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Tumor Size and Depth Predict Rate of Lymph Node Metastasis and Utilization of Lymph Node Sampling in Surgically Managed Gastric Carcinoids

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ABSTRACT

Background. Radical resection with regional lymphadenectomy is recommended for all sporadic gastric carcinoids. Local resection, however, is accepted for some carcinoids from other gastrointestinal sites (i.e., appendix and rectum). We sought to examine the relation of tumor size and depth to lymph node metastasis to determine whether gastric carcinoids can be selected for endoscopic resection. We also sought to quantify the utilization of lymph node sampling.

Methods. 984 patients with localized gastric carcinoids who underwent cancer-directed surgery between 1983 and 2005 were identified from the Surveillance, Epidemiology, and End Results (SEER) registry database.

Results. Tumor size and depth predicted probability of lymph node metastasis. Lymph node metastasis was not seen in intraepithelial (IE) tumors <2 cm. Of tumors <1 cm invading into the lamina propria or submucosa (LP/SM), 3.4% had lymph node metastasis. Excluding IE tumors <2 cm and LP/SM tumors <1 cm, all other subgroups based on size and depth had rates of lymph node metastasis ≥ 8%. Tumor size and depth predicted probability of lymph node sampling. Overall, only 21% of tumors had lymph node sampling. Excluding IE tumors <2 cm and LP/SM tumors <1 cm, only 43% of tumors had lymph node sampling.

Conclusions. Tumor size and depth predict lymph node metastasis for gastric carcinoids. Endoscopic resection may be appropriate for intraepithelial (IE) tumors <2 cm and perhaps tumors <1 cm invading into the lamina propria or submucosa. Lymph node sampling is underused for gastric carcinoids at high risk for lymph node metastasis.

The term "carcinoid" refers to low-grade, well-differentiated, neuroendocrine tumors arising from argentaffin cells found throughout the gastrointestinal and bronchopulmonary systems.[1] Carcinoid tumors are rare neoplasms, accounting for 1.25% of all malignancies.[2] Their incidence, however, is increasing by approximately 3–10% per year, probably due to improved diagnosis with the widespread use of endoscopy and cross-sectional imaging.[2] Most carcinoid tumors arise in the gastrointestinal tract, which is the site of origin for 67.5% of all carcinoids.[3] Gastric carcinoids are extremely uncommon, accounting for only 2% of all carcinoid tumors and 8.7% of gastrointestinal carcinoids.[3,4] Gastric carcinoids arise either spontaneously or in response to a hypergastrinemic state. Due to the rarity of gastric carcinoid tumors and the diversity in their biology, the rates and predictors of lymph node metastasis have not been rigorously quantified.

To help predict behavior of gastric carcinoids, three clinicopathological categories have been described.[5] Type I and type II gastric carcinoids arise in the setting of hypergastrinemia. Gastrin acts as a powerful mitogen of enterochromaffin-like cells in the gastric wall, and is required, at least in the early stages, for the growth of type I and type II tumors.[6] For type I gastric carcinoids,

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hypergastrinemia is due to chronic atrophic gastritis, while for type II tumors, it results from a gastrinoma (Zollinger–Ellison syndrome). Type I and type II tumors often follow a benign course. The recommended management of the tumor usually entails observation or endoscopic resection, with surgical resection reserved for more advanced tumors. Management can also be directed at alleviating the underlying source of gastrin.[7,8]

Type III tumors occur sporadically in the absence of a hypergastrinemic state. As their growth is independent of gastrin, they are thought to follow a more aggressive course. Widely accepted consensus guidelines recommend radical resection with regional lymph node dissection for all sporadic gastric carcinoids.[7,8] Local resection, however, is accepted for selected carcinoids from other gastrointestinal sites such as appendix and rectum due to the fact that tumors with a low rate of lymph node metastasis can be identified.[7–9]

We sought to identify predictors of lymph node metastasis in order to determine whether a group of gastric carcinoids with a low rate of lymph node metastasis could be selected for endoscopic or local resection without regional lymphadenectomy. We also sought to determine the association of lymph node metastasis with survival and to quantify the utilization of lymph node sampling as determined in a large population-based registry.

METHODS

The Surveillance, Epidemiology, and End Results (SEER) registry was used to identify patients. All clinicopathological variables used were available from the SEER database. Only patients with no metastatic disease at time of diagnosis and who underwent cancer-directed surgery were selected. Tumors histologically classified as "neuroendocrine carcinoma" (ICD-0-3 code 8246) were eliminated to exclude cases of poorly differentiated (high grade; small cell and large cell) neuroendocrine carcinoma.[10–12] Tumor grade was only available for 20% of cases. Information about gastric carcinoid subtypes (gastrin dependent or sporadic) was not available.

The classification of tumor depth was based on the American Joint Committee on Cancer (AJCC) 6th edition stomach cancer tumor (T) staging system.[13] For cases diagnosed during the period 1983–1987 ($n = 36$), tumors were determined to have undergone lymph node sampling unless the regional lymph node status was coded as "unknown" by the SEER database. For cases from 1988 to 2005 ($n = 948$), the SEER database specifically coded whether or not regional lymph nodes were examined.

Survival curves were generated by the Kaplan–Meier method.[14] The log-rank test and Cox multivariate analysis were used to assess associations with survival. Significance for associations between categorical variables was assessed using the Fisher's exact or Pearson chi-square test. The adjusted Wald method was used to generate confidence intervals for proportions. *P*-Values <0.05 were considered significant. Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS, Chicago, IL) was used for statistical analysis.

The study protocols were approved by the appropriate institutional review committee and meet the guidelines of the responsible governmental agency.

RESULTS

Using the SEER database, 984 patients with locoregional gastric carcinoid tumors diagnosed from 1983 to 2005 were identified. Demographic data for the patients are presented in Table 1. Median patient age was 63 years (there was a single patient <20 years of age and 8

TABLE 1 Patient and tumor characteristics

Variable	Median (range) or *n* (%)
Age (years)	63 (8–96)
Gender	
Male	392 (40)
Female	592 (60)
Race	
White	802 (82)
Black	123 (12)
American Indian/Alaskan Native	7 (0.7)
Asian/Pacific Islander	48 (4.9)
Unknown	4 (0.4)
Period	
1983–1990	77 (7.8)
1991–1998	236 (24)
1999–2005	671 (68)
Size (mm)	10 (1–110)
Depth of penetration	
Intraepithelial	355 (49)
Lamina propria or submusosa	223 (31)
Muscularis propria or subserosa	101 (14)
Serosa	28 (3.9)
Adjacent organ involvement	11 (1.5)
Lymph node metastasis	61 (8.4)
Lymph node sampling	202 (21)
Number of lymph nodes removed	
1–5	79 (48)
6–10	34 (20)
11–15	18 (11)
> 15	35 (21)

patients <30 years of age). Females accounted for 60% of the patients, while males accounted for 40%. Whites constituted 82%, 12% were Black, and 6% were other races. All but 3 of the 61 patients found to have lymph node metastasis were coded as having lymph node sampling, thus 29% of the patients who underwent lymph node sampling were found to have lymph node metastasis.

The association of clinicopathological variables with survival was analyzed. Median follow-up was 39 months in the entire cohort and 44 months in survivors. The median survival of the entire cohort was 171 months. Presence of lymph node metastasis was adversely associated with survival ($P < 0.001$) (Fig. 1). This association was also present in the subgroup of patients selected to undergo lymph node sampling ($P = 0.01$). This association, however, was not independent of tumor size, tumor depth, and patient age on multivariate analysis (Table 2).

Tumor size (stratified as <1 cm, ≥1 cm and <2 cm, ≥2 cm) was found to be strongly correlated with the likelihood of lymph node metastasis ($P < 0.001$) (Fig. 2a). Only 2% [95% confidence interval (CI) 0.6–5.3%] of all tumors <1 cm in size had lymph node metastasis, whereas 32% (95% CI 24–40%) of tumors ≥2 cm had lymph node metastasis. As patients who did not undergo lymph node sampling may have had lymph node metastasis that was not identified, we examined the rate of lymph node metastasis in patients who were selected to undergo lymph node sampling. Rates of lymph node metastasis were higher when evaluated for patients with the same parameters who underwent lymph node sampling (Fig. 2a). In the subset of patients who underwent lymph node sampling, even tumors <1 cm had a 6.4% rate of lymph node metastasis (95% CI 1.6–18%).

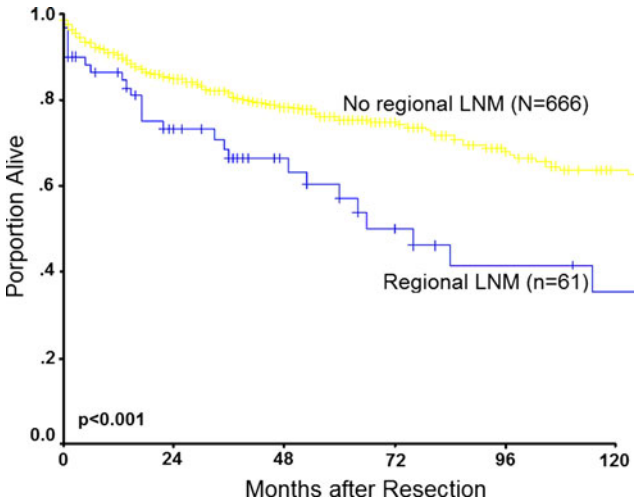

FIG. 1 Lymph node metastasis is associated with overall survival. Patients with regional lymph node metastasis (LNM) had worse Kaplan–Meier predicted overall survival than those without

TABLE 2 Cox multivariate analysis of variables associated with overall survival

Variable	*P*-Value	Relative risk (95% confidence interval)
Age (years)	<0.001	1.079 (1.057–1.101)
Depth[a]	0.008	1.359 (1.083–1.706)
Size (mm)	0.013	1.016 (1.003–1.028)
Lymph node metastasis	0.745	1.104 (0.607–2.008)
Male gender	0.329	1.251 (0.798–1.960)

[a] Depth of penetration is stratified as intraepithelial, lamina propria or submucosa, muscularis propria or subserosa, serosa, and adjacent organ involvement

Tumor depth was also strongly correlated with presence of lymph node metastasis (Fig. 1b). Only 1.5% (95% CI 0–3.0%) of intraepithelial tumors (IE) had lymph node metastasis, whereas 80% (95% CI 48.0–95.4%) of tumors invading adjacent organs (AO) had lymph node metastasis. In cases with lymph node sampling, even IE tumors had an 11.8% rate (95% CI 4.1–27%) of lymph node metastasis.

Age, gender, and race were not significantly associated with the rate of lymph node metastasis. Depth and size were correlated with each other ($P < 0.001$).

To attempt to improve predictions of the rate of lymph node metastasis, tumors were subgrouped by both depth and size (Table 3). Tumor depth was significantly associated with the rate of lymph node metastasis in each of the tumor size categories ($P < 0.001$ for tumors <1 cm, $P = 0.004$ for tumors ≥1 cm and <2 cm, $P < 0.001$ for tumors ≥2 cm). Lymph node metastasis was not seen in IE tumors <2 cm in size (95% CI 0–2.8%). Tumors <1 cm invading the lamina propria or submucosa (LP/SM) had lymph node metastasis in 3.4% of cases (95% CI 0.3–12%) and in 5.6% of cases with lymph node sampling (95% CI 0–28%). Excluding IE tumors <2 cm and LP/SM tumors <1 cm, the other subgroups based on size and depth had rates of lymph node metastasis ranging from 8.0 to 86%.

Therefore, patients could be divided into two groups: those at low risk for lymph node metastasis (IE tumors <2 cm and LP/SM tumors <1 cm) and those at high risk (all other cases). The low-risk group had an overall lymph node metastasis rate of 1.2% (95% CI 0–10%) compared with 24.7% (95% CI 19–31%) for the high-risk group ($P < 0.001$). In patients who underwent lymph node sampling, the rate of lymph node metastasis was 2.6% (95% CI 0–15%) in the low-risk group and 51.1% (95% CI 41–61%) in the high-risk group.

Overall, only 21% of patients had lymph node sampling. Smaller and superficial tumors were less likely to have lymph node sampling ($P < 0.001$, for each comparison) (Fig. 3). The rate of lymph node sampling did not correlate

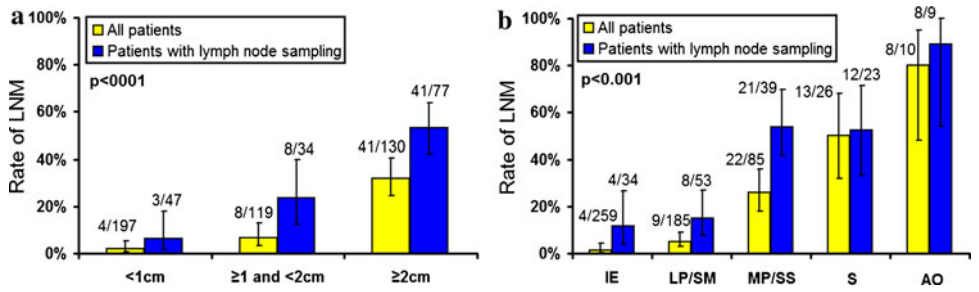

FIG. 2 Tumor size and depth are associated with lymph node metastasis. The rate of lymph node metastasis (LNM) is shown by **a** tumor size and **b** tumor depth for all patients as well for the subset of patients who had lymph node sampling. Depth of penetration is stratified as intraepithelial (IE), lamina propria or submucosa (LP/SM), muscularis propria or subserosa (MP/SS), serosa (S), and adjacent organ involvement (AO). The ratios depicted are the number of patients with lymph node metastasis versus the total number of patients in each group. Error bars represent 95% confidence intervals

TABLE 3 Rate of lymph node metastasis by size and depth groupings in the entire patient population

	Depth of penetration				
	Intraepithelial	Lamina propria or submucosa	Muscularis propria or subserosa	Serosa	Adjacent organ
Size					
<1 cm	0/89 (0)	2/59 (3.4%)	2/5 (40%)	0	0
1–2 cm	0/23 (0)	5/47 (11%)	2/25 (8.0%)	0	1/1 (100%)
≥2 cm	3/20 (15%)	2/27 (7.4%)	15/37 (41%)	12/25 (48%)	6/7 (86%)

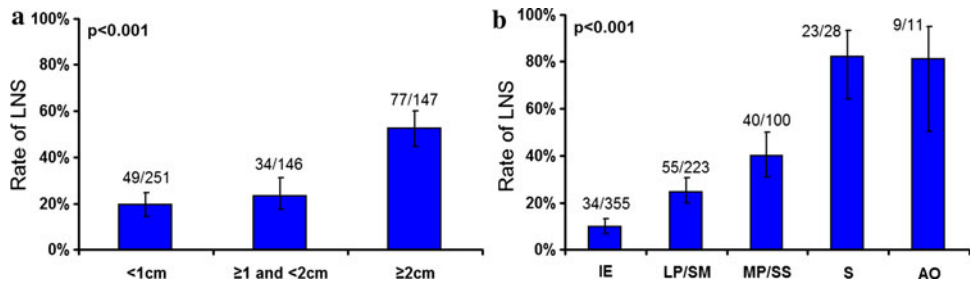

FIG. 3 Tumor size and depth are associated with utilization of lymph node sampling. The rate of lymph node sampling (LNS) is shown by **a** tumor size and **b** tumor depth. Depth of penetration is stratified as intraepithelial (IE), lamina propria or submucosa (LP/SM), muscularis propria or subserosa (MP/SS), serosa (S), and adjacent organ involvement (AO). The ratios depicted are the number of patients with lymph node sampling versus the total number of patients in each group. *Error bars* represent 95% confidence intervals

with age or gender. Race also correlated with the rate of lymph node sampling ($P = 0.04$). Asians and Pacific Islanders had a 38% rate of lymph node sampling compared with 21% for Whites, 19% for Blacks, and 14% for American Indians and Alaskan Natives. Of note, Asians and Pacific Islanders had deeper tumor invasion ($P < 0.001$). The rate of lymph node sampling decreased over the time periods in the study from 61% in the period 1983–1990 to 17% in the period 1999–2005 ($P < 0.001$). This correlated with the increased diagnosis of smaller and more superficial tumors ($P < 0.001$, for each comparison). Even in the high-risk group, however, there was a decline in the use of lymph node sampling from 67% in the period 1983–1990 to 41% in the period 1999–2005 ($P = 0.02$).

Lymph node sampling was not associated with survival in the entire group of patients ($P = 0.16$) or in the group of patients at high risk for nodal metastasis ($P = 0.18$). Lymph node sampling was also not significantly associated with survival when added to the multivariate model ($P = 0.762$).

Only 43% of patients at high risk for lymph node metastasis underwent lymph node sampling.

DISCUSSION

Gastric carcinoid tumors were first reported by Max Askanazy in 1923.[15] Since then, much has been learned regarding the diagnosis, biology, clinical pathology,

endocrinology, and natural history of these tumors. Nevertheless, the rate and predictors of lymph node metastasis in sporadic gastric carcinoids have not been precisely quantified. We aimed to identify predictors of lymph node metastasis to determine whether a group of gastric carcinoids with a low rate of lymph node metastasis could be selected for endoscopic or local resection without regional lymphadenectomy. We also sought to quantify the utilization of lymph node sampling as determined in a large population-based registry.

The classification of gastric carcinoids into three distinct clinical types has been proposed.[5] Type I and II are associated with hypergastrinemia due to chronic atrophic gastritis and gastrinoma (Zollinger–Ellison syndrome), respectively. Type I is most common with a relative incidence of 70–85% of all gastric neuroendocrine tumors (NETs), while type II gastric carcinoids are rare.[7] Both type I and II tumors are typically multicentric and occur in the fundus as normal fundic enterochromaffin-like (ECL) cells proliferate in response to gastrin. They are usually small in size (<1–2 cm) and typically follow a benign course, although type II carcinoid tumors may be slightly more aggressive in behavior.[6]

Type III gastric carcinoids occur sporadically. They represent the second most common type of gastric carcinoid with a relative incidence of 13–20% of gastric NETs.[7] Type III gastric carcinoids are usually solitary. They are typically large with median size of 2 cm and are often located in the antrum or corpus of stomach.[6] Type III gastric carcinoids can have an aggressive course with frequent metastasis.[6]

A fourth type of gastric carcinoids has been proposed by some authors to include non-ECL cell tumors [i.e., serotonin-, gastrin-, or adrenocorticotrophic hormone (ACTH)-secreting tumors], poorly differentiated endocrine carcinomas, and mixed endocrine–exocrine tumors. These tumors are highly malignant, solitary, and larger in size.[16]

Well-established consensus guidelines recommend radical resection with regional lymph node dissection for the treatment of sporadic gastric carcinoid tumors. The European Neuroendocrine Tumor Society (ENETS) and the National Comprehensive Cancer Network (NCCN) guidelines specify that all sporadic gastric carcinoids be treated by subtotal or total gastrectomy with regional lymphadenectomy similar to the treatment of gastric adenocarcinoma.[7,8] The United Kingdom Neuroendocrine Tumor Group (UKNET) recommendations allow for endoscopic resection of tumors < 1 cm in size with no extension into muscle on endoscopic ultrasound (EUS) or computed tomography (CT).[9]

These recommendations are likely based on the high rate of lymph node metastasis observed with sporadic gastric carcinoid tumors. To our knowledge, however, accurate rates and predictors of lymph node metastasis have not been determined from large series of resected localized gastric carcinoids.

Endoscopic resection and laparoscopic wedge resection have been offered as potential treatments for selected gastric carcinoids.[9,17,18] However, it is not clear how patients who do not need formal lymphadenectomy can be selected. Criteria for choosing patients for endoscopic or local resection (without formal lymph node dissection) have been accepted for early gastric adenocarcinomas (through endoscopic mucosal resection or laparoscopic wedge resection) and for selected carcinoids at other sites such as the appendix (by simple appendectomy) and rectum (through transanal excision).[7–9,19,20] These criteria have been developed by defining subgroups of tumors with a low rate of lymph node metastasis. The primary objective of this study is to assess whether sporadic gastric carcinoid tumors with a low rate lymph node metastasis could be identified.

Not surprisingly, in this study tumor size and tumor depth proved to be the main predictors of lymph node metastasis for gastric carcinoids. These variables are well-established prognostic variables for gastrointestinal carcinoid tumors at other sites. While size and depth could be subgrouped many ways, we found that using tumor size <1 cm, ≥1 cm and <2 cm, or ≥2 cm, and depth classified by AJCC sixth edition stomach cancer T stage appeared to provide for maximal stratification yet allow adequate numbers of patients in each group for comparison.[13]

To optimize the prediction of the rate of lymph node metastasis, we subgrouped the tumors by both size and depth. This allowed the tumors to be divided into those at low risk and high risk for lymph node metastasis by defining a risk of lymph node metastasis ≥ 8% to be high risk. The low-risk group consisted of intraepithelial (IE) tumors <2 cm in size and tumors <1 cm penetrating the lamina propria or submucosa (LP/SM).

Assigning a precise rate of lymph node metastasis to any subgroup of gastric carcinoids was complicated by the fact that only 21% of patients underwent formal lymph node sampling. Thus, the rate of lymph node metastases in the entire patient population is underestimated, since some patients who did not have lymph node sampling likely had lymph node metastases that were missed. Nevertheless, it is likely that patients who were selected to undergo lymphadenectomy were perceived to have a higher rate of lymph node metastasis. Indeed, patients with larger and deeper tumors had a higher rate of lymph node sampling. Thus, the rate of lymph node metastases in the group of patients who underwent lymph node sampling likely overestimates the rate of lymph node metastases in the entire patient population. The actual rate of lymph node metastases likely falls between these two values.

In this study, lymph node metastasis was not seen in IE tumors <2 cm in size [95% confidence interval (CI) 0–2.8%]. The rate of lymph node metastasis was 3.4% (95% CI 0.3–12%) for the entire group of LP/SM tumors <1 cm and 5.6% (95% CI 0–28%) for LP/SM tumors <1 cm that were selected to undergo lymph node sampling. Thus, endoscopic or local resection may be employed in the treatment of intraepithelial gastric carcinoids <2 cm in size and possibly for tumors <1 cm invading the lamina propria or submucosa.

A limitation of this study is that it is not possible to determine which tumors were gastrin dependent and which were sporadic using the SEER database. Given that endoscopic surveillance, and not resection, is often employed for gastrin-dependent (type I and II) gastric carcinoids, we suspect that sporadic gastric carcinoids will be overrepresented in this study, which is limited to those patients having cancer-directed surgery. The subset of patients who had assessment of regional lymph nodes should be composed almost entirely of those with sporadic gastric carcinoids, as it is rarely indicated to perform lymphadenectomy for the management of gastrin-dependent gastric carcinoids.

The possible inclusion of gastrin-dependent gastric carcinoids in this study could have resulted in an underestimation of the rate of lymph node metastasis, as gastrin-dependent gastric carcinoids are thought to have lower metastatic potential. This strengthens the recommendation for the use of lymphadenectomy in the treatment of high-risk gastric carcinoids as determined by this study. Similarly, omission of lymphadenectomy in gastric carcinoids <1 cm invading the lamina propria or submucosa should be used with caution. Nevertheless, as lymph node metastasis was not seen in any intraepithelial gastric carcinoids <2 cm, use of local or endoscopic resection for sporadic gastric carcinoids meeting this criteria should be associated with a very low or negligible risk of recurrence.

The utility of recommendations for the management of gastric carcinoids based on size and depth are limited by the fact that it may not always be possible to determine the depth of penetration preoperatively. In many cases, gastric carcinoids may be removed on endoscopic detection prior to pathological diagnosis. In these cases, size and depth of invasion may have to be reconstructed from pathology and endoscopy reports. It may be practical to attempt endoscopic mucosal resection for gastric carcinoids <2 cm while reserving surgical resection and lymphadenectomy for tumors ultimately found to be ≥1 cm and invading the lamina propria or submucosa, 1–2 cm and invading the muscularis, or where complete endoscopic resection could not be achieved. Endoscopic ultrasound may also serve a role in determining depth of invasion in some cases.

Despite the significant rate of lymph node metastasis seen in this study, few patients underwent lymphadenectomy (21%). While lymph node dissection was used more frequently in larger and deeper tumors, only 43% of patients with tumors found to be at high risk for lymph node metastasis by this study underwent lymphadenectomy. Furthermore, usage of lymph node dissection for gastric carcinoids appears to be on the decline.

Surprisingly, while lymph node metastasis was found to be adversely associated with survival for gastric carcinoid tumors, this relationship was not independent of size and depth. Thus, lymph node dissection does not appear to add any prognostic information beyond what can be obtained from histopathological analysis of the primary tumor. It is not known whether lymph node dissection offers any survival benefit beyond resection of the primary gastric carcinoid. Nevertheless, due to the lack of effective systemic therapy for gastrointestinal carcinoid tumors, their susceptibility for recurrence from lymph node metastases, as well as their propensity to present with bulky mesenteric lymphadenopathy that can cause obstruction from mass effect or an associated desmoplastic reaction, lymphadenectomy is warranted for gastric carcinoids at significant risk of harboring involved regional lymph nodes.

CONCLUSIONS

Lymph node metastasis is associated with survival after cancer-directed surgery for localized gastric carcinoids, although the relationship is not independent of tumor size, tumor depth, and age. Tumor size and depth predict lymph node metastasis for gastric carcinoids.

Local or endoscopic resection may be appropriate for intraepithelial tumors <2 cm and perhaps tumors <1 cm invading the lamina propria or submucosa. Lymph node sampling is underused for gastric carcinoids at high risk for lymph node metastasis.

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