Secondary Appendiceal Tumors: A Review of 139 Cases

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Background/Aims: This study evaluated the clinicopathologic characteristics of patients with secondary appendiceal tumors (SATs). **Methods:** We performed a single-center, retrospective study of patients with pathologically confirmed SATs. **Results:** Among 180 cases of appendiceal malignancies diagnosed between 2000 and 2007, 139 cases (77.2%, 46 male) were SATs. The median age at SAT diagnosis was 55 years. The most common primary origin was the ovary. The mode of appendiceal involvement was metastasis in 122 and invasion in 17 patients. Extra-appendiceal involvement was present in 134 patients. The only manifestation that could be attributed to the SAT itself was appendicitis (n=8). Serosal involvement was predominant. The median survival after diagnosis of SAT was 22.6 months. In the Cox regression analysis, chemotherapy included in the treatment was the only factor associated with prolonged survival (hazards ratio, 0.12; 95% confidence interval, 0.06-0.23; $p < 0.001$). Complete resection of the SAT had no influence on survival. **Conclusions:** SATs accounted for 77.2% of all pathologically diagnosed appendiceal malignancies. The most common origin was the ovary. SATs were usually associated with widespread disease, and the median survival after SAT diagnosis was 22.6 months. Complete resection of the SAT had no influence on survival. (*Gut Liver* 2010;4:351-356)

Key Words: Neoplasms; Appendix; Secondary

INTRODUCTION

Secondary appendiceal tumors (SATs) are rare. In a review of 8,699 appendectomy specimens over a 23-year period, no more than 15 cases were identified as SATs.¹

Most SATs have been reported in the form of case reports. The primary sites include the urogenital tract,²⁻⁴ gastrointestinal tract,^{5,6} breast,⁷ and lung.^{6,8}

To the best of our knowledge, there is no prior report of a large series of SATs to date. One large scale review of appendectomy specimens dates back to the 1970s.¹ Another large scale review of appendectomy specimens only included those from patients that were treated for a clinical diagnosis of appendicitis, with no report of SATs.⁹ In addition, there is little data on the clinicopathologic features of patients with SATs.

The aim of this study was to investigate the clinicopathologic characteristics of patients with SATs diagnosed over a period of 8 years at a single tertiary hospital.

MATERIALS AND METHODS

We reviewed the pathology reports of 7,759 surgically removed appendices, as independent appendectomies or as a part of other surgical procedures between January 2000 and December 2007 at our hospital. For neuroendocrine tumors of the appendix, the malignancy was categorized according to the WHO classification.¹⁰ The diagnosis of SAT was made when the appendix was directly invaded by the primary malignancy or was involved as a result of metastasis.

Gender, the primary origin and the pathology of the SAT, ages at diagnosis of the primary malignancy and SAT, presenting symptoms and signs associated with the SAT, the interval between the diagnosis of the primary malignancy and the SAT, involvement of organs other than the appendix, the diagnosis of secondary involvement of the appendix before surgery on imaging, de-

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tection of the SAT during surgery, the mode of appendiceal involvement (i.e., metastasis or direct invasion), treatment after the diagnosis of the SAT, and survival after the diagnosis of the SAT were evaluated. Metachronously diagnosed SATs were defined as SATs not diagnosed at the first surgery. The endpoints of this study were patient death or December 31, 2008. This study was approved by the institutional review board of our hospital.

The median survival was estimated using the Kaplan-Meier method. Factors associated with prolonged survival were determined using the log-rank test. The factors including gender, age at diagnosis of the SAT, and factors associated with survival in the univariate analysis at a $p < 0.20$ were included as covariates in the Cox regression analysis. Values are reported as the median. Two-sided p values of < 0.05 were considered statistically significant. All analyses were performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Overview of the patients (Table 1)

Among 7,759 appendiceal specimens, 1,497 appendices were removed under the impression of appendicitis and 44 under the impression of primary appendiceal tumor; 6,218 appendices were removed incidentally. A total of 180 cases of appendiceal malignancies were identified. Among these, 139 cases (46 male and 93 female) were SATs, accounting for 77.2% of all pathologically confirmed appendiceal malignancies. All SATs were diagnosed from surgical specimens. The median age at diagnosis of the SAT was 55 (range, 3-90 years). The median age at diagnosis of the primary malignancy was 55 (range, 3-90 years). The primary origins were the ovary ($n=59$), colorectum ($n=36$), stomach ($n=23$), uterine corpus ($n=3$), uterine cervix ($n=2$), pancreas ($n=2$), peritoneum ($n=2$), prostate ($n=1$), omentum ($n=1$), lung ($n=1$), jejunum ($n=1$), ileum ($n=1$), gallbladder ($n=1$), fallopian tube ($n=1$), bladder ($n=1$), testis ($n=1$), and others (1 case of diffuse large B cell lymphoma, 1 case of acute lymphoblastic leukemia, and 1 case of retroperitoneal sarcoma). The mode of appendiceal involvement was metastasis in 122 and invasion in 17 patients. SATs were diagnosed synchronously with the primary malignancy in 111 and metachronously in 28 patients. Peritoneal seeding was present in 110 patients; extra-appendiceal involvement of the primary tumor was present in 134 patients.

SATs were anticipated in preoperative computed tomography or ultrasonography in 5 patients. Full colonoscopic exam was done in 29 patients. Of the 29 patients, 25 pa-

Table 1. Overview of the 139 SAT Patients

Age at diagnosis of SAT, yr	
Median	55
Range	3-90
Age at diagnosis of primary malignancy, yr	
Median	55
Range	3-90
Gender, n (%)	
Male	46 (33.1)
Female	93 (66.9)
Mode of appendiceal involvement, n (%)	
Metastasis	122 (87.8)
Invasion	17 (12.2)
Chronology of appendiceal involvement, n (%)	
Synchronous	111 (79.9)
Metachronous	28 (20.1)
Peritoneal seeding, n (%)	110 (79.1)
Extra-appendiceal involvement, n (%)	134 (96.4)
Appendiceal wall involvement, n (%)*	
Serosa only	45 (45.4)
Serosa to proper muscle layer	18 (18.2)
Subserosa only	9 (9.1)
Serosa to subserosa	6 (6.1)
Serosa to mucosa	5 (5.1)
Serosa to submucosa	5 (5.1)
Subserosa to proper muscle layer	4 (4.0)
Subserosa to mucosa	3 (3.0)
Subserosa to submucosa	2 (2.0)
Proper muscle layer only	1 (1.0)
Proper muscle layer to mucosa	1 (1.0)

SAT, secondary appendiceal tumor.

*Results from the 99 patients with detailed description of the appendiceal wall involvement.

tients showed a normal appendiceal opening. In the remaining 4 patients, cecal involvement of the tumor was noticed. Positron emission tomography was performed in 18 patients. Four patients showed no abnormality in the abdominopelvic cavity, 9 patients evidence of peritoneal seeding, 4 patients hypermetabolic lesion in the right lower quadrant, and 1 patient hypermetabolic lesions in the pelvic area.

A detailed description of the appendiceal wall involvement was available in 99 patients. They were: serosa only ($n=45$), serosa to proper muscle layer ($n=18$), subserosa only ($n=9$), serosa to subserosa ($n=6$), serosa to mucosa ($n=5$), serosa to submucosa ($n=5$), subserosa to proper muscle layer ($n=4$), subserosa to mucosa ($n=3$), subserosa to submucosa ($n=2$), proper muscle layer only ($n=1$), and proper muscle layer to mucosa ($n=1$). In the 79 patients with serosal involvement, 74 patients had appendix involved by metastasis; among these 74 patients, 65 patients (87.8%) had peritoneal seeding. Only 11 patients had appendiceal metastasis without evidence of peritoneal seeding. However, even in these patients, se-

rosal involvement was present in 9 patients (serosa only in 3, serosa to proper muscle layer in 3, serosa to submucosa in 2, and serosa to mucosa in 1).

2. Synchronously diagnosed patients

A total of 111 SATs were diagnosed synchronously with the primary malignancy. Twenty-nine patients were male. The median age at diagnosis was 57 (range, 3-90 years). The origin and pathology of the primary malignancies are listed in Table 2. Four patients presented with acute appendicitis, i.e., a secondary malignancy was diagnosed on appendectomy, and subsequent work up revealed the primary malignancy. In the other patients, no symptoms or signs attributable to SAT were noted. SAT was anticipated preoperatively, i.e., on imaging, in only 4 patients. SAT was anticipated intraoperatively in 28 patients. The mode of appendiceal involvement was metastasis in 96 and invasion in 15 patients. Extra-appendiceal involvement of the primary tumor was present in 107 patients. Peritoneal seeding was identified in 89 patients.

Treatment consisted of surgery plus chemotherapy (n=92), surgery (n=13), surgery plus chemotherapy plus radiation therapy (for bony metastasis) (n=3), surgery

plus radiation therapy (n=1), surgery plus chemotherapy plus gamma knife surgery plus craniotomy (for brain metastasis) (n=1), and surgery plus chemotherapy plus gamma knife surgery plus radiation therapy (for brain metastasis) (n=1).

3. Metachronously diagnosed patients

Twenty-eight SATs were diagnosed metachronously with a median interval of 20.9 months (range, 1.7-70.7 months). The median ages at diagnoses of the SAT and primary malignancy were 51 years (range, 18-73 years) and 49.5 years (range, 17-72 years), respectively. Seventeen patients were male and 11 patients were female. The origin and pathology of the primary malignancies are listed in Table 3.

Four patients presented with acute appendicitis. Other symptoms and signs included abdominal pain (without appendicitis) (n=9), palpable mass (n=3), and constipation (n=2); however, these symptoms were not attributed to the SATs, but to metastatic lesions at other sites. Ten cases of SATs were diagnosed while undergoing surgery for Krukenberg tumors (n=5), other metastatic sites (n=1), colostomy repair (n=1), recurrence at the remain-

Table 2. Origin and Pathology of the Primary Malignancies in Synchronously Diagnosed SAT Patients

Origin	Pathology
Ovary (n=56)	Serous adenocarcinoma (n=45) Serous surface papillary adenocarcinoma (n=3) Undifferentiated carcinoma (n=3) Clear cell adenocarcinoma (n=1) Mixed serous adenocarcinoma and undifferentiated carcinoma (n=1) Mixed large cell neuroendocrine carcinoma and adenocarcinoma (n=1) Immature teratoma (n=1)
Colorectum (n=35)	Endometrioid adenocarcinoma (n=1) Adenocarcinoma (n=20) Mucinous adenocarcinoma (n=7) Signet-ring cell carcinoma (n=3) Diffuse large b cell lymphoma (n=4) Burkitt lymphoma (n=1)
Stomach (n=7)	Adenocarcinoma (n=5) Adenocarcinoma, diffuse type (n=2)
Uterine corpus (n=3)	Endometrial serous adenocarcinoma (n=1) Endometrial adenocarcinoma (n=1) Endocervical adenocarcinoma (n=1)
Uterine cervix (n=2)	Carcinosarcoma (n=1) Minimal deviation adenocarcinoma (n=1)
Peritoneum (n=2)	Malignant mesothelioma (n=2)
Prostate (n=1)	Adenocarcinoma (n=1)
Lung (n=1)	Adenocarcinoma (n=1)
Jejunum (n=1)	Malignant gastrointestinal stromal tumor (n=1)
Gallbladder (n=1)	Adenocarcinoma (n=1)
Fallopian tube (n=1)	Serous adenocarcinoma (n=1)
Others (n=1)	Diffuse large B cell lymphoma (n=1)

SAT, secondary appendiceal tumor.

Table 3. Origin and Pathology of the Primary Malignancies in Metachronously Diagnosed SAT Patients

Origin	Pathology
Stomach (n=16)	Signet-ring cell carcinoma (n=10) Adenocarcinoma (n=2) Adenocarcinoma, diffuse type (n=2) Adenocarcinoma, intestinal type (n=1) Mucinous adenocarcinoma (n=1)
Ovary (n=3)	Serous adenocarcinoma (n=2) Mucinous adenocarcinoma (n=1)
Pancreas (n=2)	Ductal adenocarcinoma (n=1) Intraductal papillary mucinous neoplasm (n=1)
Colorectum (n=1)	Adenocarcinoma (n=1)
Omentum (n=1)	Malignant gastrointestinal stromal tumor (n=1)
Ileum (n=1)	Diffuse large B cell lymphoma (n=1)
Bladder (n=1)	Adenocarcinoma (n=1)
Testis (n=1)	Seminoma (n=1)
Others (n=2)	Acute lymphoblastic leukemia (n=1) Retroperitoneal sarcoma (n=1)

SAT, secondary appendiceal tumor.

ing primary site (n=1), and in patients undergoing a second look operation for primary ovarian malignancies (n=2). SAT was anticipated preoperatively in only 1 patient. SAT was anticipated intraoperatively in 4 patients. The mode of appendiceal involvement was metastasis in 26 and invasion in 2 patients. Recurrence at the remnant primary site was found in 4 patients. Extra-appendiceal involvement of the primary tumor was present in 27 patients. Peritoneal seeding was identified in 21 patients.

Treatment consisted of surgery plus chemotherapy in 17 patients and surgery in 11 patients. Although complete resection of the SAT was achieved in 27 patients, R0 resection was achieved in only 2 patients.

4. Survival

The median survival after diagnosis of the SAT was 22.6 months (Fig. 1). The univariate analyses showed that female gender ($p<0.001$), synchronously diagnosed SATs ($p<0.001$), genitourinary organs as the primary origin ($p<0.001$), anticipation of SAT during surgery ($p=0.016$), and chemotherapy included in the treatment ($p<0.001$) were associated with prolonged survival (Table 4). The multivariate analysis showed that chemotherapy included in the treatment was the only factor associated with prolonged survival (hazards ratio, 0.12; 95% confidence interval, 0.06-0.23; $p<0.001$) (Table 5).

DISCUSSION

The purpose of this study was to investigate clin-

Fig. 1. Cumulative survival after diagnosis of secondary appendiceal tumor.

icopathologic features of patients with SATs. SATs accounted for 77.2% of all pathologically confirmed appendiceal malignancies. The ovary was the most common primary origin, followed by the colorectum and stomach. The SATs were usually associated with widespread disease, as demonstrated by the high percentage of extra-appendiceal involvement and peritoneal seeding. The median survival after diagnosis of the SAT was 22.6 months.

In a review of 8,699 appendectomy specimens by Schmutzer *et al.*,¹ a total of 17 malignancies were identified. They were primary adenocarcinoma (n=2), metastatic adenocarcinoma (n=12), and lymphoma (n=3). The details of the metastatic adenocarcinoma and lymphoma were not presented in that study; we can speculate that the number of SATs in their study range between 12 and 15 cases. In a review of 2,216 appendectomy specimens from patients treated for the clinical diagnosis of appendicitis, no SATs were reported.⁹ The origins of SATs reported include the ovary,² uterus,^{3,4} gallbladder,⁵ stomach,⁶ lung,^{6,8} and breast.⁷ In our study, the most common primary site was the ovary, followed by the colorectum and stomach. Since the ovary is in proximity to the appendix and ovarian malignancies have tendency to spread beyond the pelvis at the time of diagnosis,¹¹ this observation may reflect the natural course of the ovarian malignancies. The colorectum is in continuity with the appendix, which may explain the relatively higher rate of SATs. The high rate of stomach cancer can be explained by the fact that it is the most common cancer in Korea.¹²

In our study, the few symptomatic patients presented with acute appendicitis, abdominal pain without appendi-

Table 4. Univariate Analysis of the Factors Associated with Survival after Diagnosis of SAT

Factor	Median survival*	p-value
Gender		<0.001
Male (n=46)	9.3	
Female (n=93)	34.1	
Age at diagnosis of the SAT		0.178
≥50 yr (n=92)	30.9	
<50 yr (n=47)	17.5	
Chronological relationship between primary malignancy and SAT		<0.001
Synchronous (n=111)	30.9	
Metachronous (n=28)	6.8	
Primary origin		<0.001
Genitourinary organs (n=68)	37.0	
Non-genitourinary organs (n=71)	10.9	
Presentation with acute appendicitis		0.168
Yes (n=8)	9.3	
No (n=131)	24.6	
Anticipation of SAT on imaging		0.264
Yes (n=5)	37.2	
No (n=134)	21.5	
Anticipation of SAT during surgery		0.016
Yes (n=32)	39.3	
No (n=107)	19.1	
R0 resection		0.252
Yes (n=11)	28.7	
No (n=128)	21.5	
Complete resection of SAT		0.901
Yes (n=137)	22.6	
No (n=2)	0.7	
Secondary involvement of organs other than the appendix		0.478
Yes (n=134)	35.6 [†]	
No (n=5)	38.8 [‡]	
Mode of appendiceal involvement		0.923
Invasion (n=17)	17.6	
Metastasis (n=122)	23.5	
Peritoneal seeding		0.727
Yes (n=110)	23.5	
No (n=29)	17.6	
Treatment		<0.001
Chemotherapy included (n=114)	33.2	
Surgery only (n=25)	2.3	
Recurrence at primary site		0.847
Yes (n=4)	10.5	
No (n=135)	23.5	

Results of log-rank test.

SAT, secondary appendiceal tumor.

*Value in months; [†]Mean survival; [‡]Mean survival (median survival not reached).**Table 5.** Multivariate Analysis of the Factors Associated with Survival after Diagnosis of SAT

Factor	HR	95% CI	p-value
Female gender	0.92	0.53-1.60	0.768
Age at diagnosis of the SAT ≥50 yr	0.75	0.49-1.16	0.196
Genitourinary organs as the primary origin	0.68	0.39-1.18	0.169
Presentation with acute appendicitis	1.10	0.49-2.50	0.818
Synchronous diagnosis of primary malignancy and SAT	0.76	0.42-1.38	0.363
Anticipation of SAT on surgery	0.57	0.32-1.02	0.057
Chemotherapy included in the treatment	0.12	0.06-0.23	<0.001

HR, hazards ratio; CI, confidence interval; SAT, secondary appendiceal tumor.

citis, palpable mass, and constipation. However, the only manifestation that could be attributed to the SAT itself was acute appendicitis. In four of eight patients that presented with appendicitis, the appendicitis was the initial manifestation of the primary malignancy; the appendectomy revealed the secondary malignancy, and the primary malignancy was diagnosed on subsequent work up.

The mode of appendiceal involvement was predominantly metastasis. The majority of metastases are likely to be the result of peritoneal seeding; this is supported by the high percentage of patients with peritoneal seeding. Serosal involvement was common in the SATs. The serosal involvement is presumed to be due to transcoelomic spread.¹³ This is further supported by the results of our study. However, it should be noted that even in patients without evidence of peritoneal seeding, serosal involvement was predominant.

Isolated metastasis to the appendix was rare in our study. Only two cases (colorectal signet-ring cell carcinoma and acute lymphoblastic leukemia) had isolated metastasis to the appendix.

In some malignancies, resection of secondarily involved organs may lead to prolonged survival. Such examples are liver metastases from colorectal cancer¹⁴ and pancreatic metastases from renal cell carcinoma.¹⁵ However, this does not seem to apply to SATs. The multivariate analysis showed that chemotherapy included in the treatment was the only factor associated with prolonged survival. Complete resection of the SAT had no influence on survival.

Our study has limitations. This study is based on the information collected from patients with pathologically diagnosed appendiceal malignancies only. The primary malignancies are of a heterogeneous nature. In addition, treatments are varied. Due to heterogeneous nature of the patients, the survival analysis performed in this study may be of limited value. Nevertheless, this is the first large-scale review of SATs, and provides some insight into the nature of SATs.

In conclusion, SATs accounted for the majority of pathologically confirmed appendiceal malignancies. The ovary was the most common primary origin, followed by the colorectum and the stomach. The SATs were usually associated with widespread disease. Metastasis was the predominant mode of involvement, and serosal involvement was common. The median survival after diagnosis

of SAT was 22.6 months. Complete resection of SAT had no influence on the patient prognosis.

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