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Analysis of appendiceal neoplasms in 1,423 appendectomy specimens: a 10-year retrospective cohort study from a single institution

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SUMMARY

OBJECTIVE: This study aimed to reveal the incidence, clinicopathological, and oncological outcomes of appendiceal neoplasms.

METHODS: This is a retrospective cohort study from a single institution. Patients with a pathological diagnosis of malignancy who underwent appendectomy between January 2011 and 2021 were included in the study, and groups were formed according to pathological type. Clinical, pathological, and oncological results were compared in these groups.

RESULTS: The incidence of neoplasia was 2.38% (n=34) in a cohort of 1,423 appendectomy cases. Of the cases, 56% (n=19) were female. The median age in the entire cohort was 55.5 (range: 13–106) years. In the cohort, the rate of neuroendocrine tumor mucinous cystadenoma adenocarcinoma, and low-grade appendiceal mucinous neoplasm, according to the American Joint Committee on Cancer classification of appendiceal neoplasms, was 32.3% (n=11), 26.4% (n=9), 26.4% (n=9), and 14.7% (n=5), respectively. Neuroendocrine tumor patients (median age: 35 years) were younger than the other groups (p=0.021). Secondary complementary surgery was performed in 66.7% (n=6) of adenocarcinoma patients and 27.3% (n=3) of neuroendocrine tumor patients. Right hemicolectomy was performed in all neuroendocrine tumor patients requiring secondary surgery, while right hemicolectomy was performed in three adenocarcinoma patients and cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in three adenocarcinoma patients. After a median follow-up of 44.4 months (95% confidence interval: 18.6–70.1), the mean survival rate was 55% in appendiceal adenocarcinoma patients compared to 100% in neuroendocrine tumor patients.

CONCLUSION: Appendiceal neoplasms are rare but remain an important cause of mortality. Appendiceal adenocarcinomas are associated with poorer oncological outcomes compared to other neoplasms.

KEYWORDS: Appendectomy. Appendiceal neoplasms. Incidence. Pathology.

INTRODUCTION

The estimated incidence of appendiceal tumors was 0.12 cases per 1,000,000 people per year; however, recent large database studies have reported the incidence to be as high as 0.97 cases per 100,000 people. It is unclear whether this increase reflects an actual change in disease occurrence or simply more identification and reporting. Appendiceal tumors are rare but remain an important clinical problem in terms of optimal management. Surgeons should be familiar with the effects of appendiceal pathology[1-4].

Current classification of mucinous tumors, PSOGI (Peritoneal Surface Oncology Group International) 2012 Diagnostic and Staging Criteria for Epithelial Appendiceal Neoplasms, and the American Joint Committee on Cancer Staging Manual (AJCC, 8th edition) have been updated[5,6].

The five main histopathological subtypes of appendiceal neoplasms are as follows: neuroendocrine neoplasms (NENs), which are nonepithelial tumors; mucinous neoplasms; goblet cell adenocarcinomas; colonic-type (nonmucinous) adenocarcinomas; and signet ring cell adenocarcinomas, which are epithelial tumors. Due to the nature of the clinical presentation of acute appendicitis, preoperative or intraoperative diagnosis of appendiceal neoplasms is very rare. Although appendectomy for acute appendicitis is usually the adequate treatment for most of these neoplasms, clinical management is highly dependent on tumor type, histological grade, pathological stage, and the status of resection margins and can range from radical surgery to systemic chemotherapy or surveillance[4].

The risk factors for the presence of an underlying malignancy in a patient presenting with acute appendicitis are not

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well established. Complicated appendicitis by itself has been associated with an increased risk of underlying malignancy. The risk is even higher in patients presenting with a periappendiceal abscess compared with patients with uncomplicated appendicitis[7,8]. Neoplasms of the appendix are usually not suspected before surgery and are found during surgery or on pathological examination. Increasing awareness of the disease, its pathophysiology, and its presentation has led to increased interest in the fields of surgery and medical oncology regarding the treatment of diseases with peritoneal dissemination. An understanding of the histologic features, imaging appearances, and staging of appendiceal neoplasms facilitates an accurate radiologic description, which guides surgical and oncologic management. This requires evaluation of the appendix and mesoappendix in the setting of acute appendicitis, the peritoneum and organ surfaces in patients with mucinous tumors, and lymph nodes and solid organs in nonmucinous and NENs. Although there are studies in the literature on the biological behavior of appendiceal tumors, the evidence contains various inconsistencies, and limited data exist on the long-term outcomes of appendiceal neoplasms[9,10].

The present study aimed to assess the incidence and long-term outcomes of appendiceal neoplasms according to their histological types.

METHODS

After the approval (date: 10.09.2021, No: 114/36) was granted by our ethics committee, a retrospective analysis was made on the Çukurova University patient database from January 2011 to January 2021. While creating the database, electronic records, nurse observation forms, pathology records, and survival information obtained from the population directorate were created. Our institution is a third-level university hospital and serves as the reference hospital of a city with a population of 2 million. All adult patients aged ≥18 years with evidence of acute appendicitis or an appendiceal mass on preoperative imaging were included in the study. The final pathological diagnoses of the patients were retrospectively reviewed from the pathology records. The results of patients with neuroendocrine tumor (NET), mucinous cystadenoma (MC), adenocarcinoma, and low-grade appendiceal mucinous neoplasm (LAMN) were analyzed. Inflammatory conditions and negative appendectomy patients were not included. Imaging modalities included ultrasound, computed tomography, and magnetic resonance imaging. In our routine practice, an ultrasound examination was performed on each patient, and a computed tomography or MRI examination was performed for every suspicious finding, one of the advanced imaging methods. Age alone was not a criterion for the selection of imaging modalities. Demographic information included age, gender, tumor marker levels (measured in the postoperative period), the type of surgery (emergency or elective), intraoperative findings (perforation or mesoappendiceal invasion), pathological TNM stages, tumor size (obtained from pathology records), need for additional surgical intervention, and survival. The patients were classified into four groups: group 1 (low-grade mucinous neoplasia); group 2 (adenocarcinoma); group 3 (MC); and group 4 (NET). The data were compared between these groups.

We applied conventional or laparoscopic appendectomy to the patients. We routinely performed mesoappendix resections for all patients.

The follow-up of the cases included wound healing assessment at postoperative week 1 in our clinic and re-admission with pathology results. Patients with a pathology report of malignancy were followed up by the Colorectal Surgery department.

The main aim of the study was to identify different patterns of unusual histopathological findings in patients with provisional diagnosis of acute appendicitis and to assess their prevalence as well as their clinical significance.

The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects."

Statistical assessment

The study data were analyzed using SPSS (Statistical Package for the Social Sciences, Inc.; Chicago, IL, USA) version 23.0. The study data were evaluated using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum). The Shapiro-Wilk test was used to assess the normality of the data. The Kruskal-Wallis test was used to compare the non-normally distributed data, while Tamhane's T2 test, one of the post hoc tests, was used to analyze the intergroup differences. Categorical variables were compared using Pearson's chi-square test, Fisher-Freeman-Halton exact test, and Fisher's exact test. Survival was analyzed using Kaplan-Meier analysis and log-rank test. Since the number of patients was small, we did not look for prognostic factors. The statistical significance level was set to 0.05 for all tests.

RESULTS

The incidence of neoplasia was 2.38% (n=34) in a cohort of 1,423 appendectomy cases, 1,412 of which were performed under emergency conditions during the study period. Of the

cases, 56% (n=19) were female. The median age in the entire cohort was 55.5 (range: 13–106) years. In the cohort, the rate of NET, MC, adenocarcinoma, and LAMN, according to the AJCC (8th edition) classification of appendiceal neoplasms, were 32.3% (n=11), 26.4% (n=9), 26.4% (n=9), and 14.7% (n=5), respectively. Gender distribution was similar in the groups (p=0.223). Patients in group 4 were younger (median age: 35 years) (p=0.021). The elective surgery rate was higher in group 2 than in other groups (66.7%) (p=0.048). Two patients in group 3 and one patient in group 4 had intraoperative perforation. Demographic and clinical data are presented in Table 1.

Tumor size was similar in the groups (p=0.274). There was mesoappendiceal invasion only in group 2 (33%) (p=0.027). In group 2, 55.6% of the patients had metastases (p=0.001). Right hemicolectomy was performed in all NET patients requiring secondary surgery, while right hemicolectomy was performed in three adenocarcinoma patients and cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in three adenocarcinoma patients. Table 2 shows the pathology data.

After a median follow-up of 44.4 months (95% confidence interval [CI]: 18.6–70.1), the mean survival rate was 55% in appendiceal adenocarcinoma patients compared to 100% in NET patients. Survival was shorter in group 1 (22.7 vs. 43.6 vs. 55.6 vs. 49.1; p=0.011). The results are presented in Table 3.

DISCUSSION

The present study, which presented the clinical characteristics and oncological outcomes of appendiceal neoplasms in a cohort of appendectomy cases, identified NETs as the most common type of tumor. In our female-predominant population, adenocarcinoma patients had an advanced age and underwent appendectomy mostly under elective conditions. This group also had a high rate of mesoappendiceal invasion and therefore required additional surgical interventions. This group of patients tended to be metastatic and after a median follow-up of 44.4 months (95%CI 18.6–70.1), the mean survival rate was 55% in appendiceal adenocarcinoma patients compared to 100% in NET patients. We found appendiceal adenocarcinoma to have aggressive biology and exhibit poor oncological outcomes compared to other appendiceal tumor types.

The incidence of incidental appendiceal neoplasms is increasing. This may be due to the increased use of new imaging

Table 1. Demographic and clinical characteristics of patients who underwent appendectomy between 2011 and 2021 according to the classification of appendiceal neoplasms.

	Low grade	Adenocarcinoma	Cystadenoma	Neuroendocrine tumor	Total	p-value
Gender n (%)						
Male	3 (60)	2 (22.2)	3 (33.3)	7 (63.6)	15 (44.1)	0.223
Female	2 (40)	7 (77.8)	6 (66.7)	4 (36.4)	19 (55.9)	
Age, Med (95%CI)	50 (50–50)	60 (46–84)	54 (54–84)	35 (30–55)	50.5 (38–70)	**0.021***
Emergency/elective, n (%)						
Emergency	4 (80)[a,b]	3 (33.3)[b]	6 (66.7)[a,b]	10 (90.9)[a]	23 (67.6)	**0.048**
Elective	1 (20)[a,b]	6 (66.7)[b]	3 (33.3)[a,b]	1 (9.1)[a]	11 (32.4)	
Intraoperative perforation, n (%)						
Yes	0 (0)	0 (0)	2 (22.2)	1 (9.1)	3 (8.8)	0.339
No	5 (100)	9 (100)	7 (77.8)	10 (90.9)	31 (91.2)	
Diagnosis, n (%)						
Intraoperitive	1 (20)	3 (33.3)	2 (22.2)	0 (0)	6 (17.6)	0.119
Perioperitive	1 (20)	0 (0)	0 (0)	0 (0)	1 (2.9)	
Postoperitive	3 (60)	6 (66.7)	7 (77.8)	11 (100)	27 (79.4)	
CEA, **Med (95%CI)**	4.38 (4.38–4.38)	15.75 (2.04–37.2)	18.04 (1.89–34.19)	0.92 (0.59–1.77)	2.09 (1.53–26)	**0.020****
CEA, 19.9 **Med (95%CI)**	12.6 (12.6–12.6)	35.5 (2.7–70)	3.15 (0.8–5.5)	6.7 (2.4–22.5)	7.65 (3.5–32)	0.419

CEA: carcinoembryonic antigen. Post hoc pair-group analysis was performed using Bonferroni correction. *b–d, p=0.048; **a–d, p=0.015. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Comparison of pathological data and operation techniques in groups.

	Low-grade	Adenocarcinoma	Cystadenoma	Neuroendocrine tumor	Total	p-value
Tumor size	2.5 (1.5–3.0)	3.1 (2.5–10.8)	6.4 (2–20)	6 (2–12)	4 (1.5–20)	0.274
Mesoappendiceal invasion, n (%)						
Yes	0 (0)[a]	3 (33.3)[b]	0 (0)[a]	0 (0)[a]	3 (8.8)	**0.027**
No	5 (100)[a]	6 (66.7)[a]	9 (100)[a]	11 (100)[a]	31 (91.2)	
R0/R1 n (%)						
R0	5 (100)	7 (77.8)	9 (100)	10 (90.9)	31 (91.2)	0.339
R1	0 (0)	2 (22.2)	0 (0)	1 (9.1)	3 (8.8)	
T stage, n (%)						
T0	5 (100)[a]	0 (0)[b]	9 (100)[b]	1 (9.1)[a]	15 (44.1)	**<0.001**
T1	0 (0)[a]	3 (33.3)[a]	0 (0)[a]	2 (18.2)[a]	5 (14.7)	
T2	0 (0)[a]	1 (11.1)[a]	0 (0)[a]	2 (18.2)[a]	3 (8.8)	
T3	0 (0)[a]	0 (0)[a]	0 (0)[a]	4 (36.4)[a]	4 (11.8)	
T4	0 (0)[a]	5 (55.6)[a]	0 (0)[a]	2 (18.2)[a]	7 (20.6)	
N stage n (%)						
N0	5 (100)	5 (55.6)	9 (100)	11 (100)	30 (88.2)	0.050
N1	0 (0)	2 (22.2)	0 (0)	0 (0)	2 (5.9)	
N2	0 (0)	2 (22.2)	0 (0)	0 (0)	2 (5.9)	
M stage, n (%)						
M0	5 (100)[a,b]	4 (44.4)[b]	9 (100)[a,b]	11 (100)[a]	29 (85.3)	**0.001**
M1	0 (0)[a,b]	5 (55.6)[b]	0 (0)[a,b]	0 (0)[a]	5 (14.7)	
Ki-67, n (%)						
1–2%	0 (0)	0 (0)	0 (0)	1 (9.1)	1 (2.9)	0.148
<1%	0 (0)	0 (0)	0 (0)	3 (27.3)	3 (8.8)	
No	5 (100)	9 (100)	9 (100)	7 (63.6)	30 (88.2)	
Advanced surgery for cancer, n (%)						
Yes	0 (0)[a,b]	6 (66.7)[b]	0 (0)[a]	3 (27.3)[a,b]	9 (26.5)	**0.006**
No	5 (100)[a,b]	3 (33.3)[b]	9 (100)[a]	8 (72.7)[a,b]	25 (73.5)	
Surgery, n (%)						
Right hemicolectomy	NA	3	NA	3	6	
Cytoreductive surgery	NA	2	NA	0	2	
Cytoreductive surgery+HIPEC	NA	1	NA	0	1	

Bold values indicate statistical significance at the p<0.05 level.

Table 3. Comparison of mean monthly overall survival in groups.

	Mean	SD	95%CI		p-value
			Lower bound	Upper bound	
Low-grade mucinous neoplasm	22.7	12.4	0.0	46.9	**0.011**
Mucinous adenocarcinoma	43.6	11.3	21.3	65.8	
Mucinous cystadenoma	55.6	14.1	27.9	83.3	
Neuroendocrine tumors	49.1	7.9	33.7	64.5	

Bold value indicates statistical significance at the p<0.05 level.

modalities in health screening in relatively recent times[11]. Our appendix neoplasia rate was slightly higher than 1–2%, which is the rate in the literature. We attribute this to the fact that we are a tertiary university hospital and therefore a center where patients are referred. Appendiceal cancer is rare; however, preoperative diagnosis is difficult due to limited preoperative diagnostic tests. Furthermore, the diagnosis may be missed when some patients are treated without surgery. Previous studies have failed to identify radiological factors that may predict the presence of underlying malignancy in patients presenting with acute appendicitis[12,13]. The rate of appendiceal neoplasms in our series was 2.38%, which did not include the patients who were followed up non-operatively. The diagnosis was postoperatively established in 79% of the patients. We found results that support the literature.

The serum tumor markers CEA, CA19-9, and CA125 are frequently obtained in the diagnosis of appendiceal mucinous neoplasms and are routinely monitored to assess disease remission or progression. Although the individual predictability of disease recurrence has not been well characterized, most high-volume institutions routinely combine tumor markers with imaging at baseline, during chemotherapy, and after surgery, if present. Elevated baseline CA19-9 has also been identified as an independent predictor of worse progression-free survival and may be useful in diagnosing disease relapse after cytoreductive surgery (CRS) and HIPEC[2]. Taflampas et al. showed that disease-specific survival was significantly longer in treated patients with normal preoperative markers and suggested that tumor marker elevation may help tailor the need for perioperative systemic chemotherapy. However, surveillance imaging appears to be more sensitive than tumor markers alone for detecting peritoneal disease recurrence[14]. In our series, we found increased tumor marker levels in adenocarcinoma and cystadenoma.

Previous studies have identified several factors associated with malignancy, including female gender and age. It has been argued that malignancies should also be suspected in all patients presenting with an underlying inflammatory mass or abscess[15-17]. Our series also supports the literature; we found a higher rate of female gender and higher age, especially in the appendiceal adenocarcinoma subgroup, than in other groups. Accordingly, we believe that more common use of perioperative imaging methods in advanced-age patients will increase the success of the treatment.

Survival has improved in patients with pseudomyxoma peritoneii or peritoneal metastases with the introduction of cytoreductive surgery and HIPEC. Right hemicolectomy is indicated for invasive adenocarcinoma that allows regional lymph node resection, but this should be done at the same time as HIPEC[18]. In our series, two-thirds of the patients with adenocarcinoma required advanced surgical procedures. We also had patients who applied HIPEC within the indication.

According to the National Comprehensive Cancer Network and ENETS protocols, many factors affect the selection of treatment in appendiceal tumors, including but not limited to tumor size, tumor location, and mesoappendiceal invasion[19,20]. NENs also metastasize to the peritoneal cavity. As are other causes of carcinomatosis, CRS with or without HIPEC may improve disease control and survival in well-selected patients[21]. Adjuvant therapy should be considered in patients with surgically resected neuroendocrine carcinoma. Neoadjuvant therapy may be considered for patients with locally advanced or metastatic, resectable disease[20]. In our series, the rate of additional surgical interventions for cancer was 26%. Considering available guidelines, we determined that additional surgical intervention was required, especially in appendiceal adenocarcinoma.

The limitations of our study were the limited number of patients and its retrospective design. In addition, there may be overlooked data in the follow-up of patients. There are also problems such as ignoring poor oncological results. However, considering the scarcity of comparative studies in the literature, we believe that the present study contributes to the literature.

Appendiceal neoplasms are a rare group of malignancies with a wide variety of biological characteristics and malignant behaviors. Appendiceal adenocarcinomas are associated with poorer oncological outcomes compared to other neoplasms. Our understanding of these tumors and treatment options has enhanced dramatically in recent years, and many patients have improved survival as a result of more aggressive surgical treatments and improved systemic treatment options.

AUTHORS' CONTRIBUTIONS

AR: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft. **CA:** Conceptualization, Methodology, Project administration, Writing – original draft. **UT:** Conceptualization, Methodology, Writing – original draft. **AGS:** Data curation, Resources, Writing – review & editing. **OY:** Investigation, Validation, Visualization. **KD:** Investigation, Validation, Visualization. **ICE:** Investigation, Validation, Visualization.

REFERENCES

1. Marmor S, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. J Gastrointest Surg. 2015;19(4):743-50. https://doi.org/10.1007/s11605-014-2726-7
2. Glasgow SC, Gaertner W, Stewart D, Davids J, Alavi K, Paquette IM, et al. The American society of colon and rectal surgeons, clinical practice guidelines for the management of appendiceal neoplasms. Dis Colon Rectum. 2019;62(12):1425-38. https://doi.org/10.1097/DCR.0000000000001530
3. Hanna M, Hwang G, Moghadamyeghaneh Z, Phelan M, Carmichael J, Mills S, et al. Incidental appendiceal cancer at appendectomy: an analysis of incidence, trends and risk factors. Dis Colon Rectum. 2015;58:339
4. Kunduz E, Bektasoglu HK, Unver N, Aydogan C, Timocin G, Destek S. Analysis of appendiceal neoplasms on 3544 appendectomy specimens for acute appendicitis: retrospective cohort study of a single institution. Med Sci Monit. 2018;24:4421-6. https://doi.org/10.12659/MSM.908032
5. Overman MJ, Asare EA, Compton CC, et al. Appendix: carcinoma. In Amin MB, editor. AJCC cancer staging manual. 8th ed. New York, NY: Springer; 2017.
6. Hoehn RS, Rieser CJ, Choudry MH, Melnitchouk N, Hechtman J, Bahary N. Current management of appendiceal neoplasms. Am Soc Clin Oncol Educ Book. 2021;41:1-15. https://doi.org/10.1200/EDBK_321009
7. Kelly KJ. Management of appendix cancer. Clin Colon Rectal Surg. 2015;28(4):247-55. https://doi.org/10.1055/s-0035-1564433
8. Lietzén E, Grönroos JM, Mecklin JP, Leppäniemi A, Nordström P, Rautio T, et al. Appendiceal neoplasm risk associated with complicated acute appendicitis-a population based study. Int J Colorectal Dis. 2019;34(1):39-46. https://doi.org/10.1007/s00384-018-3156-x
9. Jedrzkiewicz J, Tateishi Y, Kirsch R, Conner J, Bischof D, McCart A, et al. Impact of referral center pathology review on diagnosis and management of patients with appendiceal neoplasms. Arch Pathol Lab Med. 2020;144(6):764-68. https://doi.org/10.5858/arpa.2019-0214-OA
10. Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C, Memis B, et al. Appendiceal mucinous neoplasms: diagnosis and management. Oncologist. 2017;22(9):1107-16. https://doi.org/10.1634/theoncologist.2017-0081
11. Tajima T, Tajiri T, Mukai M, Sugiyama T, Hasegawa S, Yamamoto S, et al. Single-center analysis of appendiceal neoplasms. Oncol Lett. 2018;15(5):6393-9. https://doi.org/10.3892/ol.2018.8134
12. Naar L, Kim P, Byerly S, Vasileiou G, Zhang H, Yeh DD, et al. Increased risk of malignancy for patients older than 40 years with appendicitis and an appendix wider than 10 mm on computed tomography scan: a post hoc analysis of an EAST multicenter study. Surgery. 2020;168(4):701-6. https://doi.org/10.1016/j.surg.2020.05.044
13. Schwartz JA, Forleiter C, Lee D, Kim GJ. Occult appendiceal neoplasms in acute and chronic appendicitis: a single-institution experience of 1793 appendectomies. Am Surg. 2017;83:1381-5. PMID: 29336758
14. Taflampas P, Dayal S, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Pre-operative tumour marker status predicts recurrence and survival after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for appendiceal Pseudomyxoma Peritonei: analysis of 519 patients. Eur J Surg Oncol. 2014;40(5):515-20. https://doi.org/10.1016/j.ejso.2013.12.021
15. Carpenter SG, Chapital AB, Merritt MV, Johnson DJ. Increased risk of neoplasm in appendicitis treated with interval appendectomy: single-institution experience and literature review. Am Surg. 2012;78(3):339-43. PMID: 22524774
16. Wright GP, Mater ME, Carroll JT, Choy JS, Chung MH. Is there truly an oncologic indication for interval appendectomy?. Am J Surg. 2015;209(3):442-6. https://doi.org/10.1016/j.amjsurg.2014.09.020
17. Sadot E, Keidar A, Shapiro R, Wasserberg N. Laparoscopic accuracy in prediction of appendiceal pathology: oncologic and inflammatory aspects. Am J Surg. 2013;206(5):805-9. https://doi.org/10.1016/j.amjsurg.2013.05.002
18. Carr NJ. Updates in appendix pathology: the precarious cutting edge. Surg Pathol Clin. 2020;13(3):469-84. https://doi.org/10.1016/j.path.2020.05.006
19. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, et al. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). Neuroendocrinology. 2016;103(2):144-52. https://doi.org/10.1159/000443165
20. National Comprehensive Cancer Network (NCCN). Neuroendocrine and adrenal tumors (Version 1.2019). New York, NY: Harborside Press; 2019.
21. Goéré D, Passot G, Gelli M, Levine EA, Bartlett DL, Sugarbaker PH, et al. Complete cytoreductive surgery plus HIPEC for peritoneal metastases from unusual cancer sites of origin: results from a worldwide analysis issue of the Peritoneal Surface Oncology Group International (PSOGI). Int J Hyperthermia. 2017;33(5):520-27. https://doi.org/10.1080/02656736.2017.1301576