### Title
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# Lymph Node Positivity in Appendiceal Adenocarcinoma: Should Size Matter?

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BACKGROUND: The management algorithm for appendiceal adenocarcinoma is not well defined. This study sought to determine whether tumor size or depth of invasion better correlates with the presence of lymph node metastases in appendiceal adenocarcinoma, and to compare these rates with colon adenocarcinoma.

STUDY DESIGN: A retrospective review of the National Cancer Database was performed to identify patients with appendiceal or colonic adenocarcinoma from 2004 to 2013 who underwent surgical resection. Cases were categorized by tumor size and by T stage. Rates of lymph node metastases were examined as a function of size and T stage.

RESULTS: A total of 3,402 appendiceal and 314,864 colonic cases were identified. For appendiceal adenocarcinoma, larger tumor size was associated with higher T stage: Pearson correlation of 0.41 (95% CI 0.408 to 0.414; $p < 0.001$). Lymph node metastases were present in 19.1%, 27.8%, 39.6%, 39.4%, 42.4% and 39.1% for tumor sizes <1 cm, >1 to 2 cm, >2 to 3 cm, >3 to 4 cm, >4 to 5 cm, and >5 cm, respectively. Lymph node metastases were present in 0%, 11.2%, 12.3%, 35.5%, and 40.0% for in situ, T1, T2, T3, and T4 tumors, respectively. There was no difference in the rates of lymph node metastases between appendiceal and colonic adenocarcinoma for tumor sizes <3 cm, or for in situ and T1 tumors. Rates of lymph node metastases are higher in colonic adenocarcinoma for tumor sizes >3 cm and for T2, T3, and T4 tumors ($p < 0.01$).

CONCLUSIONS: In appendiceal adenocarcinoma, the rate of lymph node metastases is substantial, even for small tumors. Tumor size should play no role in the decision of whether to perform a hemicolectomy. Appendectomy alone does not produce an adequate lymph node sample. Right hemicolectomy should be performed for all appendiceal adenocarcinomas.

Appendiceal cancer is a rare disease, with an approximate incidence of 1 per 100,000 people per year. Two of the most common types of appendiceal cancer are colonictype adenocarcinoma and mucinous adenocarcinoma, together accounting for >60% of all cases.[1,2] Because of the rarity of appendiceal cancer, most surgeons will encounter this disease only infrequently, which can result in an overall lack of familiarity with its treatment.[3] In addition, the management algorithm for appendiceal adenocarcinoma is not well defined. Classically, the extent

of surgical resection has been based on tumor size, rather than depth of invasion (American Joint Committee on Cancer [AJCC] T stage), in which small tumors (<1 cm) were sometimes treated with appendectomy alone.[4] Although T stage has supplanted tumor size as the main pathologic measurement, there does not currently appear to be consensus about whether a right colectomy is necessary in all situations. Some have advocated for a hemicolectomy in all cases,[3,5] and others believe that appendectomy alone can be sufficient in certain in situ or T1 tumors.[6] However, appendectomy alone results in suboptimal lymph node sampling, potentially leading to understaging and inappropriate omission of adjuvant therapy.[5] Within the National Comprehensive Cancer Network treatment guidelines, there exists no specific algorithm for appendiceal adenocarcinoma, with only a footnote mention that the use of adjuvant therapy might be similar to that of colonic adenocarcinoma.[7]

Lymph node sampling is an integral part of the management and staging of colonic adenocarcinoma, but studies examining the rate of lymph node metastasis in appendiceal adenocarcinoma are lacking. Therefore, the need for lymph node sampling in appendiceal adenocarcinoma is not fully known. The purpose of this study was 3-fold: to examine whether there is an association between tumor size and depth of invasion (T stage), to determine whether tumor size or depth of invasion better correlates with the presence of lymph node metastases in appendiceal adenocarcinoma, and to compare these rates of lymph node metastases with colon adenocarcinoma.

## METHODS

### Database

The National Cancer Database (NCDB) is a joint project of the American Cancer Society and the American College of Surgeons Commission on Cancer. Established in 1989, the NCDB is a nationwide, facility-based, comprehensive clinical oncology data set that pulls hospital registry data collected in more than 1,500 Commission on Canceraccredited facilities. The NCDB currently captures 70% of all newly diagnosed malignancies in the US annually.[8] Approval for the use of the NCDB was obtained from the American College of Surgeons Commission on Cancer and from the IRB of the University of California, Irvine.

### Participant selection

A retrospective review of the NCDB was performed to identify patients with appendiceal or colonic adenocarcinoma from 2004 to 2013 who underwent surgical resection. Patients with appendiceal adenocarcinoma were identified using an ICD-O-3 topography code of C18.1 and an ICD-O-3 histology code of 814 or 848. Patients with colonic adenocarcinoma were identified using a ICD-O-3 topography code of C18.0, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, or C18.9 and an ICD-O-3 histology code of 814 or 848. The type of resection was identified using Facility Oncology Registry Data Standards codes 30, 31, or 32 for appendectomy and 40 or 41 for colectomy.

### Demographics and outcomes variables

Cases were categorized by tumor size (1-cm increments) and by pathologic T (pT) stage. Pathologic T stage is the pathologically determined tumor extension into the colon wall or nearby structures, as defined by the AJCC.[9] Rates of lymph node metastasis were then calculated for each tumor size and for each pT stage. Lymph node metastasis was classified as "positive" if at least 1 of the nodes examined contained metastatic disease. To ensure adequate lymph node sampling, cases with fewer than 12 lymph nodes examined were excluded from analysis. Cases with a pT stage of pT0 or pTX were also excluded from analysis.

A secondary analysis was performed to determine the rate of lymph node sampling associated with appendectomy alone. All appendix patients that underwent appendectomy alone during the study period were examined and the number of lymph nodes harvested was tabulated.

### Statistical analysis

All data acquisition and statistical analyses were conducted using SAS, version 9.4 (SAS

Institute) and the R Statistical Environment (R Foundation for Statistical Computing). Chi-square (categorical variables) was used for univariate analysis. A Pearson correlation was estimated to quantify the association between size and T stage. Statistical significance was declared if $p < 0.05$.

## RESULTS

There were a total of 318,266 evaluable colonic and appendiceal cancer cases reported in the NCDB study period 2004 to 2013. A total of 15,888 cases were excluded with pT stage of pT0 or pTX, and a total of 95,990 cases were excluded for having had fewer than 12 nodes examined. Of those that met inclusion criteria, there were a total of 3,402 cases of appendiceal adenocarcinoma and 314,864 cases of colonic adenocarcinoma. Of the appendiceal cancer patients, 19.6% underwent appendectomy and 80.4% underwent colectomy. Of the appendiceal cancer patients, 1,145 (33.7%) had at least 1 positive lymph node.

Table 1. Comparison of Appendiceal Adenocarcinoma Tumor Size with American Joint Committee on Cancer Pathologic T Stage

| | Appendiceal adenocarcinoma tumor size | | | | | | |
|---|---|---|---|---|---|---|---|
| Stage | <1 cm | 1 to 2 cm | 2 to 3 cm | 3 to 4 cm | 4 to 5 cm | >5 cm | Total |
| pTis | 10 | 3 | 0 | 3 | 3 | 3 | 22 |
| pT1 | 30 | 26 | 12 | 11 | 8 | 21 | 108 |
| pT2 | 41 | 64 | 41 | 27 | 26 | 49 | 248 |
| pT3 | 61 | 201 | 196 | 140 | 108 | 221 | 927 |
| pT4 | 49 | 142 | 196 | 158 | 176 | 507 | 1,228 |
| Total | 191 | 436 | 445 | 339 | 321 | 801 | 2,533 |

The estimated Pearson correlation between tumor size and T stage was 0.41 (95% CI 0.408 to 0.414; $p < 0.0001$).

A comparison of appendiceal adenocarcinoma tumor size to AJCC pT stage is shown in Table 1 and in Figure 1. Cases with missing tumor size or T stage information were excluded from this subgroup analysis, for a total of 2,533 cases. Larger tumor size was associated with higher T stage, with an estimated Pearson correlation of 0.41 (95% CI 0.408 to 0.414; $p < 0.001$). Accordingly, there were some small tumors with a high T stage and some large tumors with a low T stage. For example, a total of 108 pT1 tumors were identified. Of these, 30 were <1 cm in size, 26 were 1 to 2 cm in size, 8 were 4 to 5 cm in size, and 21 were >5 cm in size. Similarly, a total of 1,228 pT4 tumors were identified. Of these, 49 were <1 cm in size and 142 were 1 to 2 cm in size, and 176 were 4 to 5 cm in size and 507 were >5 cm in size. The presence of lymph node metastases for each tumor size and AJCC pathologic T stage is shown in Table 2 and in Figure 2. For appendiceal adenocarcinoma, the overall rate of lymph node metastasis was 33.7%. Lymph node metastases were present in 19.1%, 27.8%, 39.6%,

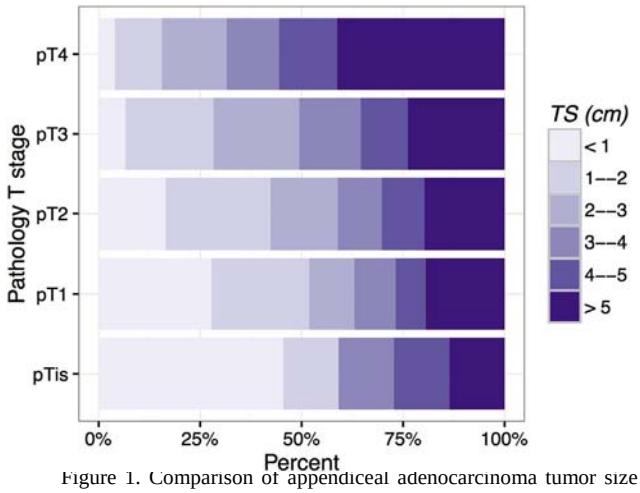


Figure 1. Comparison of appendiceal adenocarcinoma tumor size to American Joint Committee on Cancer pathologic T stage. The estimated Pearson correlation between tumor size and T stage was 0.41 (95% CI 0.408 to 0.414; $p < 0.0001$).

39.4%, 42.4%, and 39.1% for tumor sizes <1 cm, >1 to 2 cm, >2 to 3 cm, >3 to 4 cm, >4 to 5 cm, and >5 cm, respectively. Lymph node metastases were present in 0%, 11.2%, 12.3%, 35.5%, and 40.0% for in situ, T1, T2, T3, and T4 tumors, respectively. For colonic adenocarcinoma, lymph node metastases were present in 19.7%, 28.7%, 41.2%, 47.6%, 49.1%, and 48.6 % for tumor sizes <1 cm, >1 to 2 cm, >2 to 3 cm, >3 to 4 cm, >4 to 5 cm, and >5 cm, respectively. Lymph node metastases were present in 0.9%, 12.4%, 20.9%, 48.7%, and 67.2% for in situ, T1, T2, T3, and T4 tu mors, respectively.

There was no difference in the rates of lymph node metastases between appendiceal and colonic adenocarcinoma for tumor sizes <1 cm (p ¼ 0.835), >1 to 2 cm (p ¼ 0.692), and >2 to 3 cm (p 0.505), as well as for in situ (p 0.523) and T1 (p ¼ 0.651) tumors. Rates of lymph node metastases are higher in colonic adenocarcinoma for tumor sizes >3 cm and for T2, T3, and T4 tumors (p < 0.01).

We then performed a secondary analysis of all appendiceal adenocarcinoma cases in NCDB between 2004 and 2013 who underwent appendectomy only as the definitive surgical treatment. A total of 1,900 cases were identified. Of these, 1,244 cases (65.5%) had fewer than 12 nodes examined, including 772 cases (40.6%) that had zero lymph nodes examined.

## DISCUSSION

Appendiceal adenocarcinoma is a rare disease. Consequently, research in this area is challenging. Previous studies have largely been from single-institution data with small sample sizes, which makes drawing conclusions from those results difficult. To our knowledge, the current study represents the largest population-based analysis evaluating lymph node involvement in appendiceal adenocarcinoma. In addition, we could find no previous studies examining the correlation between tumor size and depth of invasion. This study highlights a few

Table 2. Rate of Lymph Node Metastasis for Appendiceal and Colonic Adenocarcinoma by Tumor Size and American Joint Committee on Cancer T Stage

| | Appendiceal adenocarcinoma | | | Colonic adenocarcinoma | | |
|---|---|---|---|---|---|---|
| | | Node positive | | | Node positive | |
| Variable | n | n | % | n | n | % |
| Tumor size, cm | | | | | | |
| <1 | 194 | 37 | 19.1 | 6,699 | 1,318 | 19.7 |
| 1 to 2 | 439 | 122 | 27.8 | 19,896 | 5,701 | 28.7 |
| 2 to 3 | 447 | 177 | 39.6 | 43,694 | 17,982 | 41.2 |
| 3 to 4 | 343 | 135 | 39.4 | 59,708 | 28,428 | 47.6 |
| 4 to 5 | 323 | 137 | 42.4 | 57,127 | 28,034 | 49.1 |
| >5 | 810 | 317 | 39.1 | 116,907 | 56,817 | 48.6 |
| Missing | 846 | 220 | d | 10,833 | 4,624 | d |
| American Joint Committee on Cancer T stage | | | | | | |
| pTis | 43 | 0 | 0 | 1,911 | 18 | 0.9 |
| pT1 | 178 | 20 | 11.2 | 2,137 | 2,137 | 12.4 |
| pT2 | 318 | 39 | 12.3 | 44,554 | 9,315 | 20.9 |
| pT3 | 1,215 | 431 | 35.5 | 199,208 | 97,025 | 48.7 |
| pT4 | 1,610 | 644 | 40.0 | 49,822 | 33,474 | 67.2 |
| Missing | 38 | 11 | d | 2,075 | 935 | d |

important points: there was poor correlation between tumor size and T stage in appendiceal adenocarcinoma, the rate of lymph node metastasis in small tumors was substantial at 19% for those <1 cm and 27% for those 1 to 2 cm, and the role of an appendectomy as an oncologic procedure is limited, as it often results in a poor lymph node harvest and examination (40.6% of appendectomies had no recovered lymph nodes).

The appropriate operative procedure in appendiceal adenocarcinoma has long been, and continues to be, an area of controversy and confusion. Some surgeons believe that all noncarcinoid cancers of the appendix should be treated with a right hemicolectomy,[3,5] and

others believe that appendectomy alone might be appropriate for certain in situ or T1 tumors,[6,10] for tumors <1 cm,[4] or for any stage I or II disease.[11] In addition, there are no published guidelines from the National Comprehensive Cancer Network, surgical societies, or other large organizations on the most appropriate surgical management. Although there appears to be a growing consensus within the literature that a right colectomy is the appropriate operation in all cases of noncarcinoid appendiceal cancer, there continues to be a substantial portion of patients that undergo appendectomy alone. This controversy was demonstrated in a study by McGory and colleagues,[12] using the Surveillance, Epidemiology, and End Results program database from 1973 to 2001, which showed that for patients with tumors <1 cm, at least 53% underwent appendectomy alone, and for patients with tumors between 1 and 2 cm, at least 35% underwent appendectomy alone.

We found an overall positive lymph node rate of 33.7%, which is comparable with previous reports. In another study using the Surveillance, Epidemiology, and End Results program database from 1973 to 1998, McCusker and colleagues[1] reported a lymph node involvement rate of approximately 28%, although there was no stratification by size or depth of invasion. In a single-institution study with 62 patients who underwent right hemicolectomy, there was a 38% positive lymph node rate.[5] When lymph node status is examined based on tumor size, our data showed that there is an incremental increase in the rate of lymph node involvement for tumors up to 2 cm, with a plateau of approximately 40% for tumors >2 cm. In addition, the rate of lymph node positivity in appendiceal carcinoma appears to correspond to the rate of lymph node positivity in colonic adenocarcinoma. We found that for smaller tumors (up to 3 cm in size) and lower depth of invasion (Tis and T1), the rate of lymph node positivity was similar between adenocarcinoma of the appendix and of the colon, but for larger tumors (>3 cm in size) and higher depth of invasion (T2 to T4), the rate of lymph node positivity was higher in adenocarcinoma of the colon.

Based on these results, we believe that tumor size should play no role in the decision of whether to perform an appendectomy or a hemicolectomy. In colonic adenocarcinoma, tumor size has no prognostic significance and plays no role in outcomes.[13] Gross pathologic examinations continue to measure and report tumor size, but this assessment is only useful for quality-control

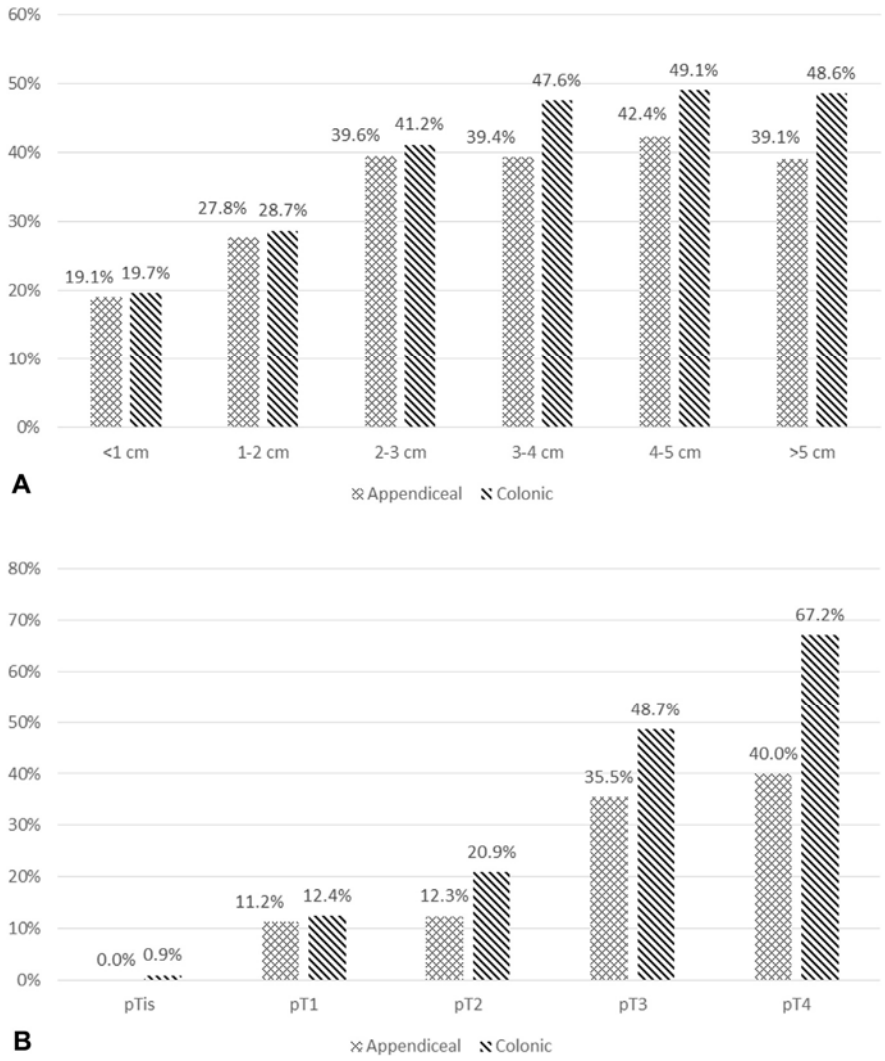


Figure 2. Rate of lymph node metastasis for appendiceal and colonic adenocarcinoma by (A) tumor size and (B) American Joint Committee on Cancer T stage.

purposes.[14] A previous study by Ito and colleagues[10] reported that T stage appears to be associated with survival in appendiceal adenocarcinoma, with lower T stages having improved survival compared with higher T stages. Our data demonstrate that there is a poor correlation between tumor size and T stage, suggesting that tumor size should not be used as a surrogate measure for T stage. Our results also revealed that there is a relatively high rate of lymph node positivity in small appendiceal tumors. Therefore, a significant portion of small tumors treated with appendectomy alone likely have lymph node disease that goes unrecognized, which can affect prognosis and the decision to pursue adjuvant treatment. In our analysis, we found that 19.6% of the appendix cases that had at least 12 lymph nodes examined were treated with appendectomy alone. In addition, in our secondary analysis, we found that 34.5% of appendectomies for adenocarcinoma resulted in at least 12 lymph nodes harvested. It is difficult to explain how one would be able to harvest 12 lymph nodes with a simple appendectomy. First, this could represent a coding error in which the patient initially had an appendectomy but went on to have a colectomy, and the index case was recorded rather than the second case in the procedure data. Second, it might be that some surgeons cherrypicked lymph nodes during the operation or performed a slightly more extensive operation (but not colectomy) that was coded as an appendectomy. Therefore, the actual rate of suboptimal lymph sampling might be higher than 65%. Nevertheless, our results demonstrate that the lymph node harvest is overall poor in an appendectomy.

The controversy about extent of surgical resection in appendiceal adenocarcinoma exists mainly for small tumors and low-T stage tumors, and our data demonstrate that the rate of lymph node metastasis is no different between the appendix and the colon for these small or low-T stage tumors. Our data demonstrated that there is a substantial rate of lymph node metastasis in appendiceal adenocarcinoma, regardless of size or depth of invasion, with the exception of in situ tumors. Because in situ tumors do not invade the submucosa, there is theoretically no risk for lymph node disease. We found a 0% rate of lymph node for in situ appendiceal tumors, but found a 0.9% rate in colon tumors, suggesting that pathology is an imperfect science or that a small portion of in situ tumors will, in fact, have lymph node involvement. Regardless, because of this low rate, appendectomy alone seems to be the appropriate surgical option for in situ appendiceal adenocarcinomas.

Some have advocated that some low-risk T1 appendiceal adenocarcinomas can be treated with appendectomy alone.[6] The appendix is a true diverticulum of the colon, so it might be reasonable to treat T1 adenocarcinomas of the appendix with a strategy similar to that of malignant colon polyps. T1 malignant polyps without high-risk features and negative margins are treated with polypectomy alone, and all other T1 tumors require a formal segmental colectomy.[15,16] In our analysis, we did not sub-stratify based on histologic features, so additional research is needed to determine how histology can affect lymph node involvement and outcomes. Based on our results, the rare patient with a T1 appendiceal cancer would have an overall risk of lymph node metastasis of 11.2%, and it would be reasonable to include this information in a discussion with the patient about the risks and benefits of additional right hemicolectomy.

There are a few limitations to this study due to its retrospective design and the inherent biases within the database. As with all database studies, coding errors can exist and affect the accuracy of the data. There are few demographic and comorbidity data collected within the NCDB database, which limits our ability to perform a risk-adjusted analysis. We chose 12 lymph nodes as the minimum number for an adequate examination based on colorectal data because there is no consensus for appendiceal adenocarcinoma. Our study provides a comprehensive analysis of lymph node involvement in appendiceal adenocarcinoma, with stratifications by tumor size and depth of invasion.

## CONCLUSIONS

In appendiceal adenocarcinoma, the rate of lymph node metastases is substantial, even for small tumors. These rates are similar to those of equally sized colonic tumors. Therefore, tumor size should play no role in the decision of whether to perform a hemicolectomy. There is a poor correlation between tumor size and T stage, suggesting that tumor size should not be used a surrogate measure for T stage in appendiceal adenocarcinoma. Right hemicolectomy should be considered the definitive oncologic procedure for all invasive appendiceal adenocarcinomas, because of the rate of lymph node metastasis and the finding that appendectomy alone does not produce an adequate lymph node sample. Future research should be directed at identifying histologic features, such as grade or differentiation, which can help predict tumors at highest risk for metastatic disease.

## Author Contributions

Study conception and design: Gahagan, Whealon, Phelan, Carmichael
Acquisitionof data: Gahagan, Whealon, Phelan, Carmichael
Analysis and interpretation of data: Gahagan, Whealon, Phelan, Mills, Pigazzi, Stamos, Nguyen, Carmichael
Drafting of manuscript: Gahagan, Carmichael
Critical revision: Gahagan, Whealon, Phelan, Mills, Pigazzi, Stamos, Nguyen, Carmichael

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## Discussion

DR SCOTT KELLEY (Rochester, MN): As we know, appendiceal neoplasms are rare. They make up only about 1% of appendectomy specimens, and these are rarely diagnosed preoperatively. Of these neoplasms, approximately 60% to 65% are adenocarcinoma in origin. Appendiceal adenocarcinoma is made up of 2 variants: mucinous and nonmucinous subtypes. The nonmucinous subtypes behave very similarly to colonic adenocarcinoma. In the mucinous subtype, there is a signet ring cell carcinoma that is a very aggressive sub-entity. Poor differentiation is associated with poor outcomes in both of these subtypes.

The 7th edition of the American Joint Commission on Cancer guidelines provides us with staging criteria for appendiceal neoplasms, which are very similar to those for colon and rectal neoplasms. Due to the rarity of this disease process, there is not a defined algorithm on how to treat these patients. Dr Gahagan and colleagues retrospectively reviewed the National Cancer Data Base over a 9-year period in an attempt to determine if appendiceal adenocarcinoma size was predictive of lymph node positivity.

As they appropriately pointed out, the study had 3 separate aims: to examine if there was an association between the tumor size and depth of invasion; to determine whether tumor size or depth of invasion better correlates with the presence of the lymph node metastasis; and to compare rates of lymph node metastasis between appendiceal and colonic adenocarcinoma.

Based on their review, there were approximately 280 cases per year diagnosed. From what they found, there was a poor correlation between tumor size and depth of invasion; greater depth of

invasion is associated with increased percentage of lymph node positivity; and lymph node metastases are higher for colonic adenocarcinomas for depth of invasion of T2 and greater. They concluded that size should not be used as a surrogate for node positivity, but rather, depth of invasion, and a right hemicolectomy should be considered the definitive oncologic procedure for all appendiceal adenocarcinomas. I have 3 questions.

First, because you did not evaluate outcomes in this study, why exclude appendiceal adenocarcinoma cases with fewer than 12 nodes examined if the nodes were positive because you were only trying to figure out if the depth of invasion correlated with node positivity?

Second, in your study, you performed a secondary analysis, as was appropriately pointed out, of the patients who underwent an appendectomy alone. You identified 1,900 cases to review. Of that cohort, 1,244 cases had fewer than 12 nodes examined. What was the purpose of performing the secondary analysis? And what information did it provide you other than noting that lymph nodes were not removed with a simple appendectomy?

Last, your conclusion states a right hemicolectomy should be considered the definitive oncologic procedure for all appendiceal adenocarcinomas. Do you advocate a right hemicolectomy for adenocarcinoma in situ because that is not the standard of care for colonic adenocarcinoma?

DR NINH T NGUYEN (Orange, CA): We excluded patients with less than 12 lymph nodes because we wanted to analyze the association between the depth of invasion and the lymph node positivity. So in order to do that, we selected only cases that had 12 lymph nodes or more because that is a widely accepted number for adequacy of lymphadenectomy in colon cancer.

The second question asked why we did a secondary analysis of a patient undergoing appendectomy alone. We wanted to find out if appendectomy alone is sufficient in obtaining 12 lymph nodes. We found that the majority of appendectomies alone did not retrieve any lymph nodes. However, approximately 40% of the cases did have some lymph node present in it.

For your last question, we agree that right hemicolectomy should be the operation of choice for appendiceal carcinoma. However, for a patient with TIS or T1 lesion without high-risk features, appendectomy alone may be sufficient.

DR NEAL WILKINSON (Kalispell, MT): The take home message is clearddo a right hemicolectomy. That being said, the last 5 appendiceal cancers that I referred had laparoscopic appendectomies in the setting of peritoneal disease. Peritoneal disease trumps lymph nodes, and patients were usually advised to get hyperthermic intraperitoneal chemotherapy or something of that nature. Where would those patients fall in this study? At the index operation, they would probably have no lymph nodes. Is that a reason why those patients are not here, and where would they be?

DR NINH T NGUYEN (Orange, CA): We did not evaluate patients with peritoneal disease. Those patients would be lumped into T4 disease.

DR JAMES TYBURSKI (Detroit, MI): I would like clarification on the appendectomy alone. Sixty percent of them did not have 12 lymph nodes overall; in other words, a great many did not have any. Does that mean that 40% of the patients with simple

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