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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Strategies for Managing Intraoperative Discovery of Limited Colorectal Peritoneal Metastases

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ABSTRACT

Background. Management of limited synchronous colorectal peritoneal metastases (CRPM) is critical to outcome. Resection of the primary tumor and CRPM can be performed concurrently, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) either immediately, during the same procedure (one-stage), or during a systematic second-stage procedure (two-stage).

Objective. The aim of this study was to compare these two strategies for morbidity, mortality, and survival.

Methods. All patients presenting with limited (initial Peritoneal Cancer Index [PCI] $\leq$ 10) synchronous CRPM who had undergone complete cytoreductive surgery plus HIPEC between 2000 and 2016 were selected from a prospectively maintained institutional database.

Results. Overall, 74 patients were included—31 in the one-stage group and 43 in the two-stage group. During second-stage surgery, a peritoneal recurrence was diagnosed in 37 (86%) patients, 12 of whom had a PCI $>$ 10 (28%) and 2 of whom had unresectable disease (5%). Among the one-stage group, peritoneal recurrence occurred in 29% of patients after a median delay of 23 months. Overall survival at 1, 3, and 5 years was similar between the two groups, i.e. 96%, 59%, and 51% for the one-stage group, and 98%, 77%, and 61% for the two-stage group. A PCI $>$ 10 at the time of HIPEC, as well as liver metastases, were independent negative prognostic factors.

Conclusions. For incidental limited CRPM diagnosed during primary tumor resection, one-stage curative treatment is preferable, avoiding a supplementary surgical procedure. Given the critical issues associated with completeness of resection, patients should be referred to centers specialized in peritoneal surgery.

Colorectal peritoneal metastases (CRPM) occur in 8–20% of patients.[1] Despite the progress in systemic chemotherapy for managing colorectal cancer (CRC), survival is lower in patients with CRPM than in those with metastases at other isolated sites.[2] Over the last two decades, a new concept combining complete cytoreductive surgery (CRS) of CRPM followed by hyperthermic intraperitoneal chemotherapy (HIPEC) has markedly increased survival, reaching 40% at 5 years in selected patients,[3–5] and justifying the use of CRS followed by HIPEC to treat resectable and non-extensive CRPM.[6] When potentially resectable CRPM are diagnosed, patients are usually referred to a center specialized in peritoneal malignancies to be evaluated for CRS and HIPEC.

Difficulties arise in cases of intraoperative detection of CRPM during primary tumor resection in a non-specialized center, and the standard approach in this setting is currently under debate. A detailed description of the peritoneal disease that may be combined with limited surgical procedures such as an upstream colostomy, to prevent tumor-related complications, is routinely recommended by expert surgeons in this field. The aim of this strategy is to perform resection of the primary tumor combined with CRS followed by HIPEC during a single surgical procedure

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in a tertiary center. The alternative is concomitant resection of the primary tumor and CRS of limited CRPM, followed by a second-look strategy later. The aim of this study was to compare the short- and long-term results of these two strategies after incidental detection of synchronous limited CRPM.

PATIENTS AND METHODS

Cohort Description

All consecutive patients presenting with limited and synchronous CRPM who underwent CRS plus HIPEC between June 2000 and December 2016 were selected from a prospectively maintained, single-institution database. Selection criteria were patients with incidental detection of CRPM during primary tumor resection, limited peritoneal extension (defined as a Peritoneal Cancer Index [PCI][7] < 10), and referral for CRS plus HIPEC. Patients were assigned to two groups: the 'one-stage' strategy (OSS) group that included patients who underwent concomitant CRS plus HIPEC at the time of primary tumor resection, and the 'two-stage' strategy (TSS) group that included patients with concomitant resection of the primary tumor and CRPM, followed by secondary HIPEC. In the TSS group, primary surgery was performed in another institution, and no evidence of residual peritoneal disease was detected at the time of referral to our center according to a systematic second-look policy.

Preoperative Workup

Preoperative evaluation included a clinical examination, biological assessment including tumor markers, and a contrast-enhanced computed tomography (CT) scan. All cases were discussed at a multidisciplinary meeting. Contraindications for surgery were WHO performance status > 2, age > 70 years, disease progression on systemic chemotherapy, extraperitoneal extension (except for two or three liver metastases amenable to complete resection), and bulky peritoneal nodules with an appearance of diffuse invasion of the mesentery on CT scan.

Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

All patients underwent complete curative intent CRS followed by HIPEC. The extent of the peritoneal disease at the time of CRPM incidental detection was assessed according to the PCI described by Sugarbaker,[7] and defined as PCI. The peritoneal residual disease detected during systematic second-look surgery was defined as 'neo' PCI. The intent of surgery was to remove all visible intraperitoneal tumor deposits (completeness of cytoreduction [CC] score, CC0) or to remove all disease but leave small deposits ≤ 2.5 mm (CC1).[8] Only patients with a complete CRS procedure (CC0/1 < 1 mm) received HIPEC, which was delivered using the 'coliseum' open abdomen technique with oxaliplatin and irinotecan, as previously described.[9,10]

Postoperative Follow-Up

Postoperative complications were graded as per the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03; grade 1 and 2 complications were considered minor, and grade 3 and 4 complications were considered major. Postoperative morbidity included all complications until hospital discharge or postoperative day 90. Adjuvant chemotherapy was recommended, except for patients who had received 12 cycles before HIPEC. Patients were followed up every 3 months for 2 years, then every 6 months over 3 years and yearly thereafter until January 2017. Physical examination, serum carcinoembryonic antigen (CEA), and/or cancer antigen (CA) 19.9 measurements, as well as CT scans, were performed at each visit. Peritoneal or extraperitoneal relapses were defined as any newly detected lesion(s) during follow-up, with or without tumor marker abnormalities. For isolated tumor marker increases, further diagnostic modalities such as positron emission tomography and/or magnetic resonance imaging (MRI) were performed.

Statistical Analysis

Quantitative variables are presented as median (interquartile range) and are compared using the Wilcoxon's test, while qualitative variables are presented as count (percentage) and are compared using the Chi square or Fisher's exact test as appropriate. A p value < 0.05 was considered significant. Overall survival (OS) was defined as the time from diagnosis of peritoneal metastases to death, whatever the cause, and peritoneal-free survival was defined as the time from first surgery to peritoneal recurrence. OS and disease-free survival (DFS) were estimated using Kaplan–Meier curves. Prognostic factors for OS and DFS were evaluated using the log-rank test in univariate analysis. Significant factors from the univariate analysis were included in the Cox proportional hazards regression model for the multivariate analysis, and redundant factors were excluded. Hazard ratios (HRs) with 95% confidence intervals are reported. Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

Among 74 patients with synchronous and limited CRPM, 31 had concomitant resection of the primary tumor and CRPM followed by HIPEC during the same procedure (OSS group), and 43 had resection of the primary tumor and CRPM, then subsequent re-laparotomy for HIPEC sometime later (TSS group) (Fig. 1). In the TSS group, the median time between initial surgery and secondary HIPEC was 9 months [3–12]. The two groups were similar regarding age, sex, primary tumor location, and administration of systemic chemotherapy before and after HIPEC (Table 1). The initial median PCI (at CRPM diagnosis) was not statistically different between the two groups, i.e. 5 (2–10) in the OSS group and 3 (1–10) in the TSS group. Regarding primary CRC stage, T4 tumors were more common in the TSS group (69%) compared with the OSS group (29%; $p = 0.005$), as were N-positive tumors (75% and 52%, respectively; $p = 0.04$). Furthermore, synchronous liver metastases were more frequent in the OSS group (29% vs. 9%, $p = 0.02$).

Surgical Procedures

During systematic second-stage surgery in the TSS group, a peritoneal recurrence was diagnosed in 37 (86%) patients with a median 'neo' PCI (determined during second-stage surgery) of 7 (0–26). Twelve (28%) patients had a 'neo' PCI of > 10. The median 'neo' PCI was significantly higher compared with the initial PCI in both groups ($p = 0.04$). During the second stage, two (5%) patients were contraindicated for curative surgery due to disseminated and unresectable peritoneal disease (PCI of 18 and 26, respectively).

During HIPEC, surgical procedures were similar between the two groups. A diverting loop was performed more often in the OSS group (42% vs. 21%; $p = 0.05$) [Table 1] because of a higher rate of low colorectal anastomosis. Operative time did not significantly differ between the two groups ($p = 0.28$), however time of hospitalization was longer in the OSS group (20 days vs. 15 days, $p = 0.04$). Radiofrequency ablation was used to treat liver metastases in six patients in the OSS group and four patients in the TSS group, and was associated with wedge resection in three patients.

Postoperative Complications and Mortality

Postoperative outcomes after HIPEC are reported in Table 2. Grade 3–4 complications were registered in 35% of patients in the OSS group and 20% of patients in the TSS group, with a possible trend towards statistical significance ($p = 0.07$). Surgical complications included anastomotic leakage ($n = 7$), urological leakage ($n = 3$),

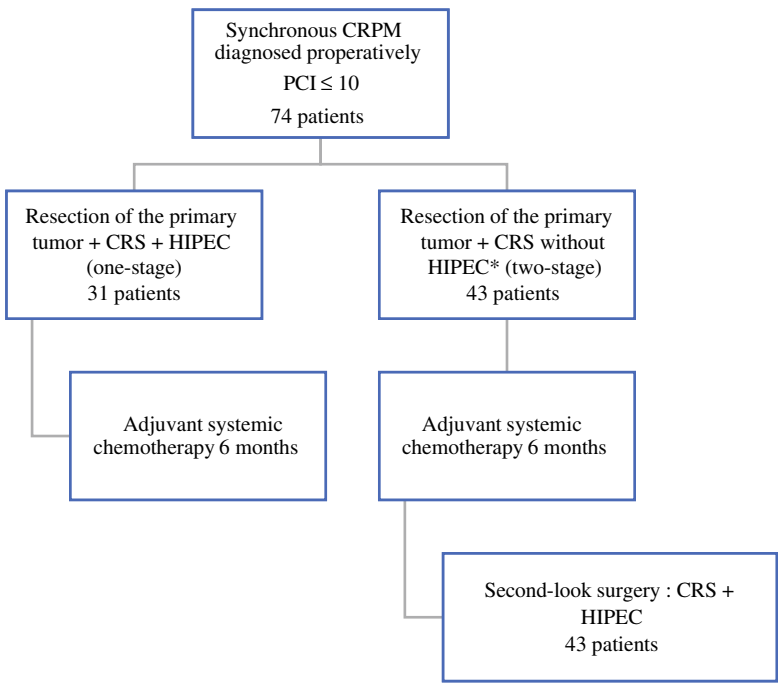

FIG. 1 Patient selection process. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* Peritoneal Cancer Index, *CRPM* colorectal peritoneal metastases

TABLE 1 Demographic and intraoperative characteristics of patients treated for limited peritoneal metastases with complete CRS and HIPEC in one or two stages

Variables	One-stage surgery [$n = 31$]	Two-stage surgery [$n = 43$]	p value
Age, years [mean (SD)]	49 (13)	49 (12)	0.90
Sex			0.04
Male	10 (32)	24 (56)	
Female	21 (68)	19 (44)	
Primary tumor location			0.33
Colon	24 (77)	37 (86)	
Rectum	7 (23)	6 (14)	
T4 status	9 (29)	30 (69)	0.005
Lymph node status			0.04
N-negative	15 (48)	11 (25)	
N-positive	16 (52)	32 (75)	
Synchronous liver metastases	9 (29)	4 (9)	0.02
Associated ovarian metastases	12 (39)	13 (30)	0.53
Chemotherapy before HIPEC	28 (90)	43 (100)	0.47
Initial PCI at diagnosis of CRPM [median (range)]	5 (2–10)	3 (1–10)	0.07
'Neo' PCI at the time of HIPEC [median (range)]	5 (2–10)	7 (0–26)	0.04
'Neo' PCI $\leq$ 10 at the time of HIPEC	31 (100)	31 (72)	0.001
Surgical procedure (during CRS + HIPEC)			0.63
Colorectal anastomosis	17 (55)	13 (30)	
Ileocolic anastomosis	4 (13)	11 (25)	
Other anastomosis	7 (23)	10 (23)	
No anastomosis	3 (10)	9 (21)	
Diverting loop	13 (42)	9 (21)	0.05

Data are expressed as *n* (%) unless otherwise specified

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* Peritoneal Cancer Index, *SD* standard deviation, *CRPM* colorectal peritoneal metastases

deep abscess ($n = 4$), and impaired wound healing ($n = 5$). Twenty patients required re-interventions, including surgical re-intervention ($n = 12$), radiologic drainage ($n = 3$), or both ($n = 5$). Non-surgical complications were pneumonitis and hematologic abnormalities in four and three patients, respectively. Two patients died postoperatively, both in the OSS group.

Survival and Peritoneal Recurrence

After a median follow-up of 36 months (3–108), 3- and 5-year OS was 66% and 51% in the OSS group, and 67% and 60% in the TSS group, respectively. Median survival was not reached in either group. At the last follow-up, 21 (68%) patients in the OSS group and 29 (67%) patients in the TSS group were alive.

During the follow-up period, 15 (48%) patients in the OSS group and 25 (58%) patients in the TSS group recurred ($p = 0.29$). Median DFS was 15.7 and 19.8 months for the OSS and TSS groups, respectively ($p = 0.08$).

In the OSS group, the peritoneal recurrence rate was 24%, with median peritoneal-free survival of 23 months. In the TSS, the rate of peritoneal recurrence after second-look surgery and HIPEC was 29%, with a median peritoneal-free survival of 24 months (Fig. 2). Among the six patients without recurrent disease during second-stage surgery, none developed peritoneal recurrence during follow-up.

OS was correlated with the PCI (Fig. 2); 1-, 3-, and 5-year OS was 85%, 77%, and 71%, respectively, for PCI $\leq$ 10, and 91%, 10%, and 10%, respectively, for PCI > 10 ($p < 0.0008$). Multivariate analyses identified two independent prognostic factors—PCI at the time of HIPEC, and the presence of associated liver metastases (Table 3). The type of strategy (OSS and TSS) was not disclosed as an independent prognostic factor. For patients without liver metastases ($n = 22$ in the OSS group; $n = 39$ in the TSS group), no difference was seen between the two groups in terms of survival (data not shown).

TABLE 2 Postoperative morbidity and long-term outcome after treatment of limited peritoneal metastases with complete cytoreductive surgery and HIPEC in one or two stages

Variables	One-stage surgery [$n = 31$]	Two-stage surgery [$n = 43$]	p value
Postoperative morbidity (NCI-CTCAE)			0.07
Grade 3–4	11 (35)	9 (20)	
Grade 5	2 (6)	0	
Blood loss, mL [median (range)]	200 (20–1000)	200 (50–1200)	0.1
Duration of surgery, min [median (range)]	330 (180–480)	360 (240–560)	0.28
Duration of hospitalization, days [median (range)]	20 (11–55)	15 (10–42)	0.04
Postoperative chemotherapy	22 (71)	26 (60)	0.17
Long-term outcome[a]			
Recurrence	15 (48)	24 (58)	0.39
Isolated peritoneal recurrence	4 (13)	8 (19)	0.13
Distant metastases	6 (19)	14 (34)	
Both	5 (16)	2 (6)	

Data are expressed as n (%) unless otherwise specified

HIPEC hyperthermic intraperitoneal chemotherapy, *NCI–CTCAE* National Cancer Institute-Common Terminology Criteria for Adverse Events

[a]Two patients in the two-stage group who had incomplete cytoreductive surgery were excluded from analysis of recurrence

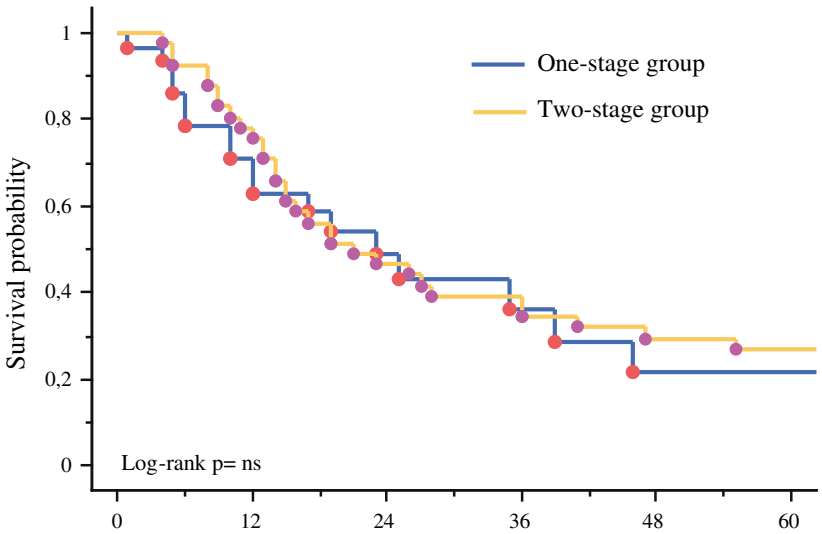

FIG. 2 Peritoneal-free survival after initial surgery according to therapeutic strategy: one- or two-stage surgery. *ns* non-significant

At risk

OST	31	17	8	4	2	1
DIF	41	31	18	15	11	10

DISCUSSION

This study demonstrates that in the case of intraoperative detection of limited CRPM during primary tumor resection, the strategies of concomitant CRS and HIPEC, or complete CRS followed by systematic second-surgery and HIPEC, achieve similar results in terms of severe postoperative morbidity and mortality, as well as for OS and peritoneal DFS.

Faced with an intraoperative diagnosis of limited resectable CRPM, several strategies can be proposed. Primary tumor resection with complete CRS can be performed, with the advantage that the disease is entirety treated in one stage. The second approach involves primary

TABLE 3 Multivariate analysis of prognostic factors for overall survival in the whole population (after one- or two-stage strategies)

Variables	HR (95% CI)	*p* value
PCI		
PCI < 10	1	0.0004
PCI > 10	9.76 (95% CI 2.76–34.4)	
Liver metastases		
No	1	0.02
Yes	4.3 (95% CI 1.2–15.3)	
Lymph node status		
Negative	0.7 (95% CI 0.22–2.19)	0.54
Positive	1	
Surgical strategy		
One-stage surgery	1.6 (95% CI 0.47–5.39)	0.44
Two-stage surgery	1	

HR hazard ratio, *CI* confidence interval, *PCI* Peritoneal Cancer Index

tumor resection with a detailed description of the peritoneal extension, to subsequently refer the patient to a center specialized in peritoneal surgery for complete CRS followed by HIPEC. Another alternative is primary tumor resection with concomitant CRS of the visible lesions, followed by a systematic second-stage surgery with HIPEC sometime later in a specialized center. In our study, analysis of patients who underwent CRS alone without a planned second-look surgery was not possible as they were not referred to our center.

In the literature, only two small retrospective series of patients who underwent surgical resection for CRC and synchronous CRPM have been reported,[11,12] with a 5-year OS of 30%, which is lower than that reported in another series of patients operated with curative intent, including CRS and HIPEC.[13] However, patients from these series are not comparable (different populations, settings, surgical procedures, and PCI) and no clear conclusions can be drawn. In 2018, the results of the phase III randomized trial PRODIGE 7 (NCT00769405 24),[14] showing no survival benefit in associating HIPEC with complete CRS for CRPM (135 patients undergoing CRS plus HIPEC vs. 136 patients undergoing CRS alone), raised several questions about the role of complete surgical resection in this setting. Excellent survival rates (median OS 41 months) were achieved in both arms of the study, highlighting the impact of the completeness of CRS that was achieved in 90% of patients in tertiary centers. We can speculate that the unexpectedly high rate of CRPM detected during surgery in our TSS group after 'theoretically' complete CRS can be partially explained by the fact that surgery was initially performed in non-specialized centers. This highlights that the main objective of surgery is the completeness of resection, which emphasizes the role of education in surgical resident programs regarding basic principles of peritoneal surgery, particularly extended exploration of the abdominal cavity and resection of limited CRPM. Peritonectomy techniques and quality of CRS can be a source of confusion in inexperienced hands. Incomplete CRS, leaving peritoneal nodules, which are 'hidden' during the first surgery, can contribute to a high rate of peritoneal recurrence.

In our study, both groups had CRS and HIPEC, and the rate of peritoneal recurrence after HIPEC was comparable between the two groups (approximately 25%), but lower than that reported in the literature.[15] This can be explained by the fact that our patients had a very low PCI (< 10 for all patients in the OSS group and for 72% of TSS patients) at the time of CRS and HIPEC. It has been demonstrated that prolonged survival, and even cure, can be obtained in patients with a low PCI (< 10).[3,4,16] However, imaging examinations still fail to diagnose early CRPM, such as small nodules (< 0.5 cm), which are visualized on CT scans with a sensitivity of only 11%,[17] and intraoperative CRPM diagnosis still occurs in at least 4% of patients undergoing CRC surgery.[1] In our opinion, the potential benefit of curative intent treatment in these patients justifies efforts to treat limited peritoneal disease with a chance of cure during a single procedure.

Our results in the TSS group are consistent with the literature[13] in terms of (1) the 80% rate of peritoneal recurrence discovered during a second-look in patients with a history of limited and resected CRPM;[5,18] (2) 5–10% of patients were not eligible for complete resection; and (3) second-look is a long and morbid surgery. In 2013, Braam and colleagues[19] compared the rate of bowel resection between patients who had one-stage surgery and patients who were secondarily referred for HIPEC. They observed a higher rate of extended bowel resection, anastomotic leakage, and permanent colostomy in the late-referral group, and concluded that patients should be referred early, i.e. at the time of diagnosis of CRPM, even though long-term survival (overall and disease-free) were similar between the two groups.[19] Preliminary results of the PROPHYLOCHIP phase III randomized trial (NCT01226394) comparing two strategies in patients at high risk of developing CRPM were reported in 2018.[20] DFS at 3 years, the primary endpoint, was not significantly different between the two strategies (surveillance vs. second-look and HIPEC). The present study differs from PROPHYLOCHIP since its objective was to evaluate the strategy in cases of intraoperative diagnosis of CRPM, rather than to compare surveillance with a proactive attitude of second-look and HIPEC.

From the results of our study, the best option appears to be one-stage surgery, including concomitant resection of the primary tumor and all CRPM, which requires expertise in peritoneal surgery. Long-term prognosis was equivalent between the two groups; however, the one-stage strategy allowed treatment of the disease in a single surgical procedure, thus avoiding the complications and hospitalization associated with two surgical procedures, as well as new visceral resections. There was a trend towards higher morbidity in the OSS group at the time of HIPEC but our results did not consider morbidity of the first surgery in the TSS group (performed in another institution), which could add up and alter the results.

To refer patients to a specialized center, it is recommended that a staging laparoscopy be systematically proposed for patients at high risk of synchronous CRPM, as is the case for gastric carcinoma.[21] Known risk factors for synchronous CRPM include T4 tumors, T3 mucinous adenocarcinoma, *BRAF* mutations, and ovarian metastases.[1,18] In these patients, the first laparoscopy via a single port may allow diagnosis of synchronous CRPM, evaluation of its extent, and patient referral to a specialized center.[22]

Our study has several limitations. First, its retrospective design may introduce biases. Nonetheless, all consecutive patients undergoing CRS and HIPEC at our institution have been prospectively registered in a computer database since 1990. The two groups were comparable except for the primary tumor stage (more advanced in the TSS group) and the rate of synchronous liver metastases (more common in the OSS group), which may represent a bias. Second, only referred patients who had HIPEC or a laparotomy with the aim of performing HIPEC were selected, meaning that patients who had complications related to systemic chemotherapy or disease progression, after either CRS or exploratory laparoscopy alone, were not taken into account. In addition, patients were highly selected in terms of performance status, disease burden, and absence of progression under systemic induction chemotherapy.[6]

CONCLUSIONS

We recommend that in the event of intraoperative diagnosis of CRPM, CRS with or without concomitant HIPEC during a single procedure should be proposed, given the clear benefit of treating patients at the same time and at an earlier stage. Neverthless, due to the hetereogeneity of surgical skills of general surgeons in the field of peritoneal surgery, it seems reasonable to refer patients to a specialized center without performing a surgical procedure if the tumor is asymptomatic in order to increase the chance of cure. In patients at high-risk of synchronous CRPM not visible on imaging examinations, an exploratory laparoscopy should be performed with the aim of diagnosing CRPM at an early stage. Specific programs of education during surgical training should be implemented in the future.

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