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INTRODUCTION

Familial adenomatous polyposis (FAP) is a rare, autosomal-dominant condition characterized by numerous colorectal polyps developing at an early age and if left untreated can lead to the development of colorectal cancer.1–10 FAP is caused by a germline mutation of the tumor suppressor gene APC, which primarily increases the cancer risk of the large bowel, but can also involve other organs including upper gastrointestinal tract, brain, adrenal glands, and thyroid gland.10 The first association of the development of thyroid cancer (TC) in patients with FAP was described by Crial in 1949.11 Additional studies suggest an increased lifetime risk for developing TC with FAP when compared to the general population. The incidence for TC in FAP patients ranges from 1% to 12%, whereas the general population risk is 0.02% to 1%. In our series, one patient of 12 (8%) had TC. Barriers to care included poor patient education about the risk of TC in FAP and miscommunication among specialties for referral for TUS. Also, patients enrolled in a FAP registry have improved care, as they are more likely to undergo TUS than those not enrolled.

Additional studies suggest an increased lifetime risk for developing TC with FAP when compared to the general population. The incidence for TC in FAP patients ranges from 1% to 12%, whereas in the general population the risk is 0.02% to 1%. Furthermore, TC in FAP predominately affects women, and papillary thyroid carcinoma (PTC) is the most common form seen, with the cribriform-morula variant of PTC typically associated with FAP.1,2,4,5,8,12 Though FAP patients have a higher risk of developing TC than the general population, the evidence for the benefit of regular surveillance for TC is weak. Currently, the National Comprehensive Cancer Network for Genetic/Familial High-Risk Colorectal guidelines recommend annual thyroid examination starting in late teenage years and consideration of thyroid ultrasound (TUS) for screening.7 The American College of Gastroenterology guideline recommends annual TUS, and many other studies advocate for annual screening.4,5,8,10,13 However, several studies also suggest that if a patient with FAP has a normal ultrasound or low-risk nodules on TUS, then screening can be extended to every 2 years.4,5

At our institution, the initial design for this study was to determine prevalence of TC in patients with FAP, establish recommendations for TC screening, and to guide workup of thyroid nodules in patients with FAP that are considered higher risk. However, during the course of our study, we encountered several barriers and pitfalls to TC screening among patients with FAP. Namely, a large majority of patients divulged that they did not recall being told that developing TC was an associated risk of FAP or that TUS was recommended. Due to the complicated nature of FAP,
these patients often see multiple specialists including medical genetics, gastroenterologists, colorectal surgeons, endocrinologists, endocrine surgeons, and primary care physicians. At certain institutions, patients diagnosed with FAP are enrolled in specialized hereditary colorectal cancer registries that can provide the resources and expertise for multidisciplinary care and support and coordinate TUS for TC screening.10 As we do not have such a registry at our institution, we shifted the focus of our study to include a case series on the referral pattern for TUS, as well as a survey of patients treated for FAP at our institution to discover if they had been referred for TUS for TC surveillance and barriers to care for those patients who had not. We also surveyed medical providers involved in the care of patients with FAP to determine who they feel should be guiding TC screening and how they feel this multidisciplinary and complicated disease could best be managed.

MATERIALS AND METHODS

Study Population
After institutional review board approval was obtained, we were able to identify patients seen at Emory University for FAP between 2007 and 2017 by using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes related to the disease. There is not a direct code for FAP; therefore, the following ICD-9 codes were used: benign neoplasm of colon (211.3), acquired absence of intestine (large) (V45.72), family history of malignant neoplasm of gastrointestinal tract (V16.0), and family history of genetic disease carrier (V18.9). The following ICD-10 codes were used: benign neoplasm of colon, unspecified (D12.6), family history of colonic polyp (Z83.71), acquired absence of other specified parts of digestive tract (Z90.49), family history of malignant neoplasm of digestive organs (Z80.0), and family history of carrier of genetic disease (Z84.81). A list was generated of patients seen at our institution that matched at least more than one of these diagnostic codes. Next, a thorough chart review was done to determine if each patient identified had the diagnosis of FAP. Exclusion criteria included history of previous TC, patients with multiple endocrine neoplasia syndrome or other underlying conditions besides FAP that could predispose individuals to TC, age <18 years, or deceased at the time of study as they could not participate in the survey.

The patients with FAP who could be included in the study underwent chart review for TUS and were contacted to answer the survey questionnaire (Table I). Basic data were recorded for each patient as applicable: gender, age, if patient had prior TUS, responses to questionnaire, location/size/characteristics of nodules on ultrasound, size of thyroid gland, fine-needle aspiration (FNA) biopsy and results of nodules, operative procedure, date of procedure, final pathology, TC type and stage, and adjuvant radioactive iodine. We included TUS readings and pathology results from both our institution and outside institutions. Patients who were unable to be contacted answered the survey portion of the study were excluded.

Additionally, a medical genetics counselor and a gastroenterologist physician from our institution as well as a FAP registry coordinator at an outside institution were asked to answer the provider survey questions (Table II) to further identify variables that either help or hinder FAP patients in getting TC screening with TUS.

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<table>
<thead>
<tr>
<th>Table I.</th>
<th>Survey Questions to Patients With Familial Adenomatous Polyposis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Have you ever been told there is a recommendation for patients who have been diagnosed with FAP for TC screening with ultrasound? If yes, have you undergone TUS, fine-needle aspiration, or surgery?</td>
</tr>
<tr>
<td>2.</td>
<td>Which medical provider/specialty manages your FAP for regular follow up? Are you in a FAP registry at your institution?</td>
</tr>
<tr>
<td>3.</td>
<td>Have you ever seen a medical genetics specialist? Did they refer you to an endocrinology or otolaryngology physician for TUS?</td>
</tr>
<tr>
<td>4.</td>
<td>Have you ever been referred to an endocrinologist or otolaryngologist for TC screening?</td>
</tr>
</tbody>
</table>

FAP = familial adenomatous polyposis; TC = thyroid cancer; TUS = thyroid ultrasound.

Surveys

Patients with FAP and medical providers involved in their care were contacted by phone or email. The questions were open ended and the answers recorded. The survey questions are listed in Table I and Table II for patients and providers, respectively.

RESULTS

Initially, 11,987 patients were found from the ICD-9 and ICD-10 code search. The majority of those patients were eliminated with chart review showing they did not have FAP; 70 patients were identified with the diagnosis of FAP. The average age of the patients was 36.5 years, ranging from 2 to 66 years old. There were 43 females (61%) and 27 males (39%). Exclusion criteria further eliminated six patients from the study, as four were under age 18 years and two were deceased, leaving a total of 64 patients both chart reviewed and contacted. Of the patients contacted, 35 patients completed the survey for a response rate of 55%. A summary of the responses from the patient survey can be seen in Figure 1. Of the patients who responded to the survey, 13 out of 35 patients (37%) were informed by a healthcare provider that TUS was recommend for screening in patients with FAP and all had undergone ultrasound. There was one patient who was informed of the guideline during the interview portion of this study and asked his surgical oncologist to order the TUS, whereas the remaining 21 patients (60%) were unaware of the guideline. The majority of patients (32 of 35 or 91%) had seen a

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<table>
<thead>
<tr>
<th>Table II.</th>
<th>Survey Questions to Medical Providers for Patients With Familial Adenomatous Polyposis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>How do patients with FAP get referred for your services?</td>
</tr>
<tr>
<td>2.</td>
<td>During your initial visit, is TUS ordered for TC screening or a referral to endocrinology or otolaryngology for TC screening?</td>
</tr>
<tr>
<td>3.</td>
<td>Is there a FAP registry and clinical care coordinator at your institution that helps navigate these patients to the various specialists involved in this disease?</td>
</tr>
<tr>
<td>4.</td>
<td>Which specialty/healthcare provider do you feel should be responsible to make sure these patients get TUS for screening?</td>
</tr>
</tbody>
</table>

FAP = familial adenomatous polyposis; TC = thyroid cancer; TUS = thyroid ultrasound.
medical genetics counselor and been diagnosed with FAP; however, none of those patients had TUS ordered from the medical genetics clinic or were referred to an endocrinologist or otolaryngologist for TC screening with TUS. In addition, 24 patients (69%) stated that they see a gastroenterologist regularly for their follow up. This is followed by four patients (12%) who are followed by their primary care physician or no physician currently at all, respectively, two patients (6%) followed by surgical oncology, and one patient (3%) by hematology/oncology.

Figure 2 reflects the pattern of how often a screening TUS was ordered by a particular medical specialty for patients with FAP. Of the patients who did have TUS, a gastroenterologist either ordered TUS or referred the patient to either endocrinology or otolaryngology in seven of 14 patients (50%). Meanwhile, four of 14 (29%) TUSs were ordered by a nurse practitioner associated with a national FAP registry, two surgical oncologists (14%), and one primary care physician (8%). Of the patients who underwent TUS, 10 of 14 patients (71%) are enrolled in a national FAP registry associated with the institution where they do follow-up clinic appointments. All patients enrolled in a FAP registry were informed of the thyroid cancer screening guideline, had undergone TUS, and reported there is a nurse practitioner or clinical coordinator who can arrange their annual TUS exams. Though the majority of patients see a gastroenterologist for their FAP follow-up, only seven of 24 (30%) ordered or referred a patient for TUS.

Table III depicts the TUS results of 12 of the 14 patients who underwent TUS. There are only 12 of 14 patient findings recorded, as one patient did not have the TUS results available at the time of completion of this study, and one patient underwent total thyroidectomy (TT) at an outside institution, but did not have pathology results available. Of the 12 patients, two of the patients underwent TT, and the pathology results are presented in Table III. One patient was diagnosed with benign follicular adenoma, whereas the other patient (one of 12 or 8%) was diagnosed with PTC, which is consistent with the prevalence of PTC among FAP patients as previously stated. Unfortunately, we did not
TABLE III.
Thyroid Ultrasound and Pathology Findings After Total Thyroidectomy.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, yr</th>
<th>Texture and Size of Gland</th>
<th>Laterality, Size, and Characteristics of Nodules</th>
<th>FNA Results</th>
<th>Operative Procedure ± RAI</th>
<th>Final Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>22</td>
<td>Homogenous; R = 4.2 cm; L = 4.0 cm</td>
<td>None present</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>42</td>
<td>Homogenous; about 4 cm each lobe</td>
<td>R = 3 x 2 x 2 mm cystic nodule; L = 3 x 2 x 4 mm mixed cystic nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>Homogenous; R = 3.5 cm; L = 3.4 cm</td>
<td>None present</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>36</td>
<td>Homogenous; about 4 cm each lobe</td>
<td>R = 3 x 2 x 2 mm colloid nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>46</td>
<td>Homogenous; R = 5 cm; L = 4 cm</td>
<td>R = 5 x 3 x 3 mm spongy nodule; L = 5 x 3 x 4 mm spongy nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>32</td>
<td>Heterogenous multinodular goiter; R = 6.2 cm; L = 5.1 cm</td>
<td>R = 2.5 cm solid, 6 x 4 x 7 mm hypoechoic solid, 10 x 8 x 8 mm solid; L = 8 x 5 x 5 mm solid</td>
<td>FLUS of 2.5 cm solid nodule</td>
<td>TT</td>
<td>Follicular adenoma</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>Homogenous; R = 5.4 cm; L = 5.7 cm</td>
<td>Small subcentimeter cysts bilaterally; L = 5 mm cystic nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>42</td>
<td>Homogenous; both lobes about 2 cm</td>
<td>L = 2 mm cystic nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>33</td>
<td>Homogenous; R = 3.8 cm, L = 3.9 cm</td>
<td>L = 4 x 2 mm cystic nodule</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>38</td>
<td></td>
<td>TT + RAI</td>
<td>T2N0M0 PTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>Homogenous; R = 4.2 cm, L = 3.9 cm</td>
<td>Bilateral subcentimeter cystic nodules</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>19</td>
<td>R = 5.3 cm, L = 5 cm</td>
<td>Homogenous; R = cervical lymph node 1.5 cm; L = cervical lymph node 1.7 cm</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FNA = fine needle aspiration; FLUS = follicular lesion of undetermined significance; L = left; PTC = papillary thyroid carcinoma; R = right; RAI = radioactive iodine; TT = total thyroidectomy.

DISCUSSION
The risk of developing TC in patients with FAP is well established,5,10 and current guidelines recommend annual TUS starting in the late teenage years.7,13 However, we found that patients seen at our institution were not consistently getting TUS or referrals to specialties such as endocrinology or otolaryngology that manage thyroid disease. Only 37% of subjects said they had been told about getting TUS to screen for TC upon initial interview. We identified that the main barriers to care were patient education and inconsistency in which specialty of healthcare providers took responsibility in managing the multidisciplinary aspects of FAP. Unfortunately, this lack of centralized care can add to the patients’ decreased understanding of the full context of the risks of their disease, thereby not undergoing recommended screening. However, our study did identify that nearly all patients enrolled in FAP registries were informed of the guideline for TUS and had annual exams, and suggests that patients who are enrolled in a FAP registry are more likely to undergo ultrasound for TC screening than those not enrolled.

Additionally, a gastroenterology physician and a medical genetics counselor from our institution as well as a FAP registry coordinator at an outside institution were asked to answer the provider survey with responses. At our institution, both the gastroenterologist and medical genetics counselor stated that they discuss risks of development of colorectal cancer and other organ manifestations of FAP, including increased risk of developing TC. However, generally, the gastroenterologists will refer the patient to medical genetics and expect that screening exams or subspecialty referrals will be made there. It is not standard that patients are referred for TUS from a gastroenterology clinic, which is consistent with the 30% referral pattern to endocrinology or otolaryngology that we found at our institution and outside institutions. Meanwhile, the medical genetics counselor stated that patients with FAP are diagnosed and counseled on the manifestations of disease, but they do not make any clinical referrals and expect either the patient’s primary care physician or the specialist that manages their FAP care to order screening exams such as TUS or make referrals to other subspecialties. All patients interviewed who are enrolled in a FAP registry at an outside institution were informed of getting TUS and underwent annual screenings. The FAP coordinator we interviewed expressed that given that FAP is a complex disease with multiple manifestations, it is important to have a clinical care coordinator that specializes in FAP to help these patients navigate all the subspecialties involved and arrange follow-up, imaging, and tests to prevent this pitfall to care.

The Collaborative Group of the Americas on Inherited Colorectal Cancer was established in 1995 and developed registries for patients with inherited colorectal cancer disorders, including FAP, at 14 cancer centers in the United States and Canada that help in selection of appropriate screening tests/therapy and managing the multidisciplinary care of the disorder. Studies have shown that FAP patients enrolled in registries for inherited colorectal cancer have improved outcomes compared to those treated in centers without such registries15–18 and can improve the prognosis of FAP due to earlier detection.19 Therefore, we argue that
patients enrolled in FAP registries have better access to screening TUS than that at institutions without registries. However, if a patient is being treated for FAP at an institution without a registry, there needs to be improved communication among medical specialties to establish who will be managing referrals to the multidisciplinary teams involved in FAP syndrome.

The risk of malignancy in a thyroid nodule of a FAP patient may be greater than in an individual in the general population, which is why TUS screening is so vital. Multiple studies suggest the reason for this increased risk is a possible association with the site of APC gene mutation and occurrence of TC in FAP. The American Thyroid Association recommends ultrasound-guided FNA of thyroid nodules >1 cm in size and/or have suspicious findings (ill-defined margins, hypoechoic echo texture, microcalcifications, or central blood flow), history of radiation exposure, or family history of TC. Therefore, otolaryngologists should be aware that FAP patients have a higher risk of developing TC when evaluating these patients and could consider a lower threshold for biopsy of concerning nodules. Herraz et al. found that six of 51 patients with FAP had PTC, for overall prevalence of 12%, with suspicious nodules diagnosed with PTC ranging from 9 to 15 mm, arguing that nodules <9 mm may also be malignant, and periodic follow-up with ultrasound and FNA should be strongly considered. Monachese et al. conducted a prospective analysis of 264 subjects with FAP to assess the outcome of TUS screening with an average follow-up 4.8 years. TC developed in six patients (2.3% prevalence), and they found that factors associated with development of TC were female sex and presence of baseline nodules on TUS that increased in size over time. This study and other reports suggest that patients with FAP who have a normal baseline TUS should get a repeat every 2 years, whereas patients with baseline nodules should get annual exams and lower threshold for nodule biopsy.

In our series, one patient of 12 (8%) had PTC, which is consistent with prevalence in previous reports. Approximately 1.2% of men and women will be diagnosed with TC at some point in their lifetime, and there is a 98.1% 5-year survival rate after diagnosis. Some investigators claim that the risk of death from TC is negligible and therefore do not recommend routine TUS screening. TUS screening is not recommended in the general population unless there are risk factors for TC and measures have been taken to decrease the frequency of FNA for thyroid nodules. However, the natural history of TC in the setting of FAP has not been fully characterized, and more studies need to be done to better define the prognosis of TC in the FAP population. Additionally, FAP patients have longer life expectancy after mortality-reducing colectomies, and therefore often have greater risk of developing TC at under 30 years old, which increases the need for earlier detection and regular screening. The cost of TUS is relatively low; therefore, we would argue that a patient with FAP should at least be informed of their higher risk of TC and undergo a baseline TUS. The cost effectiveness of TUS for avoidance of cancer has not yet been proven, and further studies need to be done to elucidate this.

There are several limitations to this study. We had a small sample size and only obtained survey data in 55% of patients originally identified to have FAP at our institution. This was due to various reasons, but mostly the inability to contact the patients due to change in contact information. Without an ICD-9 or ICD-10 code for FAP, it was difficult to fully capture all of the FAP patients seen at our institution between 2007 and 2017, and there may have been many patients excluded from the study for that reason. As a retrospective survey, there may be bias among patients who do not recall counseling about risk of TC or undergoing TUS because they were diagnosed several years prior. Also, many of these patients are seen by multiple specialists at different institutions and obtaining medical records of previous TUS and pathology was a limitation to the study.

This is the first study that demonstrates barriers for FAP patients to TC screening. Additionally, many patients who participated in this study who had not had TUS for screening requested a referral from their primary care or gastroenterologists for TUS because they wished to have baseline screening. More importantly, this study prompted a discussion at our institution to start a quarterly multidisciplinary meeting about patients with FAP to ensure these patients are being followed by appropriate specialists and getting recommended screening and ancillary testing.

CONCLUSION

FAP patients are at a higher risk of developing TC and at a younger age. Therefore, it is important for these patients to be informed and follow the recommended guideline to get a baseline TUS for screening starting in the late teenage years and as well as repeat TUS every 1 to 2 years depending on their baseline exam. FAP syndrome is a complex disease that requires a multidisciplinary approach. We identified the barriers to care for these patients as being patient education about increased risk of developing TC and miscommunication among specialties as to which provider will navigate the patient to the multiple medical and surgical specialties involved in FAP. Therefore, we recommend that at time of diagnosis of FAP, that patients are informed of their increased risk of developing thyroid cancer and are referred to either endocrinology or otolaryngology for thyroid cancer screening. Additionally, we propose that at institutions managing patients with FAP, it is important to have a clinical coordinator or registry that specializes in FAP to help these patients navigate all the subspecialties involved to arrange follow-up and imaging to prevent this pitfall to care.

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BIBLIOGRAPHY


