JBUON 2017; 22(3): 783-789
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Perioperative systemic chemotherapy for peritoneal mucinous appendiceal carcinomas treated with cytoreductive surgery & HIPEC

John Spiliotis[1], Nikolaos Kopanakis[1], Elias Efstathiou[1], Dimitra Vassiliadou[1], Orestis Argiriou[1], Athanassios Rogdakis[2], Christos Valavanis[3]

[1] 1st Department of Surgical Oncology, Metaxa Cancer Hospital, Piraeus, Greece; [2] 1st Department of Surgery, General Hospital of Nikaia, Nikaia, Greece; [3] Department of Pathology, Metaxa Cancer Hospital, Piraeus, Greece;

Summary

Purpose: *To identify the role of systemic chemotherapy in the management of appendiceal malignancies.*

Methods: *Over a 10-year period (2005 -2014), 52 patients with appendiceal neoplasms were treated at our Peritoneal Surface Malignancy Unit [14 (26.9%) disseminated peritoneal adenomucinosis (DPAM), 30 (57.7%) peritoneal mucinous carcinomatosis of appendiceal origin (PMCA) and 8 (15.4%) PMCA-I]. All patients (100%) underwent cytoreductive surgery (CRS) & hyperthermic intraperitoneal chemotherapy (HIPEC), while 20 (38.5%) of them also received perioperative systemic chemotherapy.*

Results: *Mean peritoneal cancer index (PCI) was 23.6. Completeness of cytoreduction score (CC-S) was: CC-0 in 26 patients (50%), CC-1 in 20 patients (38.5%) and CC-2 in 6 patients (11.5%). High grade malignancy was reported in 27 patients (51.9%) and low grade malignancy in 25 patients (48.1%). More than half of the patients developed recurrence (n=36, 69.2%), while death was reported in 40.4% (n=21). Median overall survival (OS) in all histologic groups was 24 months for patients who received perioperative systemic chemotherapy and 14 months for patients who did not (p=0.048). Median disease free survival (DFS) in all histologic groups was 19 months for patients who received perioperative systemic chemotherapy and 10 months for patients who did not (p=0.034).*

Conclusion: *We suggest that perioperative systemic chemotherapy serves as a helpful therapeutic tool in the management of peritoneal mucinous appendiceal carcinomas treated with cytoreductive surgery & HIPEC.*

Key words: *appendiceal neoplasms, cytoreductive surgery, HIPEC, systemic chemotherapy*

Introduction

Appendiceal epithelial neoplasms are rare malignancies that can be histologically classified into DPAM and PMCA, with some tumors having intermediate histological features (PMCA-I). Peritoneal dissemination of such a neoplasm is characterized by disseminated intraperitoneal mucous and mucinous implants on the peritoneal surfaces, the omentum and in the sub-diaphragmatic space. Locoregional treatment with CRS and HIPEC has proven to be an effective therapeutic approach, currently being set as the standard treatment [1]. The aim of the present study was to examine the role of systemic chemotherapy as a perioperative treatment modality combined with CRS and HIPEC.

Methods

Over a 10-year period (2005 -2014), 52 patients with appendiceal neoplasms were treated at our Peritoneal Surface Malignancy Unit [14 DPAM (26.9%), 30 PMCA (57.7%) and 8 PMCA-I (15.4%)]. Patients were analyzed retrospectively. Selection included patients with a histology report of an appendiceal mucinous neoplasm. Patients were analyzed on the basis of demographics,

Correspondence to: John Spiliotis, MD, PhD, FASPSM. 1st Department of Surgical Oncology, Metaxa Cancer Hospital, Botassi 51 street, 185 37, Piraeus, Greece. Tel: +30 6942 40 40 14, E-mail: jspil@hotmail.gr
Received: 02/12/2016; Accepted: 03/02/2017

sex, age, histology, histologic grade, presence of signet ring cells, PCI, CCS and finally the perioperative use of systemic chemotherapy. Perioperative systemic chemotherapy was defined as any systemic chemotherapy received within 3 months prior to or following CRS and HIPEC. Systemic chemotherapy consisted of a 5-FU- or capecitabine-based regimen with oxaliplatin. Twenty patients (38.5%) were administered perioperative systemic chemotherapy. All patients signed an informed consent form prior to surgery. The eligibility criteria for CRS & HIPEC included patients medically fit, with an ECOG performance status ≤ 2 and without extraabdominal disease. All patients underwent preoperative evaluation, including a complete history and physical exam, full blood workup (including tumor markers) and a CT scan of the chest, abdomen and pelvis. All patients (100%) underwent CRS & HIPEC. CRS was performed according to the Sugarbaker technique [2]. The operations were performed by the same surgical team. HIPEC was delivered via the closed or the coliseum technique, at 40-42°C for 60 min. The most common regimen for intraperitoneal administration was mitomycin-C.

Statistics

SPSS 19.0 software was applied for statistical analysis of data. Student's t-test was used to compare the group that received systemic chemotherapy plus CRS and HIPEC with the group that has been offered CRS and HIPEC alone and Kaplan-Meier method with log rank test to estimate and compare OS and DFS. A two-sided p value<0.05 was considered as statistically significant.

Results

The cohort consisted of 52 patients with mean age 51.8 ± 11.3 years. Patient characteristics are presented in Table 1. Twenty-three of the patients (44.2%) were males. According to histological report 57.7% of the patients were categorized as PMCA, 26.9% as DPAM and the remaining 15.4% as PMCA-I. More than half of the cases (51.9%) were high grade. Signet ring cell was found in 40.4% of the patients and 38.5% of them were administered perioperative systemic chemotherapy. Moreover, mean patient PCI was 23.6 ± 7.3. Half of the patients had zero cytoreduction score, 38.5% scored 1 and 11.5% scored 2.

More than half of the patients developed recurrence (n=36; 69.2%), while death was reported in 40.4% of them (n=21). The mean time to recurrence was 14.4 ± 25.5 months. Also, the mean time to death was 23.2 ± 37.1 months. The cumulative recurrence-free rate for the 6 months was 65.4% standard error/SD=6.6%), for the first year 59.4% (SE=6.8%), for two years 39.5% (SE=7.4%), for three years 29.7% (SE=7.4%) and for five years 12.1% (SE=7.2%). The overall survival rate for the 6 months was 98.1% (SE=1.9%), for the first year 82.4% (SE=5.3%), for 2 years 66.1% (SE=7.0%), for 3 years 53.5% (SE=8.8%) and for 5 years 46.3% (SE=10.1%).

Table 1. Patient and disease characteristics

Characteristics	*n (%)*
Sex	
Females	29 (55.8)
Males	23 (44.2)
Age, years, mean (SD)	51.8 (11.3)
Histology	
DPAM	14 (26.9)
PMCA	30 (57.7)
PMCA-I	8 (15.4)
Grade	
Low	25 (48.1)
High	27 (51.9)
Signet ring cell	
No	31 (59.6)
Yes	21 (40.4)
Perioperative systemic chemotherapy	
No	32 (61.5)
Yes	20 (38.5)
Peritoneal carcinomatosis index (PCI), mean (SD)	23.6 (7.3)
Cytoreduction score	
0	26 (50.0)
1	20 (38.5)
2	6 (11.5)

For abbreviations see text

Results from multivariate stepwise Cox regression analysis indicated that cytoreduction score, histological type and the use of perioperative systemic chemotherapy were associated with overall survival.

Figures 1 and 2 depict the Kaplan-Meier estimates for recurrence depending on histologic type and signet ring cell presence.

Regarding systemic chemotherapy (Table 2), the mean OS was 24 months for patients who received systemic chemotherapy and 14 months for patients who did not (p=0.048). Median DFS was 19 months for patients who received systemic chemotherapy and 10 months for patients who did not (p=0.034). When analyzed by subgroup, the median OS and DFS of patients with high grade histology who received systemic chemotherapy were 26 and 19 months respectively, while patients with high grade histology who did not receive systemic chemotherapy had a medi-

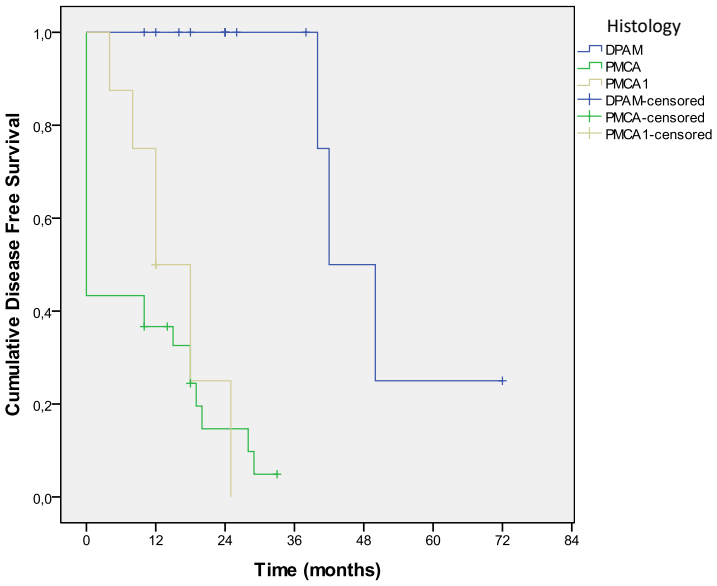

Figure 1. Kaplan-Meier estimates for recurrence according to histology. DPAM vs PMCA, p<0.05. DPAM vs PMCA1, p<0.04.

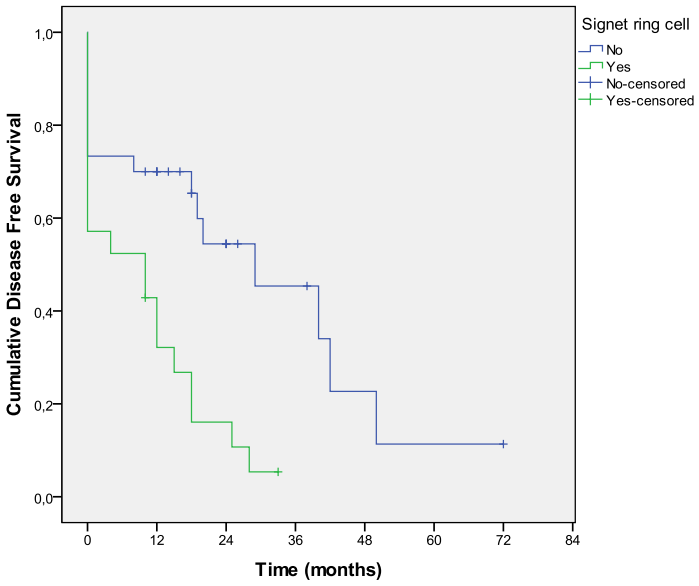

Figure 2. Kaplan-Meier estimates for recurrence according to signet ring cell (SRC).
SRC+: CRS+HIPEC+SCT vs CRS+HIPEC, p=0.038.
SRC-: CRS+HIPEC+SCT vs CRS+HIPEC, p=0.392.

an OS and DFS of 21 and 13 months respectively (p=0.029 and p=0.04, respectively). Patients with PMCA histology who received systemic chemotherapy had a median OS and DFS of 19 and 10 months respectively, while those with PMCA histology who did not receive systemic chemotherapy had a median OS and DFS of 10 and 0 months, respectively (p=0.042 and p=0.039, respectively). Patients who received systemic chemotherapy and had present signet ring cells had a median OS of 19 months, versus 16.5 months in patients with absent signet ring cells (p = 0.028). Also, patients with positive signet ring cells who did not receive systemic chemotherapy had a median OS of 11 months (p=0.033), vs patients who received chemotherapy. A similar difference was noted in median DFS. Patients in whom a CC-S 0 was achieved and received systemic chemotherapy had a median OS of 18 months vs 10 months in those who did not receive systemic chemotherapy (p=0.038). Median DFS was 18 and 9 months, respectively (p=0.021). Similar results were noted in CC-1 patients.

Discussion

Appendiceal neoplasms are rare, identified in less than 1% of appendectomy specimens [3]. They are not usually suspected before surgery, most commonly presenting during emergency operations [3-6], and they are found either intraoperatively or on pathologic examination. Histologically they can be classified as DPAM, PMCA and PMCA with intermediate (well differentiated) features. DPAM includes peritoneal lesions composed of abundant extracellular mucin with little mucinous epithelium, low cellular atypia and limited mitotic activity, with or without associated appendiceal mucinous adenoma. PMCA corresponds to an appendiceal carcinoma and peritoneal implants with abundant atypical proliferative epithelium. The intermediate type (PMCA-I) represents a predominantly adenomucinous pattern with a minor component of adenocarcinoma [7].

A characteristic feature of appendiceal neoplasms is their biologic potential for dissemination beyond the appendix, causing peritoneal carcinomatosis in the form of mucinous adenocarcinoma, otherwise known as pseudomyxoma peritonei (PMP). The diagnosis is characterized by the accumulation of extracellular mucin and epithelial mucin-secreting cells within the peritoneal cavity. The cell entrapment phenomenon [8] participates in the formation of extensive mucous masses within the peritoneal cavity, often causing organ malfunction, such as intestinal obstruction, dyspnea and malnutrition, eventually progressing to death, without timely surgical intervention.

The presence of mucin in the periappendiceal area only denotes an uncertain biologic behaviour, depending on the presence of neoplastic cells to determine the natural course of the dis-

Table 2. Median (m) overall survival and disease free survival in each patient group

	mOS (months)			*p value*	*mDFS (months)*			*p value*
CRS + HIPEC + SCT	24				19			
CRS + HIPEC	14				10			
p	0.048*				0.034*			
Histology	DPAM	PMCA	PMCA-I		DPAM	PMCA	PMCA-I	
CRS + HIPEC + SCT		19	22			10	12	
CRS + HIPEC	25	10	17		25	0	0	
p		0.042*	0.056			0.039*	0.063	
Histologic grade	High Grade	Low Grade			High Grade		Low Grade	
CRS + HIPEC + SCT	26	18.5		0.265	19		9	0.387
CRS + HIPEC	21	14		0.067	13		12	0.516
p	0.029*	0.357			0.04*		0.116	
Signet ring cells	SRC +	SRC -			SRC +		SRC -	
CRS + HIPEC + SCT	19	16.5		0.028*	10		10	0.520
CRS + HIPEC	11	14		0.717	5		18	0.366
p	0.033*	0.406			0.038*		0.392	
Peritoneal cancer index	PCI ≥20	PCI <20			PCI ≥20		PCI <20	
CRS + HIPEC + SCT	18	32.5		0.476	8		19	0.463
CRS + HIPEC	16.5	18		0.604	12		14	0.616
p	0.433	0.488			0.216		0.452	
Completeness of Cytoreduction	CC-0	CC-1	CC-2		CC-0	CC-1	CC-2	
CRS + HIPEC + SCT	32	18	6		18	18	6	
CRS + HIPEC	21	10	16		9	10	16	
p	0.038*	0.047*	0.273		0.021*	0.036*	0.343	

CRS : cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, SCT : systemic chemotherapy, mOS : median overall survival, mDFS : median disease-free survival, DPAM : disseminated peritoneal adenomucinosis, PMCA : peritoneal mucinous carcinomatosis of appendiceal origin, PMCA-I : intermediate, *statistically significant

ease. Specifically, when tumor cells are found in the mucin, pseudomyxoma peritonei will develop in 33% of the cases, while with acellular mucin it will develop in 4% [9]. Systemic metastasis is rather uncommon, occurring in 10% of the cases [10,11].

While in the past PMP was believed to stem from an ovarian tumor, there has been current immunohistochemical, molecular and genetic evidence to support that it is of appendiceal origin, in most cases with secondary involvement of the peritoneum and/or the ovaries [12,13].

Peritoneal carcinomatosis of gastrointestinal cancer was previously considered a fatal condition, with a poor OS [14,15]. However, the implementation of CRS and HIPEC has proven to be an effective treatment modality [16,19]. The characteristic diffuse malignancy caused by appendiceal neoplasms now represents a classic indication for the use of CRS and HIPEC. A recent retrospective international study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with PMP from mucinous appendiceal carcinomas treated with CRS and HIPEC [20]. Survival was found to be strongly related to the completeness of cytoreduction [20]. The use of CRS and HIPEC as the standard treatment for mucinous tumors with peritoneal dissemination has been unanimously supported at the Peritoneal Surface Oncology Congress (Milan 2006) [1].

CRS should not be confused with debulking surgery, which is surgery aimed to reduce disease burden. Instead, cytoreduction is a series of peritonectomy procedures and visceral resections, as they have been described by Sugarbaker [2], aiming at the minimum possible residual disease, with optimal cytoreduction achieved when residual tumor is 0. The PCI is scored by adding the lesion sizes in 13 abdominopelvic regions and quantifies the extent of disease [21]. The CCS assesses the extent of cytoreduction. CC-0 denotes absence of macroscopic tumor residue, CC-1 in-

dicates nodules less than 0.25 cm, CC-2 nodules between 0.25 and 2.5 cm and CC-3 nodules greater than 2.5 cm. Optimal cytoreduction includes CC scores of CC-0 and CC-1, as CC-1 disease is considered to be penetrable by HIPEC [21].

Besides CRS and HIPEC, another tool that has been recruited in the management of appendiceal neoplasms is systemic chemotherapy. Due to contradictory reports in the literature, so far no consensus has been reached as to whether the administration of systemic chemotherapy can be associated with a better disease outcome. This can be attributed to the heterogeneity of the disease, the different therapeutic regimens and the discordance in the classification and reporting of the disease. So far systemic chemotherapy has been reserved for patients who are not optimal surgical candidates, such as patients with high tumor burden, comorbidities or macroscopic residual disease after prior CRS.

In this study we have found that the median OS and DFS of patients with appendiceal neoplasms managed with CRS and HIPEC and who received perioperative systemic chemotherapy were significantly prolonged compared to those patients who were treated with CRS and HIPEC only.

Some recent studies have reached the same conclusion. The recent study by Milovanov et al. found that systemic chemotherapy was associated with a prolonged survival in patients with high grade PMCA and signet ring cell histology [22]. The study by Blackham et al. found that postoperative systemic chemotherapy was efficient in the management of patients with high grade disease [23]. Bijelic et al. also found that systemic chemotherapy may reduce the tumor burden in mucinous appendiceal carcinomas, facilitate cytoreduction and improve survival [24]. Shapiro et al. suggested that systemic chemotherapy should be used in patients suboptimal for cytoreductive surgery [25].

On the other hand, several studies have concluded that perioperative systemic chemotherapy for appendiceal neoplasms may lead to a worse outcome [20,26-29]. The study by Votanopoulos et al. observed that systemic chemotherapy lead to a worse prognosis not only for low grade but also for high grade patients. The team suggests that low volume, high grade patients undergo cytoreduction and postoperative systemic chemotherapy [29].

When subgroup analysis was conducted, the results were also interesting.

PMCA histology was associated with an improved outcome when, besides CRS and HIPEC, systemic chemotherapy was administered. The PMCA subtype has distinct features that characterize its aggressive phenotype. It has been associated with a greater frequency to metastasize to lymph nodes, since the fluid produced by the neoplastic cells is taken up by lymphatics, promoting tumor spread [30]. The PMCA subtype has been previously associated with poor survival in univariate and multivariate analysis in the large series by Chua et al [20].

Patients with high grade disease had a survival benefit (both in OS and DFS) when they received perioperative systemic chemotherapy vs patients who did not. This result is in concordance with the findings of the studies by Blackham et al. [23] and Milovanov et al. [22], in both of which the administration of systemic chemotherapy was found to be beneficial in patients with high grade disease.

Moreover, we have observed that patients with present signet ring cells (SRC) in histology who received systemic chemotherapy had a prolonged OS vs SRC-negative patients. Additionally, in the SRC-positive group, patients who received perioperative systemic chemotherapy had a survival benefit (both in OS and DFS) compared to patients treated with CRS and HIPEC only. This finding agrees with the study by Milovanov et al. [22] who found that the presence of SRC was associated with a significantly prolonged survival. In colorectal adenocarcinoma, the presence of SRC has been identified as a worse prognostic feature [31-34] and in mucinous appendiceal neoplasms they are considered evidence of high grade disease. A recent study by Siritrapun et al. [35] found that the presence of SRC floating in mucin did not alter prognosis, while tissue invasion by SRC determined worse survival in high-grade patients, suggesting that tissue invasion is a more aggressive feature of the neoplastic cells, affecting the tumor microenvironment, and also making complete cytoreduction less feasible [35].

The extent of disease, as expressed by the PCI score, appeared not to have an influence on patient survival concerning perioperative chemotherapy. However, in the Chua et al. study, a higher PCI score was associated with a poorer prognosis in multivariate analysis [20]. This discrepancy can be partly attributed to the fact that the PCI score takes into account the lesion size but does

not identify the site of disease, thus not clarifying the feasibility of surgical excision. However, as in every form of peritoneal carcinomatosis, the importance of cytoreduction becomes evident in our study as well. Patients in whom an optimal cytoreduction was achieved (CC scores of 0 or 1) benefited significantly from perioperative systemic chemotherapy. Chemotherapeutic delivery, both intraperitoneally and systematically, can improve survival when residual tumor volume is minimized, ie. when a complete cytoreduction is achieved.

When delivered preoperatively, systemic chemotherapy can cause fibrosis in the neoplastic tissue, as well as a transition of PMCA to adenomucinosis phenotype [36]. Moreover, preoperative chemotherapy can induce a reduction in tumor volume, resulting in less extensive surgical procedures, reducing accordingly the morbidity and mortality [24]. However, preoperative chemotherapy delays definitive surgery, degrades performance status and sometimes hinders complete cytoreduction, as it poses a difficulty in assessing the macroscopic findings intraoperatively [24]. On the other hand, adjuvant systemic chemotherapy can lead to eradication of microscopic disease, prevent the metastatic potential and also facilitate a second cytoreductive procedure in case it is needed.

Conclusion

We suggest that perioperative systemic chemotherapy may serve as a helpful therapeutic tool in the management of peritoneal mucinous appendiceal carcinomas treated with CRS & HIPEC, as it prolongs OS and DFS. Its effect has been found significant in high grade disease, PMCA histology (also a trend in PMCA-I), SRC presence and optimally cytoreduced patients (CC-0 and CC-1). Extent of disease (PCI) did not influence response to chemotherapy.

Since there are contradictory reports in the literature regarding the use of chemotherapy in the management of appendiceal neoplasms, more research needs to be conducted, in the setting of a large-population, randomized study.

Conflict of interests

The authors declare no confict of interests.

References

1. Moran B, Baratti D, Yan TD, Kusamura S, Deraco M. Consensus statement on the loco-regional treatment of appendiceal mucinous neoplasms with peritoneal dissemination (pseudomyxoma peritonei). J Surg Oncol 2008;98:277-282.
2. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221:29-42.
3. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum 1998;41:75-80.
4. Collins DC. 71,000 Human appendix specimens. A final report, summarizing forty years' study. Am J Proctol 1963;14:265-281.
5. Esmer-Sanchez DD, Martinez-Ordaz JL, Roman-Zepeda P, Sanchez-Fernandez P, Medina-Gonzalez E. [Appendiceal tumors. Clinicopathologic review of 5,307 appendectomies]. Cirugia y cirujanos 2004;72:375-378.
6. Murphy EM, Farquharson SM, Moran BJ. Management of an unexpected appendiceal neoplasm. Br J Surg 2006;93:783-792.
7. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. 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 "pseudomyxoma peritonei". Am J Surg Pathol 1995;19:1390-1408.
8. Spiliotis J, Efstathiou E, Halkia E, Vaxevanidou A, Datsis A, Sugarbaker P. The influence of tumor cell entrapment phenomenon on the natural history of Pseudomyxoma peritonei syndrome. Hepato-Gastroenterology 2012;59:705-708.
9. Yantiss RK, Shia J, Klimstra DS, Hahn HP, Odze RD, Misdraji J. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Am J Surg Pathol 2009;33:248-255.
10. Yan TD, Bijelic L, Sugarbaker PH. Critical analysis of treatment failure after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal mucinous neoplasms. Ann Surg Oncol 2007;14:2289-2299.
11. Zoetmulder FA, Sugarbaker PH. Patterns of failure following treatment of pseudomyxoma peritonei of appendiceal origin. Eur J Cancer (Oxford, England:1990). 1996;32a:1727-1733.
12. Mukherjee A, Parvaiz A, Cecil TD, Moran BJ. Pseudomyxoma peritonei usually originates from the appendix: a review of the evidence. Eur J Gynaecol Oncol 2004;25:411-414.
13. Szych C, Staebler A, Connolly DC, Wu R, Cho KR, Ronnett BM. Molecular genetic evidence supporting the clonality and appendiceal origin of Pseudomyxoma

peritonei in women. Am J Pathol 1999;154:1849-1855.

14. Sadeghi B, Arvieux C, Glehen O et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358-363.
15. Verwaal VJ, van Ruth S, de Bree E et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743.
16. Chua TC, Pelz JO, Kerscher A, Morris DL, Esquivel J. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. Ann Surg Oncol 2009;16:2765-2770.
17. El Halabi H, Gushchin V, Francis J et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. Ann Surg Oncol 2012;19:110-114.
18. Glehen O, Gilly FN, Boutitie F et al. Toward curative treatment of peritoneal carcinomatosis from non-ovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116:5608-5618.
19. Shaib WL, Martin LK, Choi M et al. Hyperthermic Intraperitoneal Chemotherapy Following Cytoreductive Surgery Improves Outcome in Patients With Primary Appendiceal Mucinous Adenocarcinoma: A Pooled Analysis From Three Tertiary Care Centers. The Oncologist 2015;20:907-914.
20. Chua TC, Moran BJ, Sugarbaker PH et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30:2449-2456.
21. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359-374.
22. 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 (PMCA). Eur J Surg Oncol 2015;41:707-712.
23. Blackham AU, Swett K, Eng C et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol 2014;109:740-745.
24. Bijelic L, Kumar AS, Stuart OA, Sugarbaker PH. Systemic Chemotherapy prior to Cytoreductive Surgery and HIPEC for Carcinomatosis from Appendix Cancer: Impact on Perioperative Outcomes and Short-Term Survival. Gastroenterol Res Pract 2012;2012:163284.
25. Shapiro JF, Chase JL, Wolff RA et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer 2010;116:316-322.
26. Baratti D, Kusamura S, Nonaka D et al. Pseudomyxoma peritonei: clinical pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 2008;15:526-534.
27. Cummins KA, Russell GB, Votanopoulos KI, Shen P, Stewart JH, Levine EA. Peritoneal dissemination from high-grade appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). J Gstrointest Oncol 2016;7:3-9.
28. Vaira M, Cioppa T, Dem G et al. Management of pseudomyxoma peritonei by cytoreduction+HIPEC (hyperthermic intraperitoneal chemotherapy): results analysis of a twelve-year experience. In Vivo 2009;23:639-644.
29. Votanopoulos KI, Russell G, Randle RW, Shen P, Stewart JH, Levine EA. Peritoneal surface disease (PSD) from appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): overview of 481 cases. Ann Surg Oncol 2015;22:1274-1279.
30. Sugarbaker PH. Mucinous colorectal carcinoma. J Surg Oncol 2001;77:282-283.
31. Hartman DJ, Nikiforova MN, Chang DT et al. Signet ring cell colorectal carcinoma: a distinct subset of mucin-poor microsatellite-stable signet ring cell carcinoma associated with dismal prognosis. Am J Surg Pathol 2013;37:969-977.
32. Hyngstrom JR, Hu CY, Xing Y et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol 2012;19:2814-2821.
33. Nitsche U, Zimmermann A, Spath C et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surgery 2013;258:775-782; discussion 82-83.
34. Van Sweringen HL, Hanseman DJ, Ahmad SA, Edwards MJ, Sussman JJ. Predictors of survival in patients with high-grade peritoneal metastases undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Surgery 2012;152:617-624; discussion 24-25.
35. Sirintrapun SJ, Blackham AU, Russell G et al. Significance of signet ring cells in high-grade mucinous adenocarcinoma of the peritoneum from appendiceal origin. Human Pathol 2014;45:1597-604.
36. Sugarbaker PH, Bijelic L, Chang D, Yoo D. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. J Surg Oncol 2010;102:576-581.