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Prophylactic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for low-grade appendiceal mucinous tumors with early and limited disease after completely removed

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Abstract

The necessity of prophylactic cytoreductive surgery (PCRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for low-grade appendiceal mucinous neoplasms (LAMN) after complete removal is still controversial. This study aims to determine the role of PCRS + HIPEC and identify optimal strategies for managing these patients. One hundred fifty-nine patients who sought medical advice at Aerospace Center Hospital were retrospectively analyzed from January 2011 to December 2021. All the patients were divided into the PCRS group and the observation group. The data of surgical specimens and pathology was collected, and the effect on recurrence-free survival (RFS) was analyzed. Of these 159 patients, 88 were in the PCRS group, and 71 were in the observation group. The median follow-up time was 38 months. Seven patients recurred and developed into pseudomyxoma peritonei, 1 in the PCRS group and 6 in the observation group. The analysis of RFS showed that patients who underwent PCRS ($P = .01$) and HIPEC ($P = .01$) had better survival. After multivariate analysis, the surgical specimen accompanied by disseminated peritoneal adenocarcinoma was identified as an independent prognostic factor for RFS. In the study of surgical resection content, patients with greater omentum ($P = .01$) and bilateral fallopian tubes and ovaries of women ($P = .002$) resection had a more prolonged RFS with statistical significance. The research indicated that PCRS + HIPEC could prevent recurrence. Therefore this treatment were necessary for LAMN after complete removal in patients with a high risk of recurrence. However, it was not proven to be an independent factor for RFS, and a multicenter, prospective, randomized trial was need to definitively address the role of PCRS + HIPEC for LAMN after complete resection.

Abbreviations: DPAM = disseminated peritoneal adenomucinosis, HIPEC = hyperthermic intraperitoneal chemotherapy, LAMN = low-grade appendiceal mucinous neoplasms, PCI = peritoneal carcinomatosis index, PCRS = prophylactic cytoreductive surgery, PMCA = peritoneal mucinous carcinomatosis, PMP = pseudomyxoma peritonei, RFS = recurrence-free survival.

Keywords: bilateral fallopian tubes and ovaries, greater omentum, hyperthermic intraperitoneal chemotherapy, low-grade appendiceal mucinous, prophylactic cytoreductive surgery

1. Introduction

Mucous tumors of the appendix are a rare malignancy that are the main cause of pseudomyxoma peritonei (PMP), a clinical syndrome that causes mucinous ascites and mucinous tumor implantation along the abdominal and pelvic cavity.[1,2] The mucinous epithelial neoplasms of the appendix included: serrated polyp, low-grade mucinous neoplasm (LAMN), high-grade mucinous neoplasm (HAMN), and mucinous adenocarcinoma (with or without signet ring cells). The prognosis of LAMN was significantly better than that of HAMN and mucinous adenocarcinoma. PMP mainly originated from LAMN and had separate histological subtypes (sometimes with discordance), including disseminated peritoneal adenomucinosis (DPAM); peritoneal mucinous carcinomatosis (PMCA), and PMCA with signet ring cells.[3] Primary LAMN can be detected unexpectedly in any abdominal surgery, especially acute appendicitis. Patients with PMP can achieve a pretty good prognosis after undergoing complete or near complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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chemotherapy (HIPEC),[4,5] a standard treatment for tumors with peritoneal metastases. The possibility of recurrence or progression to PMP may occur after being completely removed for a long time. This may be related to the pathological characteristics of the appendix, including appendiceal perforation, positive surgical margin, and mucus distribution. For these patients, the necessity of prophylactic cytoreductive surgery (PCRS) and HIPEC is confusing.

In this manuscript, we identify a group of patients who had a LAMN histology with complete tumor resection and long-term follow-up. Some patients underwent PCRS + HIPEC, while others did not. The purpose of studying these patients is to determine the role of PCRS + HIPEC and to identify optimal strategies for the management of these patients.

2. Materials and methods

2.1. Ethical approval

The protocol for this study was approved by the Ethics committee of the Aerospace Center Hospital, Beijing, China (No. 2022-061). All methods were performed in accordance with the relevant guidelines and regulations. The written informed consent was abandoned due to the retrospective.

2.2. Patient selection

We conducted a retrospective analysis of the clinical data of patients who had a LAMN histology with complete tumor resection from January 2011 to December 2021. All patients were required to make a decision after 3 to 6 months from the initial surgery, which could avoid misjudgment caused by postoperative inflammatory exudation. Diagnoses were confirmed by 2 experienced pathologists at our center. The patients were divided into 2 groups, the PCRS + HIPEC group, and the observation group. Indications for PCRS include: mucin or neoplastic epithelium extending into the muscularis propria/serosa, mucin on mesoappendix and/or excised specimens were affected, perforation and positive margin, abdominal and pelvic CT showed no clear lesions, normal blood tumor markers, no evidence of residual disease based on index surgeon's report and strong surgical willingness in any pathological situation. During surgery, no residual lesions were found by naked eye. All patients who received CRS were recommended to undergo HIPEC. Patients with tumors confined to the mucosa or who refused surgery were included in the observation group (Fig. 1). All patients had no serious complications and were alive during the follow-up period.

2.3. Surgical procedure

All CRS + HIPEC procedures were performed by the same surgical team with expertise in PMP. The role of PCRS was to achieve negative margins or remove tumor-prone areas, while HIPEC could further kill residual or escaped tumor cells. An abdominal and pelvic contrast-enhanced CT was performed for all patients to evaluate the condition of the abdomen. Laparoscopic exploration was the first choice for patients, and an open CRS was chosen when laparoscopic CRS was difficult or directly selected for patients with multiple organ removal. Omentectomy was performed in all CRS patients. Bilateral salpingo-ovariectomy was performed in postmenopausal females or in premenopausal women who wished resection, whether the fallopian tubes and ovaries were normal or not. The uterus was preserved if it appeared normal and was not adherent to the surrounding tissue. Ileocecal resection or right hemicolectomy was performed in patients with positive margins or implantation. Excision of the lesser omentum and ligamentum teres hepatis was performed for patients with open surgery CRS. After CRS, a HIPEC was performed with a closed procedure. Two inflow and 2 outflow catheters were placed in the abdomen and connected to a hyperthermia chemotherapy perfusion machine (Jilin Minda Company products, RHL – 2000B, Shanghai, China) with a 60-minute treatment time. Cisplatin 60 to 80 mg was used with 3500 to 4000 mL physiological saline and warmed to 41 to 43.5 °C.

2.4. Follow-up protocol

The frequency of follow-up was twice a year in the first 5 years and then once a year with abdominal pelvic enhanced CT examination. The follow-up time, that is, recurrence-free survival

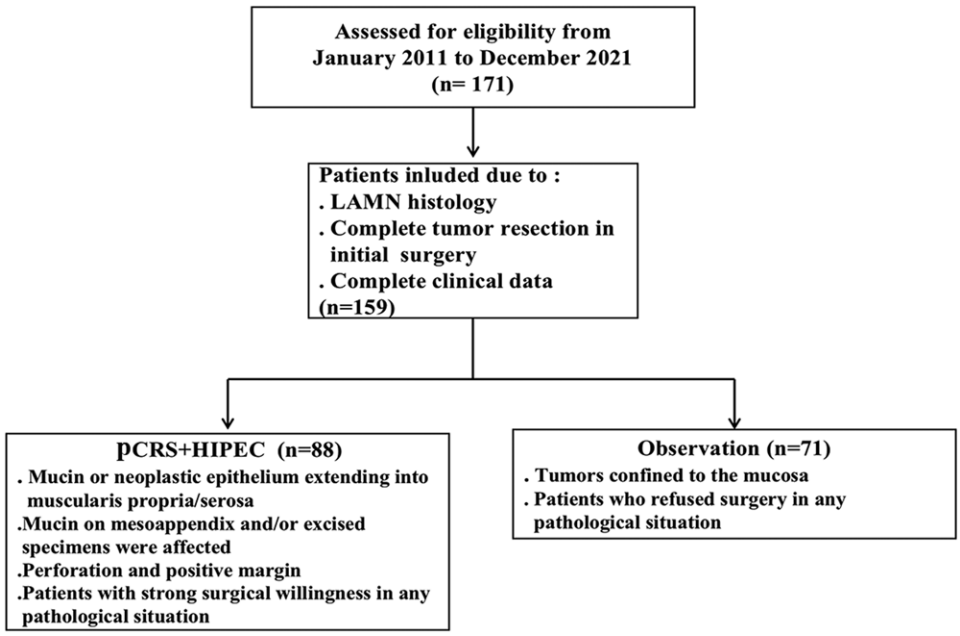

Figure 1. The flowchat.

Table 1

Clinical variable characteristics of patients.

Variable	No. All (n = 159)	No. PCRS (n = 88)	No. Non-PCRS (n = 71)	*P*-value
Age, median (IQR), y	51.0 (43.0–61.0)	53.0 (46.0–64.0)	47.0 (41.0–59.0)	.03
Sex				
Male	75	42	33	
Female	84	46	38	.87
Term of history, median (IQR), months	1.0 (1.0–2.0)	1 (1.0–2.0)	1.0 (1.0–2.0)	.88
PSS				
0–1	126	71	55	
2–3	33	17	16	.61
Perforation				
No	113	56	57	
Yes	46	32	14	.02
Appendicitis				
No	64	40	24	
Yes	95	48	47	.13
Mucinous ascites				
No	151	84	67	
Yes	8	4	4	>.99
Laparoscope				
No	72	49	23	
Yes	87	39	48	.003
PMP				
No	131	69	62	
Acellular	18	14	4	
DPAM	10	5	5	.12
HIPEC				
No	68	3	65	
Yes	92	85	7	<.001
Mucin/tumor cell dissection of appendix				
Mucosa	19	6	13	
Muscularis propria	53	26	27	
Serosa	87	56	31	.01

DPAM = disseminated peritoneal adenomucinosis, HIPEC = hyperthermic intraperitoneal chemotherapy, IQR = interquartile range, PCRS = Prophylactic cytoreductive surgery, PMP = peritoneal pseudomyxoma, PSS = prior surgical score.

Table 2

Surgical resection content and tumor implantation site in the PCRS + HIPEC and observation groups.

Operation	PCRS n = 88	Tumor implantation Acellular mucus	Tumor implantation DPAM	Non-PCRS n = 71	Tumor implantation Acellular mucus	Tumor implantation DPAM
Greater omentum	87	6	1	3	1	0
Lesser omentum	27	2	1	0	0	0
Ligamentum teres hepatis	38	3	1	0	0	0
Ileocecum	9	2	1	5	0	0
Right hemicolon	29	3	0	14	1	0
Peritoneum	10	2	2	1	0	0
Bilateral ovaries	43	5	0	1	0	1
Uterus	12	2	0	0	0	0

DPAM = disseminated peritoneal adenomucinosis, PCRS = prophylactic cytoreductive surgery.

(RFS), starts from the initial surgery for the appendix, and the last follow-up was conducted in December 2022 via telephone or at an outpatient clinic.

2.5. Statistical analysis

Statistical analysis was performed by using SPSS 25.0 (IBM Corporation, Armonk, NY) and R 4.1.2 (http://www.r-project.org). Continuous data were expressed as median (interquartile range) and analyzed by the Mann–Whitney *U* test. Categorical data were presented as frequencies and compared using chi-squared or Fisher exact test. All continuous variables, such as age and term of history, were converted to categorical variables to facilitate the presentation of results in clinical practice. Survival analysis was then performed using the Kaplan–Meier method and tested by a log-rank test, and a multivariable Cox proportional hazards model was established. In the model, we included variables, such as appearance and pathological features, PMP pathology and whether PCRS + HIPEC was performed, in order to obtain independent prognostic factors for nutritional RFS. The significance level for all statistical tests was set at 0.05.

3. Results

3.1. The patient characteristics

A total of 159 patients were included in this study, 75 women, and 84 men. Eighty-eight patients were included in the PCRS group, and 71 patients were included in the observation group. The median age was 51.0 (interquartile range, 43.0–61.0) years. In the PCRS group, 3 patients did not undergo HIPEC due to circulatory instability during surgery. In the observation group, 13 patients were not recommended surgery because the lesion was limited to the appendiceal mucosa, and 58 patients who were recommended PCRS opted for observation. There was a significant difference between the 2 groups in whether laparoscopy and HIPEC were performed and mucus and/or neoplastic epithelium distributed in the appendix. All the patient characteristics were shown in Table 1.

Table 3

Clinical variable characteristics of 7 recurrent patients.

	Primary surgery	PCRS
	No.	No.
Appendiceal perforation	3	–
Appendicitis	3	–
PMP		
No	5	–
Acellular	1	–
DPAM	1	5
PMCA/PMCA-S	–	1/1
CCR		
0/1	–	1/4
2/3	–	1/1
PCI		
≤20	–	2
>20	–	5

CCR = completeness of cytoreduction, DPAM = disseminated peritoneal adenomucinosis, PCI = peritoneal carcinomatosis index, PCRS = prophylactic cytoreductive surgery, PMCA = peritoneal mucinous carcinomatosis, PMCA-S = peritoneal mucinous carcinomatosis with Signet ring cells, PMP = peritoneal pseudomyxoma.

3.2. The result of surgery and pathology

As shown in Table 2, the primary surgical procedures in the PCRS group include omentectomy and bilateral salpingo-ovariectomy. The mean length of hospital stay was 12 days, and the mean operative time was 6 hours. Eighteen patients had mucus in their excised specimens after PCRS. Fourteen had acellular mucus, and 4 had DPAM. In the observation group, the treatment was mainly focused on the primary lesion. Only 3 patients had mucus in their specimens. Two were acellular mucus and 1 was LAMN.

3.3. The analysis of RFS

The median follow-up time for 159 patients was 38 months. The median RFS time was not achieved. Seven patients relapsed during follow-up and developed PMP through CRS, 1 in the PCRS group and 6 in the observation group. The pathological diagnosis was DPAM in 5 patients, PMCA in 1 patient and another one was PMCA with signet ring cells. The 7 patients with recurrence all received CRS + HIPEC, 1 patient each for completeness of cytoreduction score 0, 2, and 3, with 4 patients achieving CCR1. The clinical variable characteristics of 7 recurrent patients was shown in Table 3. Patients who underwent PCRS and HIPEC had longer RFS with significant survival differences (Fig 2A and B). Univariate analysis showed that the presence of DPAM was an independent factor affecting the prognosis for RFS (Table 4).In the analysis of surgical content, only the omentectomy and bilateral salpingo-ovariectomy were significantly associated with RFS (Fig. 3A and B, Table 5).

4. Discussion

The interaction between cancer cells and specific structures on the surface of the peritoneum creates a microenvironment favorable for cancer cell colonization and proliferation in the peritoneum, leading to peritoneal implantation and metastasis, which is the theoretical basis of CRS + HIPEC.[6] The role of CRS and HIPEC in the treatment and prevention of peritoneal metastasis of colorectal cancer colorectal cancer has been recognized.[7,8]

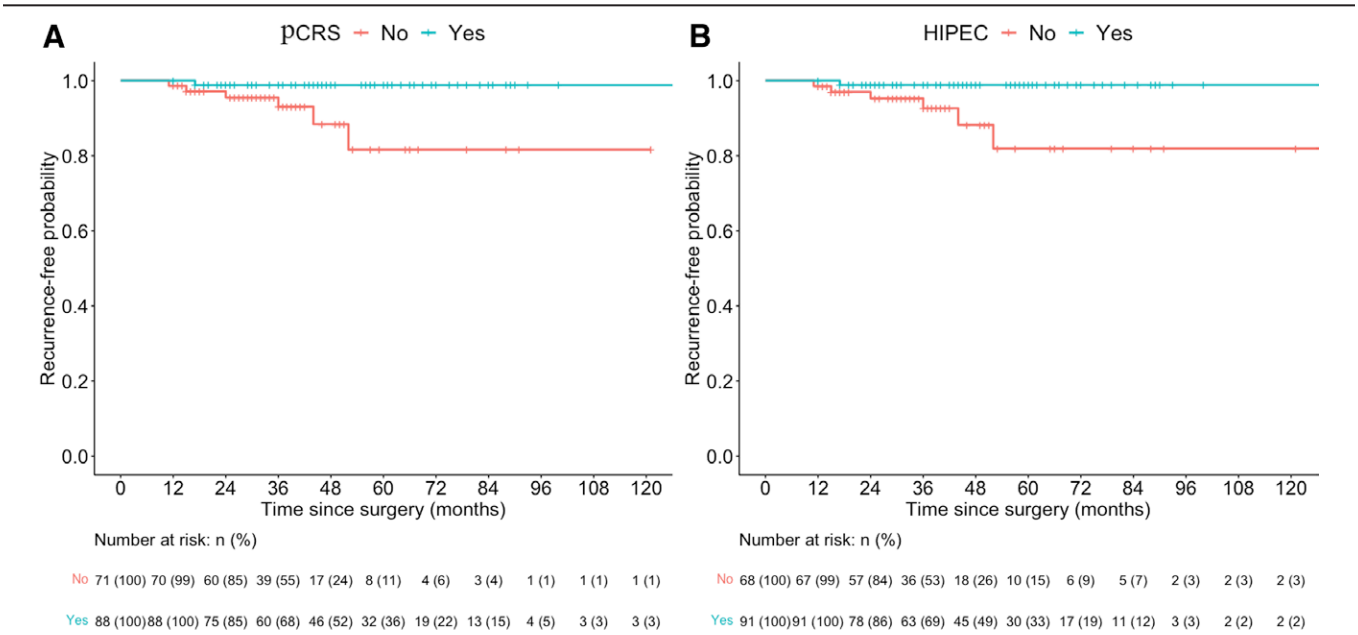

Figure 2. Kaplan–Meier curves show the survival difference in PCRS (A, $P = .01$) and HIPEC (B, $P = .01$). HIPEC = hyperthermic intraperitoneal chemotherapy; PCRS = prophylactic cytoreductive surgery.

Table 4

Univariate and multivariate analyses for prognostic factors affecting RFS.

Variables	No.	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age(years)					
≤50	75	1	–	–	–
>50	84	5.058 (0.608–42.045)	.13	–	–
Gender					
Female	84	1		–	–
Male	75	0.470 (0.091–2.243)	.36	–	–
Term of history, month					
≤1	117	1		–	–
>1	42	0.032 (0.001–49.317)	.35	–	–
PSS					
0–1	126	1	–	–	–
2–3	33	1.489 (0.288–7.682)	.63	–	–
Perforation					
No	113	1	–	–	–
Yes	46	1.701 (0.380~7.626)	.48	–	–
Appendicitis					
No	64	1	–	–	–
Yes	95	1.624 (0.314–8.386)	.56	–	–
Mucinous ascites					
No	151	1	–	–	–
Yes	8	3.529 (0.423–29.425)	.24	–	–
Laparoscope					
No	72	1	–	–	–
Yes	87	0.177 (0.021–1.492)	.11	–	–
PMP			–	–	–
No/Acellular	140	1	–	–	–
DPAM	9	7.477 (1.448–38.615)	.01	5.682 (1.066–30.297)	.04
HIPEC					
No	68	1	–	–	–
Yes	91	0.095 (0.011–0.797)	.03	–	–
Mucin/tumor cell dissection of appendix					
Mucosa/muscularis propria	72	1		–	–
Serosa	87	1.924 (0.373~9.933)	.43	–	–
PCRS					
No	71	1	–	–	–
Yes	88	0.097 (0.011–0.823)	.03	–	–

DPAM = disseminated peritoneal adenomucinosis, HIPEC = hyperthermic intraperitoneal chemotherapy, PCRS = prophylactic cytoreductive surgery, PMP = peritoneal pseudomyxoma, PSS = prior surgical score.

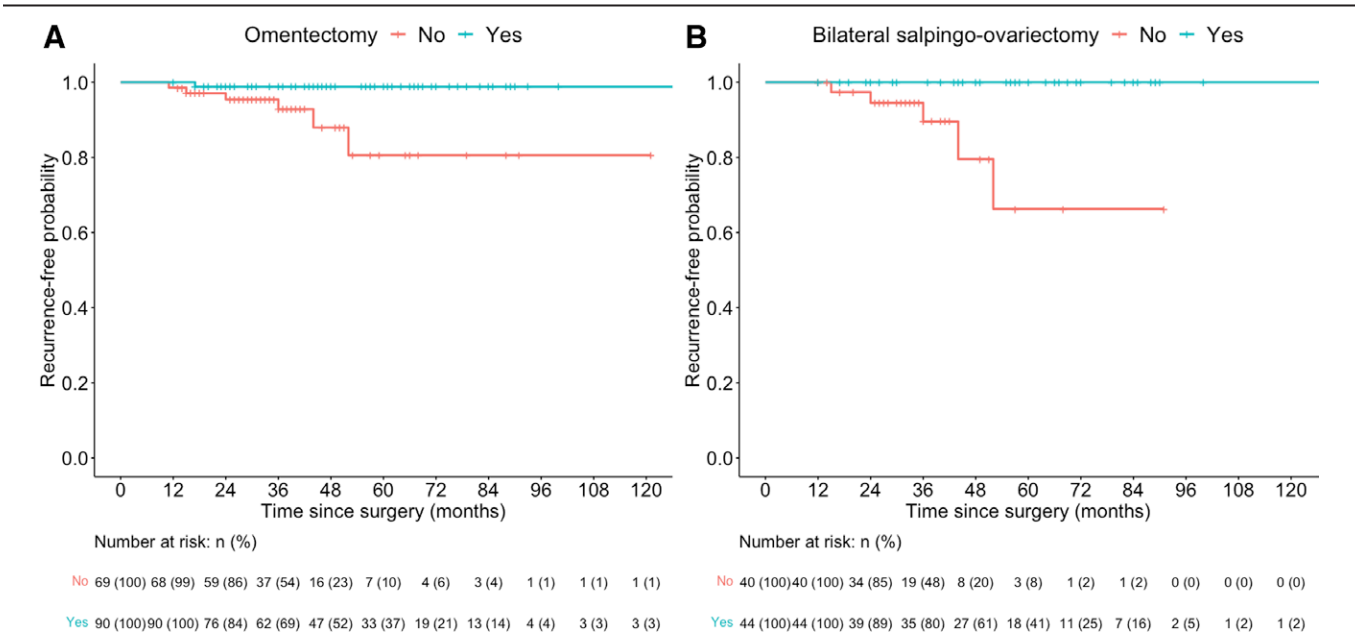

Figure 3. Kaplan–Meier curves show the survival difference in greater omentum (A, *P* = .01) and bliateral fallopian tubes and ovaries(B, *P* = .002).

Table 5

Survival analysis of surgical resection content after log rank test.

Organ or tissue resection	No.	*P* values
Greater omentum		
No	75	
Yes	84	.01
Lesser omentum		
No	84	
Yes	75	.13
Ligamentum teres hepatis		
No	117	
Yes	42	.27
Operation		
Appendix	126	
Ileocecum/RH	33	.72
Peritoneum		
No	156	
Yes	3	.45
Bilateral fallopian tubes and ovaries		
No	40	
Yes	44	.002
Uterus		
No	72	
Yes	12	.25

Although CRS + HIPEC also has been recognized as a highly effective treatment for PMP,[3–9] its role in patients with LAMN with early and low tumor burden that has been completely removed is still controversial given the possibility of progression to PMP. As the largest center for the diagnosis and treatment of PMP in China, we have treated many LAMN patients with early and low tumor burden that have been completely removed. Some patients underwent PCRS + HIPEC, while others chose observation. By analyzing the 159 patients included, we found that PCRS + HIPEC could prevent recurrence.

It is extremely difficult to identify high-risk recurrence populations from such patients. Some early studies showed that LAMN confined to the mucosa of the appendix that was completely resected without rupture represent no further risk of developing PMP.[10,11] Even with perforation and distribution of acellular mucin, the risk of developing PMP also was shallow.[12] By observing the macroscopic and microscopic characteristics of LAMN, Hegg et al found that more than 80% of cases with PMP had a microscopic presence of acellular mucin on the surface of the serosa, which was twice as high as in cases without PMP. Meanwhile, none of the cases that later developed into PMP had acellular mucin confined to the mucosal layer, and none of the cases where mucin was confined to the mucosa later developed into PMP.[13] When cellular mucin was found in the specimen, the probability of PMP occurring was higher.[14] Among the 7 relapsed patients in this study, 2 were affected by the appendicular muscular layer, 5 by the appendicular serosa, one had acellular mucin distribution and one was accompanied by DPAM. These results indicated that tumor invasion of the muscular and/or serosal layers of the appendix, and the distribution of acellular and/or cellular mucus are important factors in the occurrence of PMP.

The risk of developing PMP in patients with perforation and surgical margin remains difficult to predict. Some studies have found that appendix perforation is an important factor in the development of PMP.[15,16] However, perforation of the appendix does not necessarily mean the formation of PMP. Mehta et al found that appendiceal perforation did not increase the risk of progression to PMP compared with non-perforated patients.[17] Among the 7 patients with recurrence in this study, 3 had appendiceal perforation, and the perforation had no significant impact on RFS. A negative surgical margin has always been an ideal state pursued by surgeons, which could significantly reduce the risk of recurrence.[18] However, Misdraji study found that 16 patients with positive margins did not develop PMP.[19] In the observation group of this study, all patients had negative surgical margins, but 6 patients still developed PMP. These findings indicate that the development of PMP caused by surgical margin positivity is not absolute. In other words, a negative margin cannot completely block the occurrence of PMP.

The factors contributing to the development of PMP from LAMN remain unclear. However, based on the results of the above research, patients with mucin on mesoappendix or neoplastic epithelium extending into muscularis propria/serosa, perforation, and positive margin have a higher risk of developing into PMP. Therefore, we suggested and performed PCRS + HIPEC on these patients. For patients with tumors limited to the mucosa and strong surgical intention, we also performed the same treatment. Enomoto et al found that HIPEC had no significant advantage in preventing recurrence in patients with appendiceal neoplasms after complete resection.[20] However, in this study, the PCRS + HIPEC significantly prolonged the RFS.

Currently, there is no clear recommendation for the removal content of PCRS. From the characteristics of tumor implantation, PMP usually manifests as tumor deposition throughout the entire peritoneal cavity, which is composed of a redistribution pattern related to peritoneal fluid flow and gravity, which can also easily cause metastasis to the greater omentum and ovaries.[21] Meanwhile, the unique physiological characteristics of the ovary provide favorable conditions for tumor implantation.[22] All 4 recurrent female ovaries were involved in this study. Mehta et al discovered that the ovarian tumor metastasis rate in the appendiceal tumor group was 58.1%. Even when both ovaries appear normal macroscopically, 17% of patients were still affected.[23] Hench, omentectomy was performed in all patients who underwent PCRS in our center, and bilateral salpingo-ovariectomy was performed in postmenopausal women or premenopausal women with a desire to resection, whether the fallopian tubes and ovaries were normal or not. Although omentectomy and bilateral salpingo-ovariectomy were not independent factors affecting RFS in this study, they significantly prolonged the patient's RFS. In addition, we also removed other organs or tissues that were suspected or had potential implantation risks. However, they had no impact on RFS. Interestingly, as shown in Table 2, some specimens may have had microscopic implantation.

This study was associated with 2 limitations. First, this is a retrospective cohort study with a small number of patients and a lower recurrence rate. The follow-up time of the case was also short for this inert tumor. These factors may lead to some limitations in the results. Secondly, the important indicator of tumor markers was not included in the study due to severe data loss.

5. Conclusions

To our knowledge, this is the largest study evaluating PCRS + HIPEC in patients with LAMN after complete resection. The research indicated that PCRS + HIPEC could prevent recurrences, which may further block the formation or progression of PMP. Therefore this treatment is necessary for LAMN after complete removal in patients with a high risk of recurrence. We recommend removal of at least the greater omentum and bilateral fallopian tubes and ovaries in women. Women who do not wish to have their bilateral fallopian tubes and ovaries removed should be fully informed of the risks. However, as PCRS + HIPEC was not an independent factor for RFS, a multicenter, prospective, randomized trial is needed to be required to definitively address the role of PCRS + HIPEC for LAMN after complete removal.

Author contributions

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Writing – review & editing: Ruiqing Ma.

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