population-based study with no patient identifiers involved, our study was exempt from institutional research board review.

Case selection

Using the International Classification of Diseases, Ninth Revision, codes 8240 to 8249, all patients with carcinoid tumors diagnosed between 1998 and 2008 were identified in SEER (n = 42,482). Patients with stage IV disease were identified by using extent-of-disease code 85 (1988–2003) and American Joint Committee on Cancer M stage of M1 (2004 onward). This left a cohort of 6,660 patients. Patients with duplicate records, no histologic confirmation of the diagnosis, and autopsy-only data were removed. Finally, only patients with single primary tumors at the following sites were included in the study population: bronchial, stomach, small intestine, pancreas, colon, appendix, and rectum, for a final study population of 4,853.

Statistical analysis

Continuous variables were analyzed using independent-samples *t* tests and categorical variables using chi-square analyses. Predictors of surgical resection were identified using multivariate logistic regression analysis. Variables included were age, year of diagnosis, grade, primary site, and history of radiation. Predictors for survival were identified by Cox regression analysis using proportional-hazards modeling. Variables included were age, year of diagnosis, grade, history of radiation, history of surgery, and site of primary tumor. Kaplan-Meier curves and log-rank tests were used to determine differences in overall survival. All tests were 2 tailed, with significance levels set at $P < .05$ and a confidence interval of 95%. Statistical analysis was performed using SPSS version 16.0 (SPSS, Inc, Chicago, IL).

Results

Demographics

Our study population comprised 4,853 patients with metastatic carcinoid tumors. As outlined in Table 1, the median age was 65 years, and 52% were men. The lung

Table 1 Demographics, primary tumor characteristics, and predictors of undergoing surgery (n = 4,853)

Characteristic	Number of patients	Number undergoing surgical resection	*P*
Sex			
Male	2,532 (52%)		
Female	2,532 (48%)		
Age (y)			
Median	65		
<50	790 (16%)	351 (45%)	<.001
51–65	1,668 (34%)	559 (34%)	
66–80	1,934 (40%)	547 (29%)	
>80	461 (10%)	120 (26%)	
Race			
White	4,112 (85%)	1,338 (33%)	.37
Black	488 (10%)	166 (34%)	
Other	253 (5%)	73 (29%)	
Primary site			
Appendix	351 (7%)	296 (85%)	<.001
Colon	287 (6%)	183 (64%)	
Lung	2,386 (49%)	323 (14%)	
Pancreas	925 (19%)	172 (19%)	
Rectum	118 (2%)	47 (33%)	
Small intestine	635 (13%)	505 (80%)	
Stomach	151 (3%)	51 (44%)	
Year			
1998–2000	1,008 (21%)	369 (37%)	<.001
2001–2004	1,896 (39%)	696 (37%)	
2005–2008	1,949 (40%)	512 (26%)	
Grade			
Low	529 (11%)	300 (58%)	<.001
High	1,398 (29%)	433 (31%)	
Unknown	2,926 (60%)	844 (29%)	
Radiation			
Yes	1,109 (23%)	218 (20%)	<.001
No	3,653 (75%)	1,324 (37%)	
Unknown	91 (2%)	35 (40.7%)	

Table 2 Primary tumor site and surgical intervention

Surgery Site	Surgery on primary site	Surgery on distant site	Surgery on both sites	No surgery
Appendix	210 (60%)	2 (1%)	84 (24%)	53 (15%)
Colon	140 (49%)	9 (3%)	34 (12%)	102 (36%)
Lung	64 (3%)	231 (10%)	28 (1%)	2,050 (86%)
Pancreas	72 (8%)	35 (4%)	65 (7%)	742 (81%)
Rectum	27 (19%)	8 (5%)	12 (8%)	98 (68%)
Small intestine	355 (56%)	8 (1%)	142 (23%)	123 (20%)
Stomach	42 (36%)	2 (2%)	7 (6%)	66 (56%)

was the most common primary site (49%), followed by the pancreas and small bowel at 19% and 13%, respectively. Surgery was performed in 33% of patients: 19% had surgery at the primary site, 6% had surgery on distant disease, and 8% had resection of both.

Predictors of undergoing surgery

On univariate analysis, patients who underwent any surgical resection were more likely to be <50 years of age, to be diagnosed from 1998 to 2000, to have low-grade tumors, to have appendiceal or small bowel primary tumors, and to receive no radiation (Table 1). A breakdown of surgical resection for the primary site only, distant site only, or both by site of the primary tumor is shown in Table 2. On multivariate analysis, small bowel and appendiceal primary (vs lung) tumors, age <50 years (vs >80 years), low tumor grade (vs unknown), and no radiation (vs radiation) were all predictive of surgical resection (Table 3).

Predictors of adverse survival

On multivariate analysis, predictors of adverse survival included age >50 years (vs <50 years), high-grade disease (vs low-grade disease), primary site other than the small bowel (vs small bowel), and lack of surgical therapy (vs surgery on both sites) (Table 4). Patients who underwent no surgery or surgery on only primary or distant disease had hazard ratios of 2.5 (95% confidence interval, 2.1 to 3.0) and 1.5 (95% confidence interval, 1.3 to 1.8) compared with those who underwent surgery on both sites (hazard ratio, 1). Survival for patients undergoing no surgery was 5% at 5 years compared with 28% for patients undergoing surgery on either site and 46% for patients undergoing surgery at both sites ($P < .001$; Fig. 1).

Comments

In this study, we investigated the use and outcomes of surgical resection in patients with metastatic carcinoid tumors across the United States using data from the SEER database. Surgery was performed in 33% of patients: 19% at the primary site only, 6% on distant disease only, and 8% at both the primary and distant sites. Survival at 5 years was 46% when surgery was performed at both sites, compared with 28% for surgery at either site and 5% for no surgery. Our data lend support to surgical intervention improving outcomes for patients with metastatic carcinoid tumors. Even without being able to separate those patients who underwent resection of all disease from those who underwent debulking surgery, the entire cohort of surgical patients did better.

The 79% to 84% rates of resection of primary midgut carcinoid tumors in this study appear comparable with those reported from prior studies. Soreide et al[13] reported that among 65 patients with metastatic midgut carcinoid tumors, 88% underwent resection of the primary tumor and 41% underwent resection of distant disease. Hellman et al[20] evaluated 314

Table 3 Factors predictive of undergoing any surgery on multivariate analysis

Characteristic	OR	95% CI
Age (y)		
>80	1.00	
<50	2.39	1.73–3.29
51–65	1.69	1.26–2.27
66–80	1.37	1.03–1.84
Year		
2005–2008	1.00	
1998–2000	1.17	.95–1.44
2001–2004	1.22	1.03–1.46
Grade		
Unknown	1.00	
Low	3.09	2.43–3.94
High	1.28	1.07–1.54
Site		
Lung	1.00	
Pancreas	1.29	1.02–1.62
Small intestine	27.20	21.01–35.21
Appendix	36.19	25.97–50.45
Colon	12.34	9.20–16.53
Stomach	4.29	2.88–6.40
Rectum	3.05	2.07–4.47
Radiation		
Yes	1.00	
No	1.35	1.10–1.66
Unknown	2.50	1.48–4.22

CI = confidence interval; OR = odds ratio.

Table 4 Predictors of adverse survival on multivariate analysis

Characteristic	HR	95% CI
Age (y)		
<50	1.00	
51–65	1.24	1.12–1.38
66–80	1.66	1.50–1.84
>81	2.20	1.93–2.52
Year		
1998–2000	1.00	
2001–2004	.97	.89–1.05
2005–2008	1.04	.96–1.14
Grade		
Low	1.00	
High	2.39	2.07–2.75
Unknown	1.70	1.49–1.94
Radiation		
No	1.00	
Yes	.93	.86–1.01
Unknown	.94	.74–1.19
Surgery		
Both primary and distant	1.00	
No surgery	2.53	2.14–2.99
Any surgery	1.51	1.28–1.78
Site		
Small intestine	1.00	
Pancreas	2.06	1.77–2.39
Lung	3.46	3.00–4.00
Appendix	2.42	2.04–2.87
Colon	3.87	3.25–4.60
Stomach	2.72	2.15–3.45
Rectum	3.26	2.63–4.04

The authors conducted a retrospective review of metastatic carcinoid tumors and surgical management, analyzing the current use of surgery, factors predictive of surgery, and the potential impact on survival.

CI = confidence interval; HR = hazard ratio.

patients with midgut carcinoid tumors and reported primary resection among 80% of patients. There is more variability seen in resection of distant disease. In our analysis, distant disease was resected in 26% of patients

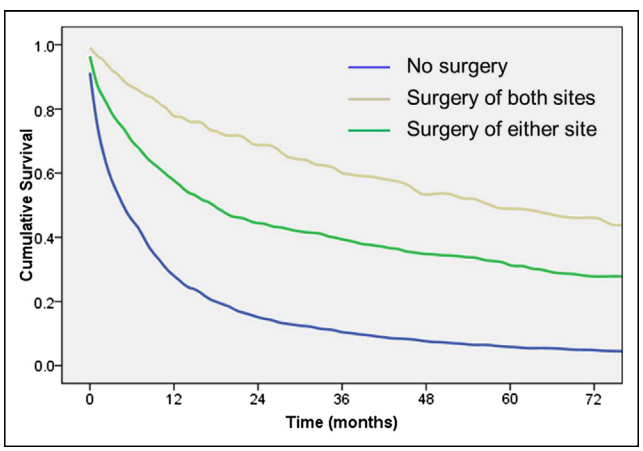


Figure 1 Overall survival in relation to surgical resection.

with appendiceal primary tumors and 24% of patients with small bowel primary tumors. This may be secondary to more aggressive debulking and debulking in the presence of liver metastases at these specialized referral centers.

In our study, predictors of surgery on multivariate analysis indicated that patients who are younger and have lower tumor grades are more likely to undergo surgery. This is likely because younger patients have fewer medical comorbidities and are overall better surgical candidates. Lower grade tumors' being associated with surgical therapy may indicate surgeon bias for patients with more "indolent" disease who are likely to receive long-term benefit from surgical resection. Histologic grade has been previously associated with survival in carcinoid tumors, with reported 5-year survival of 17% for poorly differentiated tumors compared with 70% for well-differentiated tumors.[15] In a previous SEER database review, patients with grade 1 and grade 2 neuroendocrine tumors had median survival of 124 and 64 months, respectively whereas patients with grade 3 or 4 tumors had median survival of 10 months ($P < .001$).[1] The primary site played a significant role in the rate of resection, with appendiceal and small bowel tumors undergoing surgical intervention much more commonly than those at other sites. This is likely because of relatively low morbidity and ease of operation for resection of these tumors compared with lung or pancreas primary tumors.

The most common metastatic site for all carcinoid tumors is the liver.[21] Hepatic resection has shown clinical benefit, but its feasibility may be limited. Curative surgical resection of hepatic metastases is reported to be feasible in <10% of patients and palliative resection (using the 90% criterion) in only 10% to 15% of patients.[22] We were unable to quantify the extent of metastatic disease or the specific sites of metastases from the SEER database. It is possible that the extent of disease in the liver may have led to an underlying survival advantage separate from the effect of surgical therapy itself and hence a selection bias that we are unable to account for. Furthermore, we are unable to assess the intent of surgical resection (ie, for cure or palliation).

Lack of any surgical intervention was associated with worse survival outcome on multivariate analysis. Previously reported 5-year survival rates in patients with metastatic disease range from 18% to 30%,[4,8,17,23] but in more contemporary series, patients treated with surgical therapy have survival ranging from 50% to 80%.[8,15,16,24] Soreide et al[13] demonstrated symptom palliation and prolonged survival in patients who underwent resection of midgut primary carcinoid tumors and mesenteric metastases, with survival of 139 versus 69 months when abdominal debulking surgery was not performed. Hellman et al[20] demonstrated that resection of the primary tumor reduced symptoms and improved survival, even in the presence of inoperable mesenteric lymph node and liver metastases. The data from this study add credence to such reports

suggesting that surgical intervention is beneficial for patients with metastatic carcinoid tumors. The fact that removal of both the primary and distant sites results in the greatest survival benefit suggests that, if possible, an aggressive surgical strategy should be pursued.

The use of a population-based database does provide us with a large sample size, but the trade-off is a loss of clinical detail. Many factors go into clinical decision making, and it is unlikely that any database is truly able to capture the breadth of clinical variation. We also acknowledge that a causal relationship between surgical resection in patients with metastatic carcinoid tumors and survival cannot be inferred from an observational study and that selection bias cannot be excluded as an explanation for our results. A randomized control trial is needed to definitively establish this relationship but is unlikely to be conducted, because of the rarity of these tumors. Either prospective multicenter data or case-control studies may be needed for further research.

In conclusion, we used a national cancer registry to show that surgical resection of either the primary tumor or distant metastases in patients with metastatic carcinoid tumors is associated with improved survival, with the best survival seen in patients undergoing surgery at both sites. Improved survival was also seen in patients <50 years of age, those with low-grade disease, and those with small bowel primary tumors. To our knowledge, this is the first population-based study of the role of surgery in patients with metastatic carcinoid tumors, with the largest sample size reported to date. On the basis of the data we report, we believe that aggressive surgical resection should be considered in patients with metastatic carcinoid tumors, especially in younger patients with low-grade tumors.

References

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
2. Woodside KJ, Townsend Jr CM, Mark Evers B. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg 2004;8: 742–56.
3. Akerstrom G, Hellman P. Surgical aspects of neuroendocrine tumours. Eur J Cancer 2009;45(suppl):237–50.
4. Gulec SA, Mountcastle TS, Frey D, et al. Cytoreductive surgery in patients with advanced-stage carcinoid tumors. Am Surg 2002;68: 667–71.
5. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas 2010;39:753–66.
6. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995;169:36–42.
7. Makridis C, Rastad J, Oberg K, et al. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. World J Surg 1996;20:900–6.
8. Boudreaux JP, Putty B, Frey DJ, et al. Surgical treatment of advanced-stage carcinoid tumors: lessons learned. Ann Surg 2005;241:839–45.
9. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197:29–37.
10. Norton JA. Surgical management of carcinoid tumors: role of debulking and surgery for patients with advanced disease. Digestion 1994;55-(suppl):98–103.
11. Chamberlain RS, Canes D, Brown KT, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000; 190:432–45.
12. Wangberg B, Westberg G, Tylen U, et al. Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. World J Surg 1996;20:892–9.
13. Soreide O, Berstad T, Bakka A, et al. Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. Surgery 1992; 111:48–54.
14. Yao KA, Talamonti MS, Nemcek A, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 2001;130:677–82.
15. Sutcliffe R, Maguire D, Ramage J, et al. Management of neuroendocrine liver metastases. Am J Surg 2004;187:39–46.
16. Norton JA, Warren RS, Kelly MG, et al. Aggressive surgery for metastatic liver neuroendocrine tumors. Surgery 2003;134:1057–63.
17. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990;108:1091–6.
18. Havener LE. Standards for cancer registries volume III: standards for completeness, quality, analysis, and management of data. Springfield, IL: North American Association of Central Cancer Registries; 2004.
19. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review 1975–2008. Bethesda, MD: National Cancer Institute; 2011.
20. Hellman P, Lundstrom T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002;26:991–7.
21. Phan AT, Oberg K, Choi J, et al. NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the thorax (includes lung and thymus). Pancreas 2002;39:784–98.
22. Knigge U, Hansen CP, Stadil F. Interventional treatment of neuroendocrine liver metastases. Surgeon 2008;6:232–9.
23. Dousset B, Saint-Marc O, Pitre J, et al. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. World J Surg 1996;20:908–14.
24. O'Toole D, Maire F, Ruszniewski P. Ablative therapies for liver metastases of digestive endocrine tumours. Endocr Relat Cancer 2003;10: 463–8.