

EARLY DATA OF PATIENTS WITH PSEUDOMYXOMA PERITONEI FROM APPENDICEAL ORIGIN TREATED BY A STRATEGY OF CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

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Key words: peritoneal neoplasma, appendiceal neoplasma, hyperthermic intraperitoneal chemotherapy, mitomycin.

Summary

Background. Appendiceal peritoneal pseudomyxoma (PMP) is very rare disease and its long-term prognosis is poor. The aim of this study was to evaluate the results of an aggressive treatment approach used in our institution for the last 4 years. **Methods.** We selected all patients with PMP from appendiceal origin who were treated by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) at the Klaipėda University Hospital between January 2012 and January 2016. Data from all patients with PMP arising from the appendix were retrospectively collected and analyzed. Treatment consisted of complete surgical cytoreduction, followed by hyperthermic intraperitoneal chemotherapy with mitomycin at 42°C over 90 minutes. Ronnett's histologic classification was used for tumor grading.

Results. A total of 6 patients underwent cytoreduction and peritonectomy plus HIPEC. Median age at diagnosis was 57 years (range, 39-67). All our patients were female. The previous surgery score at the moment of admission was PSS-2 for three patients, PSS-3 for 3 patients. Four patients were diagnosed as diffuse peritoneal adenomucinosis (DRAM) and two as peritoneal mucinous carcinomatosis (PMCA).

In all of the patients, optimal cytoreduction CC-0 (5 patients) and CC-1 (one patient) was achieved. The median peritoneal cancer index (PCI) was 17 (range, 14-25) as an indicator of disease extension. The median number of visceral resections performed per

patient was 3 (range, 1-5). The median duration of CRS/HIPEC was 8 hours and 10 minutes (range, 7 hours and 10 min. to 9 hours 20 min). Mean postoperative stay was 13 days (range, 8-18). The 30 days postoperative and in-hospital mortality were zero. One patient experienced temporary haemorrhagic cystitis. The mean follow-up period was 28 months (range, 8-45). At the time of analysis all patients are alive and without recurrence.

Conclusions PMP from appendiceal origin can be treated with curative intent in a large percentage of cases by cytoreductive surgery associated with HIPEC. This new approach could be performed safely with acceptable morbidity and mortality in selected patients treated in specialized centers.

Introduction

Pseudomyxoma peritonei (PMP) is a rare disease with the incidence of 1-2 cases per million per year [1,2]. It is slowly progressive condition that usually arises from perforation of appendix due to an enlarging appendiceal adenoma or carcinoma, allowing mucin producing neoplastic cells to gain access to peritoneal cavity. PMP syndrome rarely metastasizes outside the abdominal cavity but remains a fatal illness as the space in the abdomen and pelvis required for normal function of the gastrointestinal tract becomes filled with copious amounts of the mucinous tumor [1,2]. Eventually patients develop terminal starvation because of abdominal distension and increased tumour volume [2].

Most cases of cystic ovarian mucinous tumors associated with pseudomyxoma peritonei are associated with metastases from an appendiceal tumor [3]. In women, cells become entrapped within the corpus hemorrhagicum and consequently, it is the detection of an ovarian cyst that often brings about the diagnosis of pseudomyxoma peritonei [3].

The pathologic classification of PMP is controversial

and confusing. In 1995, Ronnett et al described three distinct categories of PMP on the basis of pathologic specimens (n=109): diffuse peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and an intermediate/discordant subtype (PMCA-I/D). DPAM originates from an appendiceal mucinous adenoma and produces abundant mucin but minimal mucinous epithelium that lacks significant cytologic atypia and mitoses. The prognosis of DPAM is good. An appendiceal adenocarcinoma causes PMCA, which features more mucinous epithelium and pathology that is typical of adenocarcinoma. The prognosis of PMCA is poor. The third category, PMCA-I/D, has characteristics of both DPAM and PMCA, and the prognosis is intermediate between the two. [3,5].

The conventional treatment of PMP is surgical debulking repeated, as necessary to alleviate pressure effects. However, this treatment is palliative. Repeated debulking surgeries become more and more difficult due to progressively thickened intra-abdominal adhesions[6].

A combination of cytoreductive surgery(CRS) with hyperthermic intraoperative chemotherapy (HIPEC) was proposed by Sugarbaker. The rationale behind this strategy was to resect visible disease and any occult residual disease would be treated with a high concentration of chemotherapy and hyperthermia.[7].

CRS/HIPEC era evolved in Lithuania in 2011[8].

The aim of our study was to evaluate early-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in our University Hospital.

Material and methods

Patients with appendiceal tumors and peritoneal spread who underwent CRS/HIPEC from January 2012 to January 2016 were identified from a retrospectively collected database. No one patient did not receive any preoperative chemotherapy. Ronnett's histologic classification was used for tumor grading [3]. CT scan of the chest, abdomen, and pelvis and tumor markers (CEA, CA 19-9, and CA 125) were obtained prior to surgery. After review of the CT scan and the patient's functional status (ECOG = 0, 1, or 2), CRS/HIPEC was recommended if complete cytoreduction was deemed feasible. Prior surgery score (PSS) was assessed as previously described by Jacquet et al [6]. Exclusion criteria include patients with extra-abdominal metastases, patients deemed medically unfit to undergo radical surgery based on preoperative medical assessment, and those patients whose disease was considered technically unresectable at the multidisciplinary team meeting.

Under general anesthesia, a xypho-pubic incision was made. Disease extent was assessed, at the beginning and after CRS, by calculating peritoneal carcinomatosis index (PCI) as previously described by Jacquet et al [7]. All resections were done as needed to achieve complete cytoreduction, including excision of previous scar and port sites, anterior abdominal wall peritonectomy, splenectomy, cholecystectomy, greater and lesser omentectomy, diaphragmatic and pelvic peritonectomies, stripping of peritoneum over omental bursa and porta hepaticus, and visceral peritonectomies. We classified all peritonectomy procedures to nine peritonectomy regions described by Sugarbaker [7]. Disease-free peritoneum was not removed. Bowel and solid organs were removed, if disease could not be cleared. Every attempt was made to avoid stomas and extensive small bowel resections to help preserve quality of life. In our study we used sentinel lymph node concept to help decide if right colectomy is necessary with an appendiceal tumors [7].

Complete cytoreduction (CC) was defined as no visible tumor nodules or nodules less than 2,5mm in size, using the CC score adopted by the consensus panel recommendations on peritoneal surface malignancies [7]. Following CRS, HIPEC was performed using a closed technique for 90 min before performing any anastomoses. For HIPEC we used Performer HT by Rand company. Mitomycin-C was used with a dose of 25 mg/m²; 10 mg given at time zero and 15 mg given 30 min later. The target outflow temperature was maintained at 41-42°C, which requires an inflow temperature of 42,5°. We were keeping 40-41C in pelvis and 40-41C in subdiaphragmatic space. Flow rate 1200ml/min. Urine output was maintained between 250 and 400 cc/h during perfusion to avoid renal toxicity.

Patients were maintained in the intensive care unit during the first 24 hours of the postoperative period or until stable, and then transferred to the surgical floor. Early mobilization was encouraged, with physical therapy assistance on postoperative day 1. Low molecular weight heparin, compression stockings, and early mobilization were used for deep vein thrombosis prophylaxis. Patients were discharged when clinically stable; low molecular weight heparin was continued on an outpatient basis for 21 days.

Results and discussions

From January 2012 to January 2016, 7 patients were treated for PMP from appendiceal origin in our institution; 6 of them were selected for our study following the criteria described above. One 78 years old female patients was operated in our department. PCI was 36 and complete cytoreduction was not achieved. The major tumor debul-

Table 1. Demographics, clinical and pathological characteristics of patients with pseudomyxoma peritonei (PMP)

ECOG score- the Eastern Cooperative Oncology group score. DRAM- disseminated peritoneal adenomucinosis, PMCA-peritoneal mucinous carcinomatosis, PCI- Peritoneal Cancer Index

Characteristics	Nr.1	Nr. 2	Nr. 3	Nr. 4	Nr. 5	Nr. 6
Age	57	48	65	64	68	55
Sex	Female	Female	Female	Female	Female	Female
ECOG score	0	0	1	1	1	0
Pathological subtype	DRAM	DRAM	DRAM	PMCA	PMCA	DRAM
Interval between primary and secondary surgeries (months)	5	2	2	24	2	6
Elevated CEA, CA 19-9, CA 125	-	+	+	+	+	+
Co morbidities:						
• Hypertension	+	-	+	+	+	-
• Diabetes	-	+	-	-	-	-
Prior surgical scor	2	2	2	3	3	3
PCI	16	18	14	14	12	25

Table 2. Analysis of surgical treatment

Surgery	Nr. 1	Nr. 2	Nr. 3	Nr. 4	Nr. 5	Nr. 6
Omentectomy	+	+	+	+	+	+
Sentinel node biopsy (frozen section)	+	+	+	-	+	+
Number of peritonectomy procedures	3	3	3	6	4	5
Small bowel resection	0	0	0	1	1	2
Cholecystectomy	+	+	+	+	+	+
Splenectomy	+	-	-	-	+	-
Resection of large bowel	+	-	-	-	+	+
Resection of diaphragm	-	+	-	-	-	-
Appendectomy	-	-	-	-	-	-
Hysterectomy	-	-	-	+	-	+

Table 3. Perioperative data

CC- completeness of cytoreduction. ICU- Intensive Care Unit

Procedures	Nr. 1	Nr. 2	Nr. 3	Nr. 4	Nr. 5	Nr. 6
Duration of procedure (H, min)	8h.	7h. 30 min.	8h. 20 min.	8h.10 min.	8h. 50 min.	9h. 20 min
Blood loss (ml)	1500	800	760	700	850	600
Blood transfusion (ml)	1200	900	950	800	900	600
Blood product transfusion/first 24h(ml)	2000	1550	1100	1200	1300	900
CC	0	0	0	1	0	0
ICU stay (days)	3	3	4	4	3	3
Complications	-	Haemorrhagic cystitis	-	-	-	-
Postoperative stay	12	15	10	11	10	18
Follow-up time(months)	45	38	32	25	16	8

king was undertaken. She was not included in our study. Appendiceal origin was determined by histopathologic and immunoanalysis in all of our patients. Median age at diagnosis was 57 years (range, 39-67). All our patients were female. Five of them were operated by gynaecologists for Krukenberg tumor as primary surgery and one patient for acute perforated appendicitis. The previous surgery score (PSS) at the moment of admission was PSS-2 for three patients, PSS-3 for 3 patients. In five patients even one tumor marker was elevated. Four patients were diagnosed as DRAM and two as PMCA. Patient demographic, clinical and pathological data are summarized in table 1.

A total of 6 patients underwent cytoreduction and peritonectomy plus HIPEC. In all of the patients, optimal cytoreduction CC-0 (5 patients) and CC-1 (one patient) was achieved. The median PCI score was 17 (range, 14-25) as an indicator of disease extension. The median number of visceral resections performed per patient was 3 (range, 1-5). (Table 2).

The median duration of CRS/HIPEC was 8 hours and 10 minutes (range, 7 hours and 10 min. to 9 hours 20 min). Four patients received intraabdominal hyperthermic chemotherapy, one patient – thoracoabdominal (after resection of diaphragm) and one patient (retroperitoneal PMP) retroperitoneal-peritoneal chemotherapy. Mean postoperative stay was 13 days (range, 8-18). One patient experienced temporary haemorrhagic cystitis. The 30 days postoperative and in-hospital mortality were zero. Median follow-up time was 28 months (range, 8-45). (Table 3).

At the time of analysis all patients are alive and without recurrence.

Discussion

Traditionally, debulking surgery was the standard treatment of PMP. Followed by multiple operations for successive recurrences. The short-term results of debulking surgery are excellent, but the disease is almost certain to recur after a short interval, requiring numerous operations, until the disease finally becomes inoperable [6]. CRS and HIPEC introduced by Sugarbaker [7] has led to a marked improvement in survival rate compared with historical data, reaching differences in 5-years survival rates from 40% to 74% [6].

Chua et al. evaluated outcome and long-term

survival after CRS and HIPEC consolidated through an international registry study. This was a retrospective multi-institutional registry established through collaborative efforts or participating units affiliated with the Peritoneal Surface Oncology Group International. Two thousand two hundred ninety-eight patients from 16 specialized units underwent CRS for PMP. Treatment-related mortality was 2% and major operative complications occurred in 24% of patients. The median survival rate was 98 months (16,3 years) and the median progression-free survival rate was 98 months (8,2 years), with 10- and 15-year survival rates of 63% and 59 %, respectively. Multivariate analysis identified prior chemotherapy treatment ($P < .001$), peritoneal mucinous carcinomatosis (PMCA) histopathologic subtype ($P < .001$), major postoperative complications ($P = .008$), high peritoneal cancer index ($P = .013$), debulking surgery (completeness of cytoreductions (CCR), 2 or 3; $P < .001$), and not using HIPEC ($P = .030$) as independent predictors for a poorer progression-free survival. Older age ($P = .006$), major postoperative complications ($P < .001$), debulking surgery (CCR 2 or 3; $P < .001$), prior chemotherapy treatment ($P = .001$), and PMCA histopathologic subtype ($P < .001$) were independent predictors of a poorer overall survival. Reviewers concluded the combined modality strategy for PMP may be performed safely with acceptable morbidity and mortality in a specialized unit setting with 63% of patients surviving beyond 10 years. Minimizing nondefinitive operative and systemic chemotherapy treatments before definitive cytoreduction may facilitate the feasibility and improve the outcome of this therapy to achieve long-term survival. Optimal cytoreduction achieves the best outcomes[10].

The aim of our study is to present our first experience of modern treatment of PMP of appendiceal origin in Klaipeda University Hospital.

Selecting patients for CRS/HIPEC remains challenging. Reviewing previous reports to establish guidelines for the selection is difficult partly because of the lack of consensus about pathology[4]. Ronnett's classification is the most widely used, but different classification systems have been suggested [9]. In addition, extent of disease is not reported in all studies. At our institution, we do not consider grade or extent of disease a contraindication to CRS/HIPEC. We make every effort to achieve CC, while minimizing visceral resection and preserving quality of life after surgery. These decisions are usually made intraoperatively. However, efforts for standardization of pathological reports are essential for future research and advancement in the treatment of this disease.

This study is a retrospective analysis with inherent li-

mitations and relatively short mean follow-up and small number of patients. We did not deselect patients based solely on pathology type and tumor burden, and we closely monitor our patients postoperatively. To the best of our knowledge it is the first report about surgical treatment of PMP in Lithuania.

Conclusions

PMP from appendiceal origin can be treated with curative intent in a large percentage of cases by cytoreductive surgery associated with HIPEC. This new approach could be performed safely with acceptable morbidity and mortality in selected patients treated in specialized centers.

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**APENDIKULIARINĖS KILMĖS PILVAPLĖVĖS
PSEUDOMIKSOMOS GYDYMAS
CITOREDUKACINĖS OPERACIJOMIS IR
INTRAOPERACINE HIPERTERMINE
CHEMOTERAPIJA. PIRMOJI PATIRTIS**

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Raktažodžiai: kirmėlinė atauga, pilvaplėvės pseudomiksoma, citoredukcija ir HIPEC, mitomicinas.

Santrauka

Tikslas. Pilvaplėvės pseudomiksoma (PPM) dėl kirmėlinės ataugos navikų yra labai reta, o ilgalaikė prognozė bloga. Tikslas – apibendrinti pirmąją citoredukcinių operacijų (CRS) ir hiperterminės intraperitoninės chemoterapijos (HIPEC) patirtį pacientams, sergantiems pilvaplėvės pseudomiksoma dėl kirmėlinės ataugos auglių.

Pacientai ir metodai. Atlikta retrospektyvi analizė 6 pacientų, kuriems KUL 2012/01- 2016/01 metais buvo atlikta citoredukcinė operacija ir HIPEC dėl apendikuliarinės kilmės pilvaplėvės pseudomiksomos.

Atlikta priešoperacinių (amžius, lytis, pilvaplėvės karcinomatozės indeksas (PKI), patohistologinis PPM tipas ir kt.), intraoperacinių (operacijos trukmė, radikalumas, sarginio limfmazgio būklė, netekto kraujo kiekis ir kt.) ir operacijų apimties analizė. Hiperterminė intraoperacinei terapijai naudota uždara metodika. Įtekėjimo temperatūra 42,5 laipsniai C. Visiems ligoniams naudo-

tas Mitomicinas C 25mg/m². Pilvaplėvės perfuzijos trukmė 90 min.

Rezultatai. Vidutinis operuotų ligonių amžius buvo 57 metai (svyravo, 39-57). Visos pacientės buvo moterys. Keturioms pacientėms nustatyta difuzinė peritoninė adenomucinozė, 2 pacientėms peritoninė mucininė karcinomatozė. Pilvaplėvės karcinomatozės indekso vidurkis buvo 17 (svyravo, 14-25). Radikali citoredukcija (CC-0/CC-1) buvo atlikta visiems ligoniams. Vidutinė CRS/HIPEC trukmė buvo 8 val. ir 10 min. (svyravo, 7 val. ir 10 min.- 9 val. 10 min.) Vidutinis vienam pacientui atliktų pilvo organų rezekcijų skaičius vienos operacijos metu buvo -3 (svyravo, 1-5). Pooperacinių mirčių nebuvo. Vienai ligonei po operacijos išsivystė hemoraginis cištitas. Pooperacinio stebėjimo vidutinė trukmė 28 mėn. (svyravo nuo 8 iki 45 mėn). Visi mūsų operuoti pacientai šiuo metu sveiki ir be ligos atkryčio požymių.

Apibendrinimas. Citoredukcinės operacijos ir HIPEC gydant pilvaplėvės apendikuliarinės kilmės pseudomiksomą yra pakankamai saugus būdas. Artimieji gydymo rezultatai yra geri. Ypač svarbu geriems gydymo rezultatams pasiekti yra tinkama pacientų atranka ir radikali citoredukcija.

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