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Role of right hemicolectomy in patients with low-grade appendiceal mucinous adenocarcinoma

Yosef Y. Nasseri [a, b, *], Ruoyan Zhu [a, b], Christine Sutanto [a, b], Christina Wai [c, d], Jason S. Cohen [a, b], Joshua Ellenhorn [a, b], Avo Artinyan [c, d]

[a] Surgery Group of Los Angeles, 8635 West 3rd Street Suite 880, Los Angeles, CA, 90048, USA
[b] Cedars Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA, 90048, USA
[c] Verity Medical Group, Surgical Oncology & Colorectal Surgery, 400 Race Street, San Jose, CA, 95126, USA
[d] Saint Vincent Medical Center, 2131 West 3rd Street, Los Angeles, CA, 90057, USA

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ABSTRACT

Background: There is little consensus with regards to the most appropriate surgical management for low-grade appendiceal mucinous adenocarcinomas (LAMA), though right hemicolectomy is usually recommended.
Methods: The SEER database was queried for all patients with non-metastatic LAMA. Disease specific and overall survival was compared by surgery type: 1) appendectomy, 2) formal right hemicolectomy 3) non-formal colectomy (including ileocecectomy).
Results: A total of 579 patients with non-metastatic LAMA were identified. 133 (23%), 404 (70%), and 42 (7%) of patients had stage I, II, and III disease, respectively. 99 (17.1%) had appendectomy, 87 (15%) had non-formal colectomy, and 302 (52.2%) had formal right hemicolectomy. We observed no significant differences in disease specific or overall survival by surgery type. Controlling for age and stage, surgery type was not a significant predictor of disease specific or overall survival.
Conclusion: In patients with localized LAMA, right hemicolectomy did not increase disease specific or overall survival. Right hemicolectomy should be reserved for LAMA patients with positive margins post appendectomy.

Introduction

Primary mucinous neoplasms of the appendix (MNA) are rare tumors, found in less than 2% of appendectomy specimens.[1,2] The Peritoneal Surface Oncology Group International (PSOGI) has issued a consensus statement classifying MNAs as either low grade appendiceal neoplasms (LAMN), high grade appendiceal neoplasms (HAMN), or mucinous appendiceal adenocarcinoma (MAA).[3,4] Mucinous appendiceal adenocarcinomas (MAAs) may be further subdivided into well, moderately, or poorly differentiated lesions based on cytology.[3]

Though often confused with low-grade appendiceal mucinous neoplasms (LAMN), MAAs are a distinct entity, with unique histologic characteristics, clinical course, and survival.[5,6] Given their rarity, there are no clear treatment guidelines for the management of MAAs and surgical strategies have largely been extrapolated from colon cancer treatment paradigms. In current standard of treatment, there is general agreement that formal hemicolectomy is necessary for moderately and poorly differentiated MAA with positive lymph node metastasis. However, the treatment of well-differentiated (low grade) MAAs, also known as low grade appendiceal mucinous adenocarcinoma (LAMA), is more controversial.[7] Although more extensive resection after appendectomy is generally recommended, well differentiated adenocarcinomas have a low incidence of lymph node metastasis, suggesting that formal hemicolectomy may not be warranted.[8–10]

Given the lack of clear treatment guidelines and widespread practice of hemicolectomy in these patients, we sought to address the impact of RHC on outcome in patients with LAMA using a large-scale outcome data. We hypothesized that formal hemicolectomy would provide minimal survival benefit in these patients.

* Corresponding author. 8635 West 3rd Street, Suite 880, Los Angeles, CA, 90048, USA.
E-mail address: yosefnasseri@gmail.com (Y.Y. Nasseri).

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Methods

Study population

The Surveillance Epidemiology and End Results (SEER) database (1988–2014) was queried for all patients with invasive appendiceal mucinous adenocarcinomas. Site code 18.1 was used for the appendix and ICD-0-3 histology codes 8470–8472, 8480, and 8481 for appendiceal mucinous adenocarcinomas with malignant behavior. LAMA was defined as grade 1 lesions (well differentiated), AJCC stages 1–3. Patients with stage 4 disease and with stage 0 (non-invasive) disease were excluded. The patient selection algorithm is described in Fig. 1.

Statistical analysis

A descriptive analysis of the entire population was performed. The primary risk factor of interest was extent of surgery. The primary outcome endpoints were disease specific and overall survival. With respect to extent of surgery, SEER FORDS (Facility Oncology Registry Database Standards) codes have some overlap between appendectomy, ileocecectomy and non-formal resection (codes 30–32) with or without resection of adjacent organs. Specifically, a significant number of patients who would otherwise be coded as having had appendectomy had several lymph nodes excised as well, constituting a population of patients who may have had non-oncologic resections rather than simple appendectomy. To ensure a more homogenous surgical population, we categorized codes 30–32 based on the extent of lymphadenectomy as simple appendectomy if ≤ 2 nodes were harvested and non-formal colectomy if > 2 nodes were harvested. The latter group presumably included patients undergoing ileocecectomy who could have had some oncologic benefit beyond simple appendectomy. Resection code 40, which designates a hemicolectomy, was used to classify formal hemicolectomy patients. Patients undergoing extended colectomy ($n = 10$) were included in the formal hemicolectomy group. Twenty-six patients had no surgery and 65 had missing surgical data and these were excluded from the comparative analysis (Fig. 1).

Demographic, clinical and pathologic factors were compared among the 3 surgery groups using the chi-square test for categorical variables and one-way analysis of variance for continuous variables.

Univariate disease specific and overall survival were compared among groups using the Kaplan Meier method and the log-rank test. Multivariate Cox-regression analysis was performed to determine the independent association of surgery type with survival controlling for hypothesis based confounding factors.

The results of all statistical tests of significance were presented with appropriate measures of central tendency and variance. A p-value of <0.05 was considered statistically significant.

Results

Descriptive analysis

One thousand two hundred and twenty-nine patients with low grade appendiceal mucinous adenocarcinoma (LAMA) were identified, 639 (52.0%) of which had metastatic disease and 11 (0.9%) were stage zero, leaving a final dataset of 579 patients, with well differentiated (low grade), non-metastatic mucinous appendiceal adenocarcinoma (Fig. 1). Table 1 presents the characteristics of the entire sample population. The mean age of the entire population was 60.4 ± 14.74, and sex was distributed almost equally (52% female). With respect to T-stage, the majority of patients were categorized as either T3 or T4 (T3: 37.0%, T4: 39.6%), and a large percentage (69.8%) of tumors fell in the Stage 2 category. The majority of patients (68.0%) had no nodal positivity, while only a fraction (7.3%) had one positive node. Approximately 17% of patients underwent an appendectomy, with the overwhelming

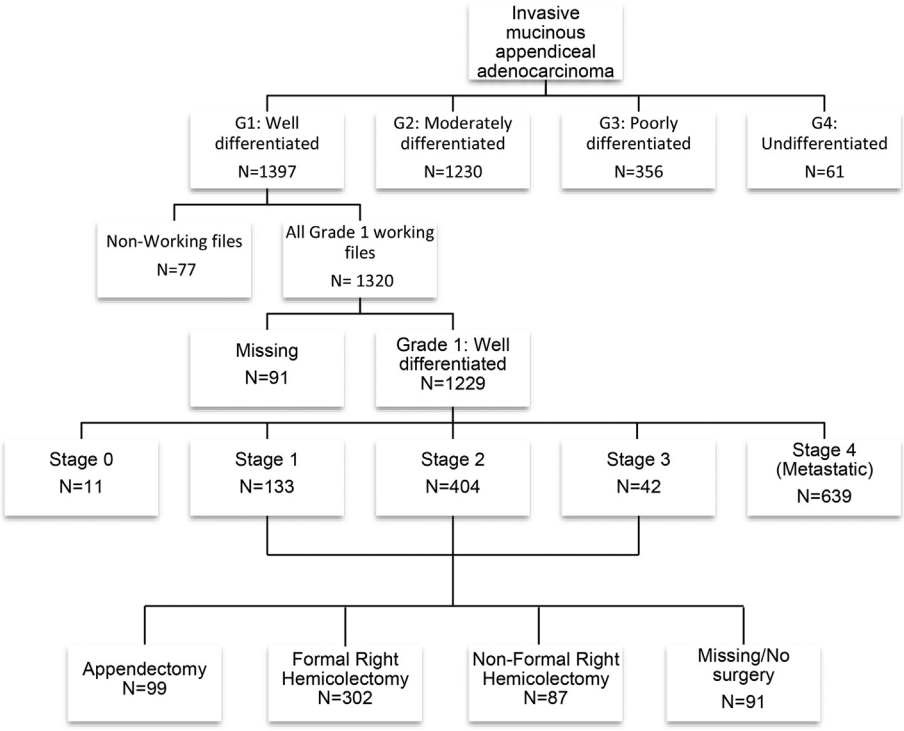

Fig. 1. Flow chart of patient selection algorithm.

Table 1
Characteristics of the sample population (N = 579).

Variable	No. (%)
Age of diagnosis (yr, mean ± SD[a])	60.4 ± 14.74 (19–94)
Sex	
Female	302 (52.2%)
Male	277 (47.8%)
Tumor Classification	
T1	68 (11.7%)
T2	68 (11.7%)
T3	214 (37.0%)
T4	229 (39.6%)
Nodal Status	
Nx	143 (24.7%)
N0	394 (68%)
N+	42 (7.3%)
Tumor Stage	
Stage 1	133 (23%)
Stage 2	404 (69.8%)
Stage 3	42 (7.3%)
Surgery Type	
Appendectomy	99 (17.1%)
Formal Right Hemicolectomy	302 (52.2%)
Non-Formal colectomy	87 (15.0%)
Missing/No Surgery	91 (15.7%)

[a] SD indicates standard deviation.

majority (67.2%) receiving either a formal right hemicolectomy (RHC) (52.2%), or a non-formal right hemicolectomy (15.0%).

Table 2 presents a comparison of clinicopathologic and demographic factors stratified by surgery treatment received. On univariate comparison, there was no significant difference in age, gender or T-stage by type of surgery. As expected, patients with formal and non-formal colectomy were more likely to have AJCC stage III disease compared to patients with appendectomy alone, although there was no difference between the two colectomy groups (data not shown). With respect to node positivity, there was no significant difference between rate of node positivity by type of hemicolectomy (8.0 vs 11.2%, non-formal vs. formal colectomy respectively, p = 0.40) (see Table 2).

Survival analysis

On Kaplan-Meier survival analysis there was no significant difference in either disease-specific survival (Fig. 2) or overall survival (Fig. 3) by surgery type (all p values $\gg$ 0.05, median survivals not reached). On multivariate Cox regression analysis controlling for age, sex, and stage, surgery type was not a predictor of either disease specific or overall survival. Specifically, formal hemicolectomy was not independently associated with improved disease specific survival (HR 0.86 [0.48–1.56], p = 0.62) (see Table 3) or overall survival (HR 0.95 [0.62–1.56], p = 0.95) (See Table 4).

The above results were repeated comparing only appendectomy and formal hemicolectomy (excluding non-formal colectomy) and again there was no difference in both disease specific and overall survival on univariate Kaplan Meier analysis, and no association on multivariate analysis.

Discussion

Recent standardized classification of mucinous neoplasms of the appendix has clarified differences in cytology and behavior amongst tumor subtypes.[3] Well-differentiated or low grade mucinous adenocarcinomas have been found to have a greater likelihood of peritoneal metastasis and lower incidence of lymph node metastasis compared to poorly differentiated mucinous adenocarcinomas.[8,11] Given the lack of studies regarding the surgical management of low grade mucinous appendiceal neoplasms (LAMA), we used a large U.S. population-based database to determine the survival benefit of formal RHC for LAMA patients.

In our study, the majority of LAMA patients from 1988 to 2014 were treated with either formal or a lesser operation with at least a limited nodal harvest (non-formal colectomy). We observed no significant differences in disease specific or overall survival by surgery type (appendectomy, formal and non-formal right hemicolectomy) with and without controlling for age and stage. This is likely in part due to the fact that only a small proportion (7.3%) of LAMA patients have node positive disease. Because nodal positivity rates are predominantly determined from potentially higher risk patients undergoing more extensive operations, the true nodal positivity rate in all LAMA patients is likely to be lower and this may contribute to the lack of benefit observed from formal resection. As noted in our patient selection process, a significant cohort of patients with LAMA have metastatic disease at diagnosis, and this is usually in the form of peritoneal disease. Thus, in this disease process, peritoneal, rather than lymph node spread, is likely a more important determinant of outcome.

In an effort to better evaluate lymph node status, another study we are working on focus on the predictors of lymph node positivity

Table 2
Comparison of clinical factors by extent of surgery.

Variables	Appendectomy (N = 99)	Non-Formal Colectomy (N = 87)	Formal Right Hemicolectomy (N = 302)	P-value
Age at diagnosis (mean ± SE)	61.2 ± 1.6	59.8 ± 1.5	60.4 ± 0.8	0.814
Sex				0.698
Female	53 (53.5%)	44 (50.6%)	147 (48.7%)	
Male	46 (46.5%)	43 (49.4%)	155 (51.3%)	
T-Stage				0.269
T1	18 (18.2%)	9 (10.3%)	31 (10.3%)	
T2	11 (11.1%)	12 (13.8%)	36 (11.9%)	
T3	32 (32.3%)	39 (44.8%)	116 (38.4%)	
T4	38 (38.4%)	27 (31.0%)	119 (39.4%)	
Nodal Status				0.40
N0	14 (100.0%)	80 (92.0%)	253 (88.8%)	
N+	0 (0.0%) (excluded) [a]	7 (8.0%)	32 (11.2%)	
AJCC Stage[b]				0.013
Stage I	29 (29.3%)	21 (24.1%)	64 (21.2%)	
Stage II	70 (70.7%)	59 (67.8%)	206 (68.2%)	
Stage III	0 (0.0%)	7 (8.0%)	32 (10.6%)	

[a] Comparison only between formal and non-formal colectomy (appendectomy patients did not have meaningful nodal harvest).
[b] Best available combined clinical/pathologic stage.

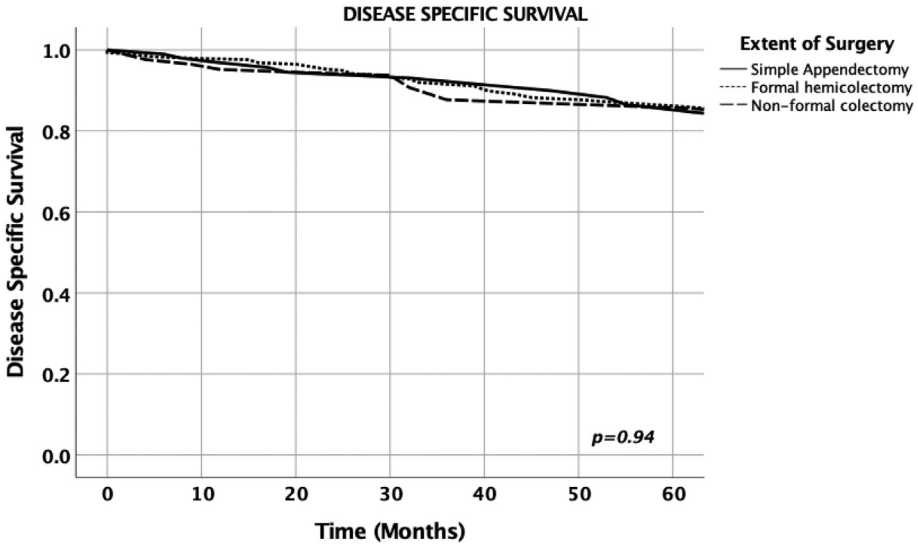

Fig. 2. Disease specific survival of patients with LAMA, by extent of surgery.

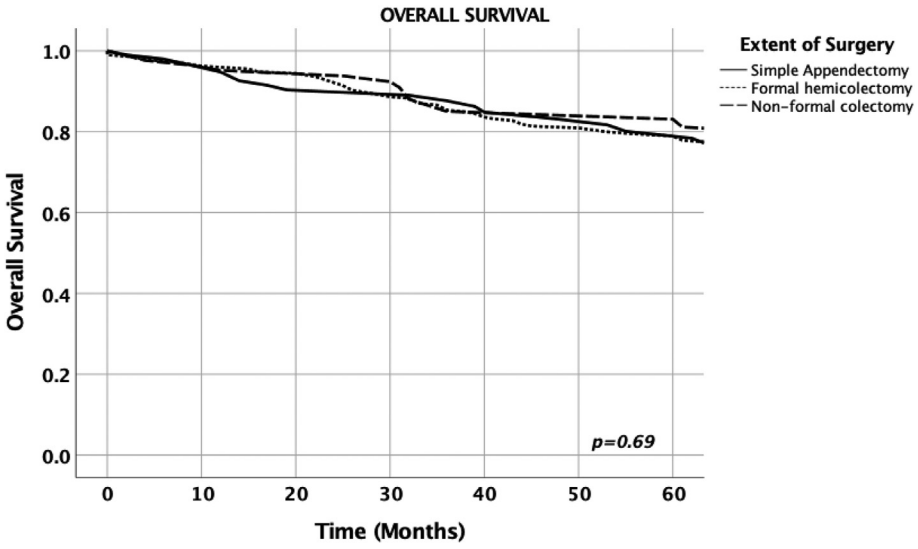

Fig. 3. Overall survival of patients with LAMA, by extent of surgery.

Table 3
Results of multivariate cox regression analysis for disease specific survival (N = 579).

	Hazard Ratio (95%CI)	P value
Surgery		0.784
Appendectomy	-Ref-	
Formal RH	0.86 (0.48–1.56)	0.62
Non Formal RH	0.77 (0.36–1.63)	0.49
Age	1.03 (1.01–1.04)	0.002
AJCC stage		0.001
1	-Ref-	
2	2.59 (1.23–5.42)	0.012
3	5.74 (0.745–3.339)	<0.001

Table 4
Results of multivariate cox regression analysis for overall survival (N = 579).

	Hazard Ratio (95%CI)	P value
Surgery		0.523
Appendectomy	-Ref-	
Formal RH	0.95 (0.62–1.56)	0.95
Non Formal RH	0.76 (0.42–1.38)	0.537
Age	1.05 (1.03–1.06)	<0.001
AJCC stage		0.002
1	-Ref-	
2	2.08 (1.23–3.53)	0.007
3	3.61 (1.74–7.49)	0.001

for mucinous neoplasms of the appendix. Within appendectomy specimens, we examined histological features that could be predictors of lymph node metastasis and discovered that patients with margin positivity and positive lymphovascular invasion (LVI) had a higher risk of 21.3% for lymph node positivity. As such, while a right hemicolectomy is instrumental in appropriately staging patients, we believe that it should be performed on a select subset of LAMA patients with either positive margins on appendectomy specimen or significant risk factors for lymph node metastasis.[12]

Our findings are consistent with a SEER database study by Turaga et al. In their study, analysis of 2101 patients with MA from 1973 to 2007 found that a right hemicolectomy did not offer any

additional disease specific survival benefit compared to appendectomy after adjusting for age, gender, T stage, metastatic disease, and grade of disease.[10] It also demonstrated that well differentiated MAA have a significantly lower risk of lymph node metastasis (6% T1, 0% T2, 7% T3, 22% T4). Similarly, in a prospective database study of 299 MAA patients (Well differentiated n = 44), it was also shown that well and moderately differentiated MAAs had significantly lower rate of lymph node positivity for (6.8% and 5.6% nodal positivity respectively) compared to poorly differentiated tumor.[9] Furthermore, in a smaller prospective database study by Grotz et al., outcomes of 265 patients with MAA ranging from well to poorly differentiated were compared.[8] They also concluded that a right hemicolectomy may not be warranted due to the low rate of lymph node metastasis (5.5%) in well differentiated MAA. Additionally, they went on to show that well, moderately and poorly differentiated MAA have distinct clinical behavior and outcome. This highlights the importance of having a more accurate classification system, to provide improved prognostic stratification that should be incorporated into treatment algorithms.

Our study has some limitations. First, the data we analyzed is retrospective in nature and there is inherent selection bias despite our effort to control for confounding variables. In addition, coding inconsistencies are inherent to large national databases such as SEER and such inconsistencies may lead to type II error. Furthermore, it is important to note that interpretation by different pathologists may be inconsistent due to the challenging classification. A multi-institutional study from seven academic centers was conducted with 43 appendiceal resections, with a total of 15 inquiries classified as low grade appendiceal mucinous neoplasm. Of those classified inquiries, 27% (n = 5) were misdiagnosed and the overall disagreement rate was 53%.[13] The SEER database also does not have data indicating whether or not patients had more than one surgery. Therefore, it is unclear if patients that underwent a formal hemicolectomy had an initial appendectomy, though most neoplasms of the appendix are diagnosed following an appendectomy. Although we accounted for confounding variables, we were unable to control for nodal positivity between the three surgical groups due to the lack of lymph node positive appendectomy patients. Patients in the RHC group may also have had more aggressive LAMA with poorer overall prognosis.

Nevertheless, this study helps fill a gap in existing literature as there are limited studies comparing patient survival following appendectomy versus RHC specifically for the subcategory of LAMA patients. Given the rarity of LAMA, it is likely impossible to perform a comparative study without utilizing large databases such as SEER. Large databases such as SEER allowed us to obtain information from a large sample of patients and helps us derive a more definitive clinical decision for this disease. Furthermore, our analysis was completed on a more uniform sample of patients with respect to appendectomy. Other studies, including the referenced Turaga et al. study, used FORDS code 30 to designate appendectomy. However, FORDS codes 30 is not detailed with respect to appendectomy and can also include ileocecectomy, non-formal partial colectomy and other procedures that include removal of the appendix without necessarily performing a formal hemicolectomy. Therefore, our study defined simple appendectomy as those patients who had no more than 2 lymph nodes resected, while the remainder of patients we categorized as non-formal colectomy. This study provides insight into surgical approach for an overlooked subgroup of appendiceal tumors and contributes to the development of a subtype specific surgical protocol.

In conclusion, the addition of right hemicolectomy in patients with margin negative appendectomy does not offer a survival benefit in patients with non-metastatic, low grade appendiceal mucinous adenocarcinoma, likely because of the low risk of lymph node metastasis in this population. The identification of predictors of lymph node positivity in appendectomy specimen with appendiceal mucinous neoplasms and adenocarcinomas may further aid in selecting patients for right hemicolectomy.

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