**Journal of Medical Biomedical and Applied Sciences**

JMBM 10 (9), 3182–3190 (2022) ISSN (O) 2589-9058 ISSN (P) 2589-904X

# Pseudomyxomaperitonei, Appendiceal Neoplasms, Survival Benefits from Cytoreductive Surgery & Hyperthermic Intraperitoneal Chemotherapy
## A 15 years analysis

**Spiliotis J[1,2,3], Iavazzo C[2], Rogdakis A[4], Stefanopoulou P[3], Spiliotis NJ[1], Koupanis C[3], Raptis A[1], Noskova I[1], Karachalios D[3], Christopoulou A[5]**

1. Athens Medical Center, Athens Greece
2. Metaxa Cancer Memorial Hospital, Piraeus Greece
3. European Interbalkan Medical Center, Thessaloniki Greece
4. St Panteleimon General Hospital Piraeus Greece
5. St Andreas General Hospital, Patras Greece

**Corresponding author:** Dr John Spiliotis
Department of Surgical Oncology, Interbalkan Medical Center, Thessaloniki, Greece

## Abstract

**Background:** This study explores the impact of cytoreductive Surgery and Hypertermic Intra PEritoneal Chemotherapy (HIPEC) on pseudomyxomaperitonei (PMP), appendiceal neoplasms through a safety analysis completed by evaluation of survival performances.

**Methods:** Retrospective chart review of 111 patients were diagnosed with appendiceal neoplasms during the period November 2005 to November 2019. Safety was evaluated by means of procedural morbidity and mortality. Survival performances included disease-free survival (DFS), and overall survival (OS) as end points.

**Results:** The median age of the patients was 52,5 years (range 28-72 years). Among them, 62 were female (55,8%) and 49 male (44,2%). The median time interval between the initial diagnosis and the definitive treatment with CRS + HIPEC was 9 months (range 4-20 months). The majority of our cases were high grade mucinous adenocarcinomas (39,6%). Postoperative complications, type 3 and 4 according to the Clavie-Dindo classification were identified in 10/111(9,2%) and postoperative deaths were observed in 4/111(3,6%). The cohort median overall survival (OS) for all patients was 57,1 months (95% CI, 42,8-71,6m). Better OS was observed in mucinous only PSM which was estimated up to 142,8 months (CI 95% 98,8-186,5 months) and worse in high grade signet-ring mucinous adenocarcinoma which was estimated down to 23,6 months (CI 95% 20,2-27,1 months). Mean DFS was 36,44m (95% CI, 24,05-48,83m).

**Conclusion:** PMP is a rare disease that presents with a wide range of histological types and disease behavior. When patients present with diffused abdominal disease and peritoneal spread, CRS plus HIPEC is an accepted treatment which showed that could improve survival in carefully selected patients treated by subspecialists in tertiary referral centers.

**Keywords:** Pseudomyxomaperitonei, Appendiceal neoplasms, survival, HIPEC

## 1. INTRODUCTION

Pseudomyxoma Peritonei (PMP) is a rare disease. The true incidence of PMP in the population in not known but estimated to be around 1 case per million populations per year (1), but this was not based on robust evidence (2). It is characterized by intra peritoneal disseminated mucons produced by adenomucinous tumor cells in implants on peritoneal surfaces. These implants are the final stage of a distribution process following the rupture of an intraperitoneal located mucinous neoplasm (3). While the epithelial neoplasms of the appendix remains the most common cause of PMP, similar features may originate from mucinous neoplasms of the colorectum, ovaries or any other abdominal organ. PMP of non-appendiceal origin probably have a worse prognosis but this evidence has failed to demonstrate in recent data (4). It is likely that the biological characteristic of the disease is the main determinant of outcome and not the site of origin. Clinically PMP is a slowly progressive disease which mainly expresses as so called “jelly belly” caused by the abundant intraperitoneal mucons. As PMP progresses, the excessive mucons accumulation causes compression of the intestines, compromised gastrointestinal motility and eventually obstruction is imminent (5).

Traditionally PMP has been treated with serial debulking procedures but repeated surgeries become increasingly difficult and lead to more complications (6). A more aggressive approach combining cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is being used. More specifically, CRS is performed with peritonectomy procedures according to Sugarbaker’s protocol combined with HIPEC that targets the microscopic residual disease and free neoplastic cells (7). Combining CRS plus HIPEC can greatly improve survival with average five year survival rate around 76% (8).

The aim of this work is to present our 15 year experience with PMP regarding the clinical, pathological and treatment characteristics retrospectively.

## 2. PATIENTS AND METHODS

From November 2005 to November 2019, 111 patients were diagnosed with PMP based on clinical symptoms, excessive abdominal mucinous with characteristic distribution on CT and identified in the final histopathology. Both primary and recurrent PMP were included in the study. Patients with evidence of liver or lung metastasis on CT scan were excluded from treatment. Demographic characteristics including age, gender number of previous surgeries that were related to PMP diagnosis and management time between initial diagnosis and definitive CRS + HIPEC are presented.

Type of neo-adjuvant or postoperative systemic chemotherapy, histological type of PMP according to the last nomenclature (classification) was also included (9-11) and postoperative Clavien-Dindo complications were included in the study.

### Statistical analysis

Data analysis was performed using the statistic software SPSS, Version 25.0. We used summary statistics to describe the data. Medians (range) or means (standard deviation) were used for continuous variables. Mann-Whitney U test for comparing median values and Student's t-test for comparing mean values were used after the Shapiro-Wilks test to confirm normal distributions.The point biserial correlation coefficient ($r_{pb}$) was used as a correlation coefficient. Survival rates were calculated using the Kaplan–Meier method. Cox regression analysis was used to identify independent risk factors for OS. A p-value<0.05 was considered to be statistically significant.

## 3. RESULTS

This study included 111 patients with appendiceal neoplasms. Their median age was 52,5 years (range 28-72 years). Among them, there are 62 female (55,8%) and 49 male patients (44,2%). The initial diagnosis was performed either with open biopsy – as an incidental finding - during abdominal surgery in 55 cases (49,5%) or core biopsy under CT scan in 18 cases (16,2%) or laparoscopic biopsy in 30 cases (27,1%) and

cytology in 8 cases. More specifically, the abdominal operations which incidentally identified PMP included hysterectomy in 25 cases (22,5%), adnexectomy in 12 patients (10,8%), cholecystectomy in 12 cases and hernia repair in 4 patients. Mucinous ascites was manifested in 61 patients (54,9%) ranging from mild to massive. Also 30 patients (27,1%) were presented with abdominal or pelvic mass. Moreover 10 patients (9%) were found with pelvic cysts while liver scalloping in CT scan was reported in 74 patients (66,7%).

In Table 1, we demonstrate patient's characteristics during hospitalization. The most important data is the time interval between the initial diagnosis and the definitive treatment with CRS + HIPEC with a median time the 9 months (range 4-20 months).

**TABLE 1:** Patients Characteristics during hospitalization.

| **Patients Characteristics** | | |
|---|---|---|
| **Age** | **Range 28-72years** | **Median 52,5 Years** |
| Time from initial diagnosis and CRS+HIPEC | 4-20m | 9m |
| Total hospital stay | 8-72d | 14d |
| ICU stay | 1-22d | 4d |
| Follow up | 8-123m | 55m |

In Table 2, we present the histological subtypes of PMP. It should be noted that the majority of our cases are high grade mucinous adenocarcinomas n=44 (39,6%).

**TABLE 2:** Histological subtypes of PMP.

| **HISTOLOGY** | | | |
|---|---|---|---|
| **PMP** | **N** | ♂ | ♀ |
| Acellular mucin only | 10 | 4 | 6 |
| Low grade mucinous adenocarcinoma | 27 | 13 | 27 |
| High grade adenocarcinoma | 44 | 17 | 27 |
| High grade signet-ring adenocarcinoma | 15 | 7 | 8 |
| Peritoneal Carcinoma | 15 | 8 | 7 |

In table 3, we present the intra-operative findings regarding the age, the peritoneal cancer index (PCI) and the completeness of cytoreduction as well as our morbidity and mortality. More specifically, postoperative complications, type 3 and 4 according to the Clavie-Dindo classification are 10/111(9,2%) with enterocutaneus fistulas in 4 patients bleeding in 2 cases and 2 cases with pulmonary emboli and 2 cases of catheter sepsis. Postoperative deaths were observed in 4/111(3,6%).

**TABLE 3:** Intra-operative findings

| **Intra-Operative Findings** | |
|---|---|
| | **N** |
| Age ≤45<br>>45 | 13<br>52 |
| PCI 0-10<br>≥10-20<br>>20 | 28<br>30<br>7 |
| CompleCyto<br>CCo<br>CC1<br>CC2<br>CC3 | 34<br>22<br>8<br>1 |

At the time of data analysis 49 patients (44,1%) were alive while 62 patients (65,9%) had died (table 4)

**TABLE 4:**At the time of data analysis 49 patients (44,1%) were alive while 62 patients (65,9%) had died.

Case Processing Summary

| Histological type | Total N | N of Events | Censored N | Censored Percent |
|---|---|---|---|---|
| Mucinous only | 10 | 2 | 8 | 80.0% |
| Low grademucinus adenoCA | 27 | 14 | 13 | 48.1% |
| High grade adenoCA | 44 | 24 | 20 | 45.5% |
| High Grade Signet Ring | 15 | 13 | 2 | 13.3% |
| Peritoneal carcinoma | 15 | 9 | 6 | 40.0% |
| **Overall** | **111** | **62** | **49** | **44.1%** |

More specifically in this study, the cohort median overall survival (OS) for all patients was 57,1 months (95% CI, 42,8-71,6m) (table 5).

**TABLE 5:** Median overall survival (OS) for all patients.

Means and Medians for Survival Time

| Histological type | Meana Estimate | Meana Std. Error | Meana 95% CI Lower Bound | Meana 95% CI Upper Bound | Median Estimate | Median Std. Error | Median 95% CI Lower Bound | Median 95% CI Upper Bound |
|---|---|---|---|---|---|---|---|---|
| Mucinous only | 142.857 | 22.445 | 98.864 | 186.850 | 160.000 | 86.850 | .000 | 330.225 |
| Low grademucinus adenoCA | 41.677 | 3.785 | 34.259 | 49.095 | 33.000 | 3.432 | 26.274 | 39.726 |
| High grade adenoCA | 31.144 | 3.147 | 24.976 | 37.312 | 28.000 | 3.650 | 20.847 | 35.153 |
| High Grade Signet Ring | 23.638 | 1.723 | 20.261 | 27.015 | 24.000 | 2.719 | 18.672 | 29.328 |
| Peritoneal carcinoma | 26.451 | 2.400 | 21.747 | 31.155 | 30.000 | 6.042 | 18.159 | 41.841 |
| **Overall** | **57.198** | **7.345** | **42.802** | **71.594** | **30.000** | **2.206** | **25.676** | **34.324** |

a. Estimation is limited to the largest survival time if it is censored.

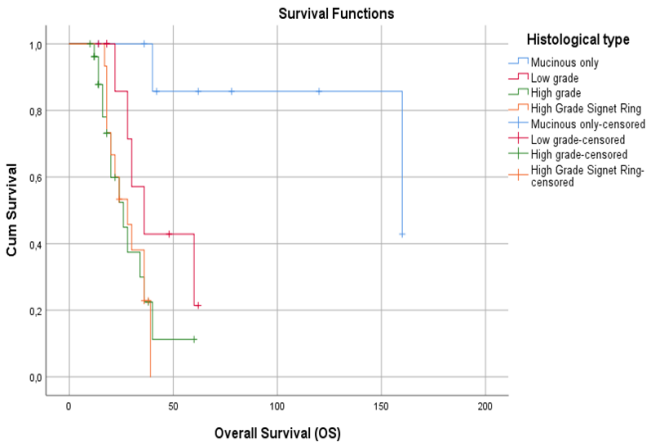
It should be highlighted that better OS was observed in mucinous only PSM which was estimated up to 142,8 months (CI 95% 98,8-186,5 months) and the worse in high grade signet-ring mucinous adenocarcinoma which was estimated down to 23,6 months (CI 95% 20,2-27,1 months).

**TABLE 6:** Disease Free Survival (DFS) of the different types of PMP

| PairwiseComparisons | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Histologicalty pe | Mucinousonly | | Lowgrade | | Highgrade | | High Grade Sig net Ring | |
| | | Chi-Square | Sig. | Chi-Square | Sig. | Chi-Square | Sig. | Chi-Square | Sig. |
| LogRank (Mantel-Cox) | Mucinousonly | | | 2.007 | .157 | 3.697 | .055 | 9.079 | .003 |
| | Lowgrade | 2.007 | .157 | | | .875 | .350 | 4.928 | .026 |
| | Highgrade | 3.697 | .055 | .875 | .350 | | | 4.250 | .039 |
| | HighGradeSig netRing | 9.079 | .003 | 4.928 | .026 | 4.250 | .039 | | |

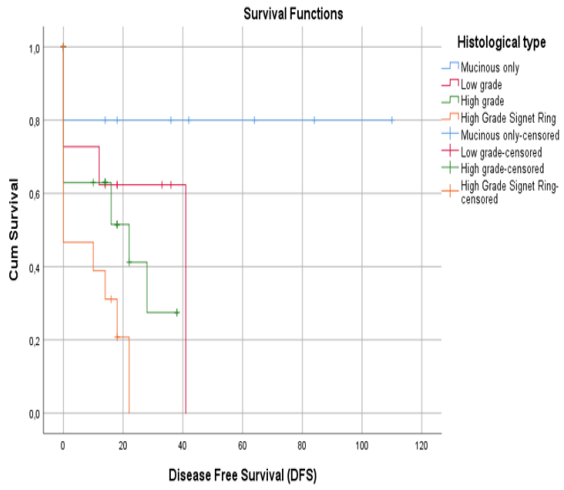
All these findings are presented in fig. 1 which depicts Kaplan Meier curve for OS. Log rank test indicated statistically significant difference between mucinous only PMP and all the other types (p=0,064) and also between low grade mucinous adenocarcinoma and high grade signet-ring cell (p=0,081).

**FIGURE 1:** Kaplan Meier curve for OS.



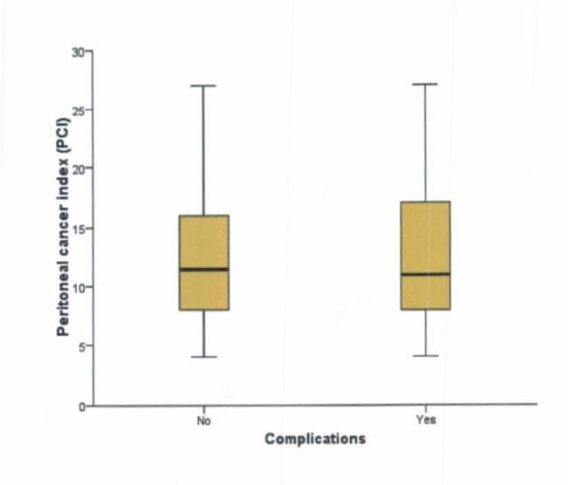

Moreover, table 6 and fig. 2 demonstrate the Disease Free Survival (DFS) of the different types of PMP despite that mean DFS was 36,44m (95% CI, 24,05-48,83m). Long-rank test showed statistically significant difference between the tumors as above (p=0,034).

**FIGURE 2:** Kaplan Meier curve for Disease Free Survival (DFS) of the different types of PMP



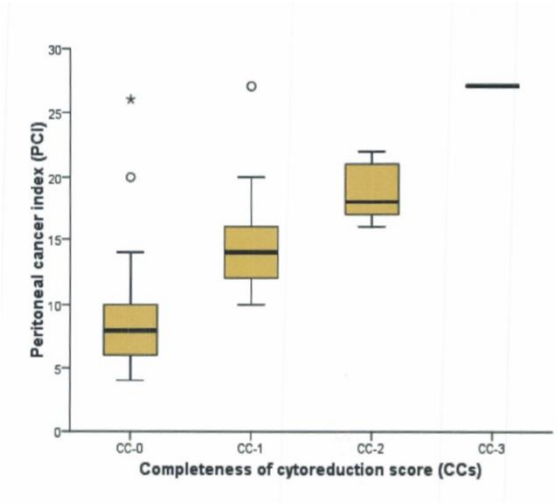

No statistically significant relationship was found between PCI and severity of complications (ρ-Spearman(111)=.082, p=.395) (fig. 3).

**FIGURE 3:** PCI and severity of complications




But, there is a strong relationship between the PCI and the completeness of cytoreduction (ρ-Spearman(111)=.770, p<.001)(fig. 4).

**FIGURE 4:** PCI and completeness of cytoreduction




## 4. DISCUSSION

Appendiceal neoplasms are rare gastrointestinal malignancies. They can be subdivided into non-epithelial and epithelial tumors and hyperthermic intraperitoneal chemotherapy has a role in the latter group. Epithelial tumors can further be subdivided in low-grade appendiceal mucinous neoplasms (LAMNs) and invasive adenocarcinomas (11). LAMNs do not invade beyond the lamina propria but can still disseminate into peritoneal cavity via appendiceal rupture (11,12).

In the past the lack of a common consensus regarding the most beneficial treatment approach offered short term survival results (11). Most recent data proposed an aggressive cytoreductive surgery plus intra peritoneal chemotherapy which offered a long term survival up to 20 years (13). Patients who have LAMNs with a non-ruptured appendix are adequately treated by appendicectomy, but in cases of appendiceal adenocarcinoma, the completion of operation includes right hemicolectomy (14).

For patients with intra-abdominal spread of a disseminated mucinous adenocarcinoma the role of CRS plus HIPEC is controversial as these tumors are more aggressive and many times the CRS plus HIPEC is difficult to control intraperitoneal recurrence, but when we compare with debulking surgery plus or not systemic chemotherapy, CRS and HIPEC offer a benefit in overall survival (15).

***Our study demonstrates***

Our study demonstrated that in our cohort of patients the median OS for all the patients was 57,1 months (95% CI, 42,8-71,6m). However, better OS was identified in the group of patients with mucinous only PSM which was estimated up to 142,8 months (CI 95% 98,8-186,5 months) and worse OS in those with high grade signet-ring mucinous adenocarcinoma which was estimated down to 23,6 months (CI 95% 20,2-27,1 months). The benefit of this surgical approach (CRS+HIPEC) is very controversial in the signet-ring subtype and is only referred to highly selected individuals with special characteristics as age, low PCI and responders in neo-adjuvant systemic chemotherapy that means in patients with limited and not metastatic disease.

The OS and DFS in signet-ring tumors of our study were 28 months and 0 months respectively and the results are similar with other previous clinical studies (16,17). Also, for patients with low-grade mucinous neoplasms, grade I, CRS plus HIPEC in our study is the treatment of choice (DFS 22 months).

Excellent long term survival we achieved even in patients with high burden of disease if complete cytoreduction can be achieved with median OS of 60 months and PFS of 16 months respectively.

Our results found to be similar with previous clinical trials in the aspect of overall survival (18-20). Patient with primary peritoneal carcinomas compared to those with low-grade neoplasms and peritoneal disease were less likely to have complete cytoreduction and we found to have worse survival rates when a high PCI was present and for this reason maybe preoperative predictive scoring system can be helpful in selection and decision making (21). Our study also demonstrated that outcomes in appendiceal tumors were highly histological depended.

While the efficacy of CRS and HIPEC for appendiceal mucinous neoplasms is well established the role of systemic chemotherapy is not well documented. Due to the rarity of the disease there are no prospective trials to guide the physicians in the decision concerning systemic chemotherapy.Two retrospective studies included mucinous appendiceal carcinomas and evaluated the possible role of systemic chemotherapy (SC) in conjuction with cytoreductive surgery and HIPEC. The first study demonstrated that post-operative SC appears to improve PFS in patients with high-grade tumors. In contrast there is no evidence to support the routine use of perioperative SC in low-grade disease (22). The other study revealed a survival benefit in OS and DFS of patients with appendiceal neoplasm (23). This result is in concordance with the findings of Blackham et al (24) and Milovanov et al (25) in both of which the administration of systemic chemotherapy was found to be beneficial in patient with low-grade disease.

Moreover, we have observed that patients with present signet-ring cells (SRC) in histology

who received systemic chemotherapy had prolonged OS vs SRC-negative patients. Additionaly, the SRC-positive group of patients who received perioperative systemic chemotherapy had a survival benefit (both in OS and DFS) compared to patients treated with CRS and HIPEC alone. This finding also agrees with the study by Milovanov et al (25).

In conclusion, appendiceal cancer is a rare disease that presents with a wide range of histological types and disease behaviors (26). When patients present with diffused abdominal disease and peritoneal spread, CRS plus HIPEC is an accepted treatment which showed that could improve survival in carefully selected patients.

On the other hand, teams performing cytoreductive surgical procedures must be expert in assessing all of the peritoneal surfaces. They need to have expertise in performing multiple visceral resections and peritonectomy procedures. They also need to have expertise in complications of hyperthermia and regional chemotherapy and must be selecting the patients with excellent documentation of the burden of disease (13).

Despite the promising results of our patient cohort treated with CRS and HIPEC, we have to acknowledge the limitations of the study, including the small number of patients and its retrospective character. Nevertheless, we showed a significant survival benefit for our cohort of patients. Although the study group is small, it is in line with other recently published studies.

Future trials evaluating the role of CRS plus HIPEC in different appendiceal tumors are needed. Due to the rarity of the tumors multicenter trials with the involvement of tertiary referral centers are proposed.

## REFERENCES

1. Bevan KE, Mohamed F, Moran BJ: Pseudomyxomaperitonei: World J. Surg. Oncol 2010; 2: 44-50.
2. Ramaswamy V: Pathology of mucinous appendiceal tumors and pseudomyxomaperitonei. Indian J. Surg. Oncol 2016;7:258-267.
3. Sugarbaker PH: Pseudomyxomaperitonei a cancer whose biology is characterized by a redistribution phenomenon. Ann Surg 1994;219:109-111.
4. Bouquot M, Dohan A, Gayat E, et al: Prediction of resectability in pseudomyxomaperitonei with a new CT scor. Ann Surg. Oncol 2018;25:694-701.
5. Rizvi AS, Syed W, Shergill R: Approach to pseudomyxomaperitonei. World J. GastrointSurg 2018;10(5):49-56.
6. Mc Bridek, Mc Fadden D, Oslet I: Improved survival of patients with pseudomyxoma peritonei receiving intra operative chemotherapy with cyto reductive surgery: a systemic review and meta-analysis. J Surg. Res 2013; 183: 246-252.
7. Alves S, Mohamed F, Yadegerfar G, et al: Prospective longitudinal study of quality of life following cytoreductive surgery and intra peritoneal chemotherapy for pseudomyxoma peritonei. Eur. J. Surg. Oncol 2010; 36:1156-1161.
8. Lord AC, Shihab O, Chandra Kumaran K, et al: Recurrence and outcome after complete tumor removal and Hipec in 512 patients with pseudomyxomaperitonei from perforated appendiceal mucinous tumors. Eur. J. SurgOncol 2014;41:396-399.
9. Carr NJ, Cecil TD, Monamed, et al: A consensus for classification and pathological reporting of pseudomyxomaperitonei and associated appendiceal neoplasms. The results of the PSOGI Modifieda Delphi process.. Am J Surg Path 2016;1:14-26.

10. Smeenk R, Verwaal V, Antonini N, Zoetmulder A: Survival analysis of pseudomyxomaperitonei patients treated by cytoreductive surgery and Hipec. Ann. Surg 2007;245(1):104-109.

11. Valasek MA, PaiPK:An update on the diagnosis, grading and staging of appendiceal mucinous neoplasms. Adv. Anat. Path 2018;25(1):38-60.

12. Ronnett BM, Zahn CM, Kurman RS, et al: Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis: a clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis and relationship to pseudomyxomaperitonei. Ann. J. Surg. Path 1995;19:1390-1408.

13. Chicago Consensus Working Group: The Chicago consensus quidelines for peritoneal surface malignancies, management of appendiceal neoplasms. Cancer 2020;126.

14. Turaga KK, Pappas S, Gamblin TC: Right hemicolectomy for mucinous adenocarcinoma of the appendix: Just right or too much. Ann. Surg. Oncol 2013;20(4):1063-1067.

15. Kelly KJ: Management of appendix cancer. Rachel Surg. 2015;28(4):247-255.

16. Munoz-Zulaga C, Sardi A, King MC, et al: Outcomes in peritoneal dissemination from signet-ring cell carcinoma of the appendix treated with cytoreductive surgery and Hipec. Ann. Surg. Oncol 2019; 26(2):473-481.

17. Shaib WL, Assi R, Shamseddine A, et al: Appendiceal mucinous neoplasms: Diagnosis and management. Oncologist 2017;22(9):1107-1116.

18. Moran B, Baratti D, Yan TD, Kusamura S, Deraco M. Consensus statement on the logo-regional treatment of appendiceal mucinous neoplasms with peritoneal dissemination (pseudomyxomaperitonei). J Surg. Oncol 2008;98:277-282.

19. Votanopoulos Kl, Shen P, Skardal A, Levine EA: Peritoneal metastases form appendiceal cancer. Surg. Oncol. Clin. N. Amer. 2018;27:551-561.

20. Sugarbaker PH, Chang D: Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann. Surg. Oncol 1999;6:727-731.

21. Yoon W, Aleme A, Berri R: Peritoneal surface disease severity score as a predictor of resect ability in the treatment of peritoneal surface malignancies. Am. J. Surg 2014;207:403-407.

22. Blackham A, Swett K, Eng C, et al: Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and Hipec. J. Surg. Oncol 2014;109(7):740-745.

23. Spiliotis J, Kopanakis N, Efstathiou E, et al: Perioperative systemic chemotherapy for peritoneal mucinous appendiceal carcinomas treated with cytoreductive surgery and Hipec. JBUON 2017;22(3):783-789.

24. Blackham AV, Swett K, Eng C, et al: Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and Hipec. J. Surg. Oncol. 2014;109:740-745.

25. Milovanov V, Sardi A, Ledakis P, et al: Systemic chemotherapy (SC) before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/Hipec) in patients with peritoneal mucinous carcinomatosis of appendiceal origin (PCMCA) Eur. J. Surg. Oncol 2015;41:707-712.

26. Narasimham V, Wilson K, Britto M, et al: Outcomes following cytoreduction and Hipec

for pseudomyxomaperitonei: 10-year experience. J. Gastrointest. Surg 2019.