JBUON 2021; 26(4): 1647-1652
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Twenty-years' experience with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for pseudomyxoma peritonei (PMP)

Evangelia Papantoni[1], Konstantinos Ntatsis[1], Dimitrios Kyziridis[2], Apostolos Kalakonas[2], Christos Hristakis[2], Antonios-Apostolos Tentes[2]

[1]Metaxa Cancer Hospital, Piraeus, Greece. [2]Euromedica Kyanous Stavros, Athens, Greece.

Summary

Purpose: *udomyxoma peritonei is treated with cytoreductive surgery (CRS) combined and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). The purpose of this study was to report the20-year experience of one surgical team inCRS and HIPEC for PMP of appendiceal origin.*

Methods: *Retrospective study of the files of patients with PMP of appendiceal origin that underwent CRS+HIPEC. Morbidity and hospital mortality were recorded. Clinical and histopathologic variables were correlated to survival and recurrence.*

Results: *The files of 41 patients with PMP of appendiceal origin that underwent CRS+HIPEC from 1999-2018 were retrieved. The mortality and the morbidity rates were 2.4% and 29.3%, respectively. The 5- and 8-year survival rate was 68.3%. The completeness of cytoreduction, and the extent of previous surgery were identified as the prognostic indicators of survival. The recurrence rate was 32.5% with the completeness of cytoreduction, the histologic type of the tumor being the prognostic indicator.*

Conclusions: *CRS in combination with perioperative intraperitoneal chemotherapy is a safe and effective treatment in the management of PMP of appendiceal origin.*

Key words: *pseudomyxoma peritonei, cytoreductive surgery, HIPEC, survival, recurrence*

Introduction

Pseudomyxoma peritonei (PMP) is arare clinical entity characterized by peritoneal dissemination of mucinous tumor implants and mucinous ascites originating from appendiceal tumors in the majority of cases. The incidence of PMP is approximately 1-2 cases per 1.000.000 people [1,2]. PMP may also originate from the ovaries, colon, pancreas and urachus [2-4]. The most prominent pathophysiologic feature of the syndrome is the redistribution phenomenon. This is characterized by the concentration of large volumes of tumor at predetermined sites of the abdominal cavity (greater omentum, right hemidiaphragm, pelvis, right retrohepatic space, left abdominal gutter and the ligament of Treitz) with no tumor at sites with increased motility as are the peritoneal surfaces of the small bowel [5]. Extensive cytoreductive surgery (CRS) in combination with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is considered to be the optimal treatment strategy by which long-term survival may be achieved [6,7].

The purpose of the study is to report the20-year experience of one surgical team with CRS and HIPEC for PMP of appendiceal origin.

Corresponding author: Evangelia Papantoni, MD. Metaxa Cancer Hospital, Botassi 1 Street, Piraeus 18537, Greece.
Tel: +30 6945581095; Email: papantonieya@yahoo.gr
Received: 22/11/2020; Accepted: 02/01/2021

Methods

The files of all patients with PMP of appendiceal origin were retrospectively reviewed in a prospectively maintained database. The patients were considered eligible for CRS+HIPEC if they had acceptable performance status (Karnofsky scale >50%), normal hepatic and renal function, and if they were capable to undergo major surgery. In contrast, patients with distant metastatic disease or limited performance status (Karnofsky scale <50%), with a second malignancy at risk for recurrence (except for skin basal cell carcinoma or cancer of the cervix adequately treated), with addicted disorders or pregnant women with severe cardiopulmonary disease, with white blood cell count <4000, or platelet count <100.000, with blood urea >50mg/dl, or creatinine level >1.5mg/dl were excluded from surgery.

The protocol was approved by the Ethical Committees of the hospitals (216/0398) and informed consent form was signed by all patients.

All patients were followed-up at 3-month intervals during the first year, and at 6 month-intervals later with physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), abdominal and thoracic CT scan, or MRI, or PET-CT scan, and endoscopic examinations if necessary. Recurrences and the sites of recurrence were recorded.

Postoperative complications were recorded and assessed according to the following criteria: the uncomplicated patients were assessed as grade 0. Grade 1 complications were those that required minor intervention, oral antibiotics, bowel rest or monitoring. Grade 2 complications were those that required IV antibiotics or bowel rest or chest tube draining. Grade 3 complications were those that required hospital readmission or surgical or radiological intervention. Grade 4 complications were those that produced chronic disability or organ resection or bowel diversion and grade 5 complications were those that resulted in death. Grade 1 and 2 were assessed as minor complications and grade 3-4 as major complications [8].

The extent of previous surgery was assessed using prior surgery score (PSS). Patients without any history of surgery for cancer were characterized as PSS-0. Those patients who had previously undergone surgery in one abdominopelvic region or simple biopsy were characterized as PSS-1. The patients that had undergone previous surgery in 2-5 regions were characterized as PSS-2 and asPSS-3 those that had undergone surgery in more than 5 abdominopelvic regions [9].

The extent of peritoneal dissemination was assessed preoperatively using abdominal CT scan and the peritoneal cancer index (PCI) was grossly estimated [9].

Treatments

All patients underwent surgical exploration with midline incision from the xiphoid process to the symphysis pubis. The extent of pseudomyxoma peritonei was assessed after lysis of the adhesions using the PCI. The size of the largest tumor nodule (LS) was measured. LS-0 was considered if no tumor was visualized in the region. LS-1 was considered the lesion with the largest diameter < 0.5cm. LS-2 was considered the lesion with the largest diameter between 0.5 cm and 5 cm, and LS-3 the lesions larger than 5 cm, or a confluence of multiple small tumor nodules with various diameter. The summation of the LS in all the 13 abdomino-pelvic regions was the intraoperative and final PCI [9].

Cytoreductive surgery was possible using standard peritonectomy procedures [10]. Visceral resection was also performed in order to achieve the best surgical result. The purpose of surgery was the complete removal of the entire macroscopically visible tumor load. The completeness of cytoreduction was assessed after surgical resection of the tumor. CC-0 indicated that no macroscopic tumor was left behind. CC-1 surgery indicated that residual tumor was left with maximal diameter < 2.5mm. CC-2 surgery indicated residual tumor with maximal diameter >2.5mm and <2.5cm, and CC-3 indicated that the residual tumor was > 2.5cm in its maximal diameter [9].

HIPEC was administered after tumor resection and before the reconstruction of the gastrointestinal tract with the open abdominal method (Coliseum technique). Those patients that underwent CC-0 or CC-1 surgery received HIPEC for 90 min at 42.5-43°C with 20 mg/m^2 of Mitomycin-C or alternatively with a combination of Mitomycin-C (10 mg/m^2)+doxorubicin (15mg/m^2), and intravenously 5-FU (400mg/m^2)+leucovorin (20mg/m^2). A few patients that underwent CC-1 surgery received early postoperative intraperitoneal chemotherapy (EPIC) with 5-FU mg/m^2 during the first 5 postoperative days. The HIPEC device (Sun Chip, Gamida Tech, Villejuif, France) consisted of a heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and four thermal probes (Sun Chip, Gamida Tech, Villejuif, France). A prime solution of 3 lit of normal saline was instilled prior to the administration of the cytotoxic drug. As soon as the mean abdominal temperature exceeded 40°C the cytotoxic drugs were administered in the abdominal cavity. The reconstruction of the alimentary tract was made after the completion of HIPEC. Hospital morbidity and mortality were recorded [8]. All patients remained in the intensive care unit (ICU) for at least 24 h postoperatively. The patients that received EPIC remained in the ICU during the first 5 postoperative days of treatment. All surgical specimens were histopathologically examined in detail. The classification of the specimens was possible according to the latest definition of PMP [4] in which there are 4 distinct types: 1) acellular mucin, 2) low-grade mucinous PMP or disseminated peritoneal adenomucosinosis (DPAM), 3) high-grade mucinous carcinomatosis or peritoneal mucinous carcinomatosis (PMCA), and 4) high-grade mucinous carcinomatosis with signet-ring cells (PMCA-s).

Statistics

Statistical analyses were performed using the SPSS17. The proportions of patients with a given characteristic were compared by chi-square test or by Pearson's test. Differences in the means of continuous measurements were tested by the Student's t-test. Kaplan-Meier method was used for the construction of the survival curves. The comparison of curves was possible using the log-rank-test. For multivariate analysis of survival the

Cox proportional hazard model for the identification of the prognostic variables of survival was used. Univariate regression analysis was used to identify the prognostic variables of recurrence. A two-tailed p value <0.05 was considered statistically significant.

Results

From 1999 until 2018, 41 patients with pseudomyxoma peritonei underwent CRS+HIPEC. The mean patient age was 57.2+14 (28-84) years. There were 9 males (22%) and 32 females (78%). The general patient characteristics are listed in Table 1 in which it is obvious that the majority of them were in acceptable performance status, and had large-volume disease. No CC-2 surgery was performed. However, 3 patients underwent palliative surgery (CC-3) because high-grade tumor was found seeding extensively the peritoneal surfaces of the small bowel among other sites. No patient with CC-3 surgery received perioperative intraperitoneal chemotherapy. Two patients with CC-1 surgery received early postoperative intraperitoneal chemotherapy (EPIC) in addition to CRS+HIPEC.

Table 1. Patient general characteristics

Characteristics	*No of patients n (%)*
M/F	9/32 (22/78)
Performance status	
90-100%	31 (75.6)
70-80%	8 (19.5)
50-60%	2 (4.9)
Tumor volume	
Small volume	4 (9.8)
Large volume	37 (90.2)
PSS	
PSS-0	5 (12.2)
PSS-1	15 (36.6)
PSS-2	16 (39)
PSS-3	5 (12.2)
CC score	
CC-0	26 (63.4)
CC-1	12 (29.3)
CC-2	3 (7.3)
CC-3	
PCI	
0-13	12 (29.3)
14-20	13 (31.7)
21-39	16 (39)
Histology	
Acellular mucin	1 (2.4)
DPAM	19 (46.3
PMCA	11 (26.8)
PMCA-s	10 (24.5)

The 30-day in-hospital mortality rate was 2.4% (1 patient), and the in-hospital morbidity rate 29.3% (12 patients). Grade 1 complications were recorded in 1 patient (2.4%), grade 2 in 1 patient (2.4%), grade 3 in another one (2.4%), and grade 4 complications in 9 patients (22%). The histopathologic examination showed that only one specimen was found with acellular mucin. For statistical reasons this case was integrated in low-grade mucinous PMP. Consequently, the low-grade tumors were approximately equal to high-grade tumors (Table 1).

Survival

The overall5- and 8-year survival rates were 68.3% (Figure 1). The median survival was not reached. Univariate analysis showed that the CC-score, the extent of peritoneal dissemination (PCI), the extent of previous surgery (PSS), and the histologic type were all related to survival. However, only the completeness of cytoreduction (CC-score) and the extent of previous surgery (PSS) were found to be prognostic indicators of survival (Table 2).

Disease recurrence

During follow-up 13 patients (32.5%) were recorded with recurrence. The median follow-up time was 30 months. The failure sites were local-regional in 6 (46.2%), and distant in 7 (53.8%) cases. The histopathologic type of the tumor, the completeness of cytoreduction, and the extent of the peritoneal disease were found to be related to recurrence. However, the prognostic indicators of recurrence were found to be the histopathologic type of the tumor and the completeness of cytoreduction (Table 3).

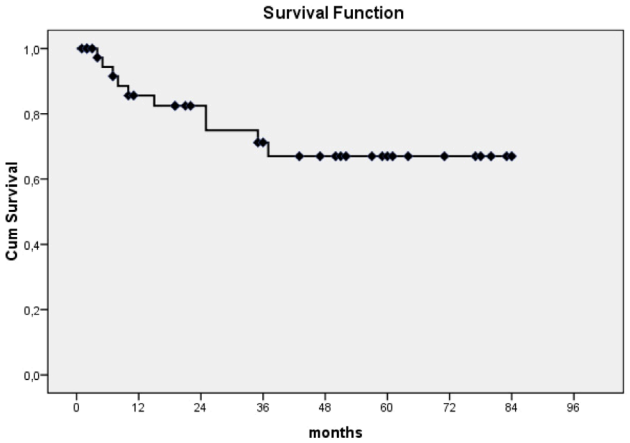

Figure 1. The overall 5- and 8-year survival rates of 41 patients with PMP.

Table 2. Analysis of survival

Variables	*Univariate*		*Multivariate*	
	p value	*HR*	*p value*	*95% CI*
Gender	0.206			
Age	0.856			
Histology	<0.001			
Tumor volume	0.219			
PSS	0.002	5.631	0.018	1.56-106.263
PCI	0.002	3.938	0.043	1.03-123.432
CC-score	<0.001	6.943	0.008	3.991-12351.989
Performance status	0.554			

Table 3. Analysis of recurrence. The prognostic indicators of recurrence were found to be the histopathologic type of the tumor and the completeness of cytoreduction

Variables	*Univariate*		*Multivariate*	
	p value	*HR*	*p value*	*95% CI*
Gender	0.314			
Age	0.211			
Histology	0.017	5.23	0.022	0.216-0.889
Tumor volume	0.192			
PSS	0.534			
PCI	0.002			
CC-score	0.034	4.407	0.036	0.041-0.886
Performance status	0.364			

Discussion

In 1994, the Mayo Clinic experience showed that PMP was a predominantly spread disease that required aggressive treatment although it appeared indolent [11]. The author of the editorial of the same issue of the journal congratulated the authors of this study and showed that PMP should definitely be considered a local-regional disease. In addition, he compared the survival curves of patients with PMP treated in 3 large volume USA centers and was conducted to the conclusion that PMP should be treated only in special centers dedicated exclusively in the management of patients with peritoneal malignancy [12].

The initial results of aggressive cytoreductive surgery in which HIPEC was integrated in the treatment of PMP were very promising [13]. Since then, a huge number of retrospective publications reproduced exactly the same results indicating that aggressive cytoreduction combined with perioperative intraperitoneal chemotherapy should be the standard treatment of PMP [14-20]. One multicentric study with 2298 patients showed that the median survival was 196 months, and the 15-year survival rate 59% [21]. In contrast, in the past, the prognosis of PMP was unfavorable with the median survival never exceeding 24 months and with only a small percentage of patients remaining alive at 5 years [11,22]. Despite the favorable results of the last 30 years it was not possible to identify the exact role of surgery and intraperitoneal chemotherapy. So far, it has not been clear whether cytoreduction with standard peritonectomy procedures [10], or HIPEC alone, or even the integration of HIPEC to surgery has drastically improved survival in PMP patients. The answer to these questions has been expected to be given by prospective randomized trials but until now, no randomized trial has been performed. It is important to note that one retrospective Australian multicentric study has provided much evidence that the most significant prognostic variable of long-term survival is the completeness of cytoreduction while the use of HIPEC is significant in controlling the disease locally and regionally [21]. Nevertheless, the British NHS has accepted cytoreductive surgery and intraperitoneal chemotherapy as the standard treatment for PMP.

The prognostic variables of PMP have been definitely identified over the past 30 years. The majority of publications have demonstrated that the histologic type of the tumor, the extent of peritoneal dissemination, the extent of previous surgery, the completeness of cytoreduction, the postoperative morbidity, the gender, and the use of neo-adjuvant chemotherapy are the most significant prognostic variables of long-term survival [7,13-21]. In the present study the gender and the morbidity were not found to be related to survival, while the completeness of cytoreduction and the extent of previous surgery were found to be prognostic of survival. A small number of patients received neo-adjuvant chemotherapy and as a consequence this variable was not correlated to survival.

The purpose of complete cytoreduction using the standard peritonectomy procedures is the removal of the entire macroscopically visible tumor. The purpose of HIPEC integrated in surgery is the eradication of the residual microscopic tumor. Despite this treatment strategy recurrence is still recorded in a respectable percentage. In one study from the United Kingdom 512 patients with complete cytoreduction were followed-up with a median time of 26.3 months and 137 of them (26.4%) were recorded with recurrence. One fourth of them underwent repeat surgery while the others were considered inoperable. Of those that underwent repeat surgery complete cytoreduction was possible in 57.7% of the cases [23]. In other series the recurrence rate varies from 28% to 41% [24-26]. The histologic type of the tumor, the extent of previous surgery, the infiltration of lymph nodes, and the extent of peritoneal dissemination of the disease have been identified as the prognostic variables of failure [26]. In our study the incidence of recurrence was 32.5%. The histopathologic type (tumor grade), and the completeness of cytoreduction were identified as the prognostic indicators of recurrence. The most frequent sites of failure have been the intra-abdominal (local-regional) [24,26]. The local-regional failures are related either to incomplete cytoreduction or inability of the intraperitoneal chemotherapy to eradicate the microscopic residual emboli because of the resistant to chemotherapy clones that remain in the abdomen. Another rare reason of early failure is the clinically aggressive type of disseminated peritoneal adenomucosinosis (DPAM) that was identified in 2004. There were 11 patients with DPAM among 501 PMP patients that underwent complete cytoreduction and developed recurrent disease repeatedly [27].

One of the initial studies from Washington Hospital Center reported grade III and IV morbidity of 27% and mortality rate of 1.5% following CRS+HIPEC [28]. The most frequent complications were peripancreatitis, fistulas, postoperative bleeding, and hematologic toxicity. There have been studies reporting as high as 51% morbidity with the use of perioperative intraperitoneal chemotherapy attributed particularly to EPIC [29]. In 2006, Sugarbaker updating his results reported that the incidence of hospital mortality was 2%, and the morbidity rate declined to 19% [30]. One of the most significant factors that make possible the decrease of both morbidity and mortality is the learning curve [31]. In our study, the hospital mortality was 2.4% (1 patient), and the morbidity rate 29.3% (12 patients) with the majority of complications reaching 22% (9 patients) of grade 3 and 4.

Conclusions

A 20-year experience with CRS combined with perioperative intraperitoneal chemotherapy showed that this is an effective and safe method offering 68.3% 8-year survival rate although half of the patients had high-grade disease.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bevan KE, Mohamed F, Moran BJ. Pseudomyxoma peritonei. World J Gastrointest Oncol 2010;2:44-50.
2. Mittal R, Chandramohan A, Moran B. Pseudomyxoma peritonei: natural history and treatment. Int J Hyperther 2017;33: 511-9.
3. Sinukumar S, Mehta S, Ramakrishnan AS et al. Analysis of Clinical Outcomes of Pseudomyxoma Peritonei from Appendicular Origin Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy-A Retrospective Study from INDEPSO. Indian J Surg Oncol 2019;10 (suppl 1): 65-70.
4. Carr NJ, Cecil TD, Faheez M et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia. The results of the Peritoneal Surface Oncology Group International (PSOGI) Modifies Delphi Process. Am J Surg Pathol 2016;40: 14-26.
5. Sugarbaker PH. Pseudomyxoma peritonei. In: P. Sug-

arbaker (ed) Peritoneal Carcinomatosis: Drugs and Diseases. Kluwer Academic Publishers, Boston 1996; pp 105-19.

6. Lord AC, Shihab O, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Recurrence and outcome after complete tumour removal and hyperthermic intraperitoneal chemotherapy in 512 patients with pseudomyxoma peritonei from perforated appendiceal mucinous tumours. Eur J Surg Oncol 2015;41:396-9.
7. 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;30:2449-56.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of surgery. Ann Surg 2004;240:205-13.
9. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: PH Sugarbaker (ed), Peritoneal Carcinomatosis: Principles of Management, Kluwer Academic Publishers, Boston, 1996; pp359-74.
10. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221:29-42.
11. Gough DB ,Donohue JH, Schutt AJ et al. Pseudomyxoma peritonei; Long-term patient survival with an aggressive regional approach. Ann Surg 1994;219:112-9.
12. Sugarbaker PH. Pseudomyxoma peritonei. A cancer whose biology is characterized by a redistribution phenomenon. Ann Surg 1994;219:109-11.
13. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg 1995;221:124-32.
14. Chua TC, Yan TD, Smigielski ME et al. Long-term survival in patients with pseudomyxoma peritonei treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy: 10 years of experience from a single institution. Ann Surg Oncol 2009;16:1903-11.
15. Elias D, Gilly F, Quenet F et al. Association Francaise de Chirurgie. Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. EJSO 2010;36:456-62.
16. Deraco M, Kusamura S, Laterza B et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of pseudomyxoma peritonei: ten years experience in a single center. In Vivo 2006;20:773-6.
17. Youssef H, Newman C, Chandrakumaran K, Faheez M, Cecil TD, Moran BJ. Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. Dis Colon Rectum 2011;54:293-9.
18. Baratti D, Kusamura S, Milione M et al. Pseudomyxoma Peritonei of Extra-Appendiceal Origin: A Comparative Study. Ann Surg Oncol 2016;23:4222-30.
19. 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;14:2289-99.
20. Omohwo C, Nieroda CA, Studeman KD et al. Complete cytoreduction offers long-term survival in patients with peritoneal carcinomatosis from appendiceal tumors of unfavorable histology. J Am Coll Surg 2009;209:308-12.
21. 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;30:2449-56.
22. Smith JW, Kemeny N, Caldwell C et al. Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer center experience. Cancer 1992;70: 396-401.
23. Lord AC, Shihab O, Chandrakumaran K et al. Recurrence and outcome after complete tumour removal and hyperthermic intraperitoneal chemotherapy in 512 patients with pseudomyxoma peritonei from perforated appendiceal mucinous tumours. EJSO 2015;41:396-9.
24. Zoetmulder FAN, Sugarbaker PH. Patterns of failure following treatment of pseudomyxoma peritonei of appendiceal origin. Eur J Cancer 1996;32:1727-33.
25. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FAN. Progression of Pseudomyxoma Peritonei after Combined Modality Treatment: Management and Outcome. Ann Surg Oncol 2007;14:493-9.
26. 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;14:2289-99.
27. Mohamed F, Gething S, Haiba M, Brun EA, Sugarbaker PH. Clinically aggressive pseudomyxoma peritonei: a variant of a histologically indolent process. J Surg Oncol 2004;86:10-5.
28. Stephens AD, Alderman R, Chang D et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg 1999;6:790-6.
29. Elias D, Benizri E, Di Pietrantonio D et al. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. Ann Surg Oncol 2006;14:509-14.
30. Sugarbaker PH, Alderman R, Edwards G et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006;13:635-44.
31. Huang Y, Alzahrani NA, Liauw D, Morris DL. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. ANZJ Surg 2015, doi: 10.1111/ans.13280