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Surveillance of Low-Grade Appendiceal Mucinous Neoplasms With Peritoneal Metastases After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Are 5 Years Enough? A Multisite Experience

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ABSTRACT

Background. Low-grade appendiceal mucinous neoplasms (LAMNs) are tumors that often present with widespread mucin in the peritoneal cavity (pseudomyxoma peritonei [PMP]). Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are effective treatment, but no published recommendations exist regarding surveillance.

Methods. Data from prospective databases of patients who underwent CRS-HIPEC from 2001 to 2017 at two high-volume institutions were retrospectively analyzed. Patients who underwent complete CRS-HIPEC for PMP secondary to LAMN were included in the analysis. Pathologic examination confirmed the diagnosis of LAMN. Cases of mucinous adenocarcinomas and neuroendocrine tumors (goblet cell carcinoids) were excluded.

Results. The study enrolled 156 patients. The median peritoneal cancer index (PCI) was 18 (interquartile range IQR1–3, 12–23), and 125 patients (80.1%) had a CC0 cytoreduction. According to American Joint Committee on Cancer (AJCC) grading, 152 patients (97.4%) presented with acellular mucin or G1 implants, 2 patients (1.3%) presented with G2 disease, and 2 patients (1.3%) presented with G3 disease. During the follow-up period (median, 45 months; IQR1–3 23–76 months), 23 patients (14.7%) experienced recurrence. All the recurrences were peritoneal and occurred within 5 years. The 1-, 3-, and 5-year disease-free survival (DFS) rates were respectively 95.5%, 83.4%, and 78.3%. Univariate Cox regression analysis showed that higher PCI scores ($p < 0.001$), a CC1 cytoreduction ($p = 0.005$), and higher preoperative levels of carcinoembryonic antigen (CEA) ($p = 0.012$) and CA-125 ($p = 0.032$) correlated with a shorter DFS. Only higher PCI scores independently predicted earlier recurrences ($p < 0.001$).

Conclusion. Most patients had recurrence within 3 years after CRS-HIPEC, and none after 5 years. High PCI was the only independently significant variable. The study findings support intensive surveillance (every 3–6 months) with tumor markers and imaging methods during the first 3 years, and annual surveillance thereafter, with follow-up assessment after 5 years yielding limited benefit.

Low-grade appendiceal mucinous neoplasms (LAMNs) are rare, and their incidence among appendectomy specimens is reported to be 0.7 to 1.7%.[1–5] Defined as tumors with low-grade cytology lacking overt epithelial infiltration,[6] LAMNs have a marked propensity to spread to the peritoneum. These tumors generally are considered

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relatively indolent without the potential for hematogenous dissemination. Overall, 20% of appendiceal mucinous neoplasms ultimately spread peritoneally and lead to pseudomyxoma peritonei (PMP), defined as the presence of intraperitoneal mucin, either acellular or associated with mucin-producing epithelium.[7]

For LAMNs presenting without evidence of PMP, appendectomy with negative margins is considered appropriate treatment, and hyperthermic intraperitoneal chemotherapy (HIPEC) is added for patients with perforated tumors.[8,9] Cytoreductive surgery (CRS) with HIPEC currently is accepted as effective treatment for most patients with PMP secondary to LAMN.[10–13]

Methods and timing of follow-up assessment after resection of non-metastatic LAMN have been reported in previous literature.[5] However, no recommendations exist regarding interval and duration of surveillance for patients with PMP secondary to LAMN (LAMN-PMP) who underwent CRS-HIPEC. Although the National Comprehensive Cancer Network (NCCN) recommends colorectal cancer (CRC) surveillance for 5 years after resection for most pathologic stages, it is unclear whether patients who undergo CRS-HIPEC due to LAMN-PMP may benefit from longer surveillance given the relatively indolent behavior of these tumors.

This study aimed to analyze patterns of recurrence among these patients in terms of location and timing. Given the rarity of this disease, we performed a multicenter study to outline recommendations for clinical and radiologic surveillance after CRS-HIPEC.

METHODS

Data from prospectively maintained databases of patients undergoing CRS-HIPEC from May 2001 to December 2017 were retrospectively obtained at two high-volume institutions for this procedure. The study was approved by the institutional review boards at both hospitals.

Demographic, perioperative, and long-term follow-up data were reviewed. Preoperative workup and surgical technique have been described previously for both institutions.[14,15]

After multidisciplinary discussion, diagnostic laparoscopy is performed and, if complete cytoreduction is deemed achievable, then converted to laparotomy. At further open exploration of the abdomen, the peritoneal disease burden is evaluated using the peritoneal cancer index (PCI) according to the Sugarbaker/Jacquet classification.[16] Cytoreduction follows, and the completeness of cytoreduction (CC) score is recorded.[16]

We deliver HIPEC in a closed fashion, with mitomycin C as the most commonly used chemotherapeutic drug, administered at a fixed dose of 40 mg for 90 min targeting an intraperitoneal temperature of 41 to 43 °C, as recommended by the consensus guidelines from the American Society of Peritoneal Surface Malignancies.[17] When necessary, anastomoses are created at HIPEC completion.

After discussion among the two institutions to ensure the adoption of common inclusion criteria, we decided to use the classification outlined by the eighth edition of the American Joint Committee on Cancer (AJCC) tumor staging system. Therefore, we included patients with primary low-grade (well-differentiated [G1]) appendiceal mucinous neoplasms. Mucinous adenocarcinomas (MACAs) demonstrating signs of infiltrative "destructive" epithelial invasion and goblet cell carcinomas were excluded from the analysis. The histology of PMP originating in the appendix was classified per the AJCC grading system as well, including low-grade (G1) and high-grade (G2/3) metastatic disease. The study included only cases for which the appendiceal primary pathology was performed at our institutions or slides from outside hospitals that were internally reviewed.

Because no standardized surveillance protocol exists, we follow up on all our patients treated who undergo CRS-HIPEC with physical examination, carcinoembryonic antigen (CEA) serum levels, carbohydrate antigen 125 (CA 125) serum levels, and computed tomography (CT) or magnetic resonance (MR) scans at 3- or 6-month intervals at least during the first 2 years, followed by a minimum 3 more years of yearly visits and imaging.

Data were analyzed using the Statistical Program of Social Sciences (SPSS 22, released in 2013; SPSS Statistics for Windows, version 22.0; IBM Corporation, Armonk, NY, USA). Categorical data are expressed as percentages and continuous data as medians. Student's t test and the Mann–Whitney test were used to compare continuous variables. Categorical variables were compared by the Chi square test or Fisher's exact test. Survival analyses were calculated using the Kaplan–Meier method. Subgroups were compared with the log-rank test. Cumulative disease-free survival (DFS) was calculated as the time from CRS-HIPEC to the first evidence of recurrence. Multivariate Cox regression was performed using all variables that in the univariate analysis yielded a p value lower than 0.05 as predictors. A p value lower than 0.05 was considered statistically significant. All p values were two-sided.

RESULTS

Baseline, Perioperative, and Pathologic Characteristics

Overall, 413 patients underwent CRS-HIPEC for PMP of appendiceal origin. However, for 147 patients (35.6%), pathologic examination of the appendiceal primary tumor was not performed at our institutions or was not internally reviewed, and these patients were therefore excluded from the study. This resulted in 266 patients who underwent CRS-HIPEC for PMP and had an internally validated appendiceal primary tumor. A pathologic review confirmed LAMN in 183 of these patients (68.8%). The patients who had a diagnosis of MACA (n = 83, 31.2%) and those who did not undergo complete cytoreduction (CC 2–3: n = 27, 10.1%) were excluded from the analysis. Our study population ultimately included 156 patients (Fig. 1).

As listed in Table 1, the median PCI score in the study population was 18 (interquartile range, IQR1–3, 12–23),

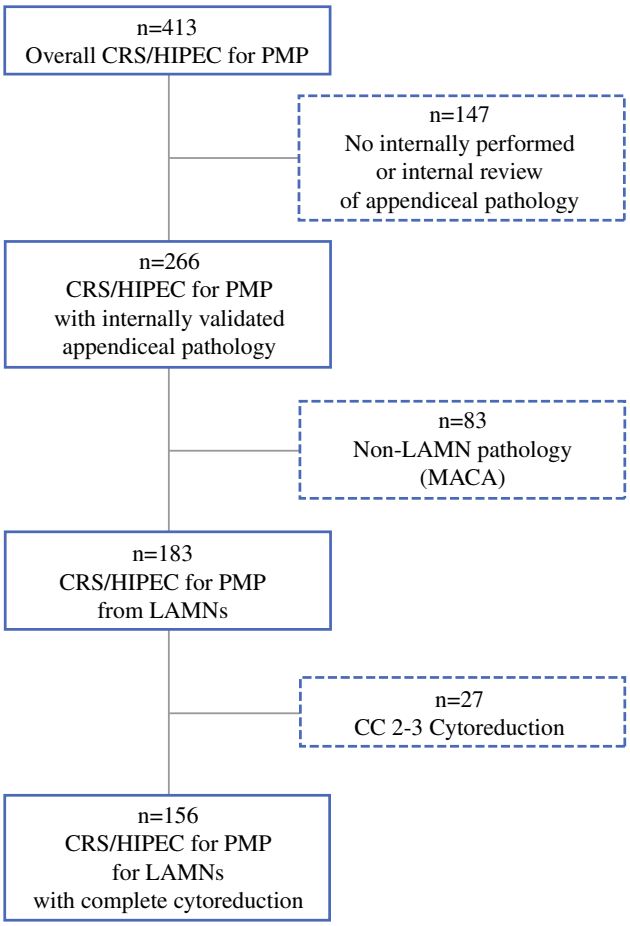

FIG. 1 Flowchart of the study population. *CRS/HIPEC* cytoreductive surgery and hyperthemic intraperitoneal chemotherapy, *PMP* pseudomyxoma peritonei, *LAMN* low-grade appendiceal mucinous neoplasm, *MACA* mucinous adenocarcinoma of the appendix, *CC* completeness of cytoreduction

TABLE 1 Baseline, perioperative, and pathologic characteristics

Variables	Overall (n = 156) n (%)
Median age: years (IQR1–3)	53 (45–62)
Gender (females)	90 (57.7)
ASA: median (IQR1–3)	3 (2–3)
Neoadjuvant chemotherapy	11 (7.1)
Adjuvant chemotherapy	5 (3.2)
Preoperative markers: median (IQR1–3)	
CEA	8.3 (2.4–28.5)
CA-125	40.6 (19.6–70.9)
PCI score: median (IQR1–3)	18 (12–23)
CC score	
0	123 (78.8)
1	33 (21.2)
HIPEC agent	
Mitomycin C	153 (98.1)
Carboplatin	3 (1.9)
Cytoreduction	
Small bowel resection	
Colectomy	40 (25.6)
Proctectomy (anterior resection)	67 (42.9)
Splenectomy	23 (14.7)
Pancreatic resection	103 (66)
Cholecystectomy	19 (12.2)
Gastrectomy	75 (48.1)
Omentectomy	19 (12.2)
Partial/full thickness	144 (92.3)
Diaphragmatic Resection	84 (53.8)
Liver capsulectomy/resection	42 (26.9)
Hysterectomy/oophorectomy	50 (32.1)
Cystectomy	5 (3.2)
Ureterolysis	70 (44.9)
Anastomosis	99 (63.5)
Number: median (IQR1–3)	1 (0–2)
Median hospital stay: days (IQR1–3)	11 (8–16)
Peritoneal carcinomatosis, AJCC grade	
Acellular mucin	25 (16)
1	127 (81.4)
2	2 (1.3)
3	2 (1.3)

Results are considered statistically significant at $p < 0.05$

IQR, interquartile range; ASA, American Society of Anesthesiology; CEA, carcinoembryonic antigen; CA-125, carbohydrate antigen 125; PCI, peritoneal carcinomatosis index; CC, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; AJCC, American Joint Commission on Cancer

and CC0 cytoreduction was achieved for 123 patients (78.8%). Mitomycin C was used in 153 HIPEC procedures (98.1%). Preoperative chemotherapy was administered to 11 patients (7.1%), whereas adjuvant chemotherapy was administered to 5 patients (3.2%). Additional intraoperative variables and median values of preoperative tumor marker levels also are shown in Table 1.

At the time of CRS-HIPEC, peritoneal disease specimens (PMP) were classified as well-differentiated (G1) in 127 patients (81.4%), moderately differentiated (G2) in 2 patients (1.3%), and poorly differentiated (G3) in 2 patients (1.3%). Acellular mucin was found in the remaining 25 patients (16%).

Survival Analysis and Patterns of Recurrence

During a median follow-up period of 45 months (IQR1–3, 23–76 months), median overall survival (OS) was not reached, and the 1-, 3-, and 5-year OS rates were respectively 97.3%, 95.8%, and 89.2%. Overall, 23 patients (14.7%) had recurrence. All recurrences were peritoneal and detected with follow-up CT scans.

In the Kaplan–Meier analysis, OS was significantly shorter for the patients with recurrence than for those free of disease during the follow-up period (median OS not reached in both cohorts, $p = 0.008$). In the study population, median disease-free survival (DFS) was not reached, and the 1-, 3-, and 5-year DFS rates were 95.5%, 83.4%, and 78.3% (Fig. 2).

The univariate Cox regression analysis showed that higher PCI scores ($p < 0.001$), CC1 cytoreduction ($p = 0.005$), and higher preoperative levels of CEA ($p = 0.012$) and CA-125 ($p = 0.032$) correlated with shorter DFS. In the multivariate analysis, only higher PCI scores predicted earlier recurrences ($p < 0.001$) (Table 2).

In a subset Kaplan–Meier analysis for DFS, the patients with PCI higher than 12, CEA higher than 5 ng/mL, and CA125 higher than 46 U/mL showed significantly poorer DFS (median DFS not reached in all groups, $p = 0.006$, 0.008, and 0.001, respectively).

In an additional subset analysis including the 23 patients who had recurrence, the median DFS was 21 months (95% confidence interval [CI], 14.7–27.3), and the cumulative 1-, 3-, and 5-year DFS rates were respectively 73.9%, 17.4%, and 0%. Thus, all recurrences were detected within 5 years, with the last recurrence detected 52 months after CRS-HIPEC.

Finally, a comparison of the patients undergoing CRS-HIPEC with acellular implants and PMP with epithelial cells showed that only 2 (8%) of 25 patients from the acellular cohort had recurrence, compared with 11 (8.4%) of the 131 patients in the remaining population. No differences were found in terms of DFS after the procedure (median DFS not reached in either cohort; p was not significant) (Fig. 3).

DISCUSSION

Our study reports the timing of recurrence for patients with LAMN-PMP to identify clinical recommendations for surveillance after CRS-HIPEC. To include an appropriate number of patients, we combined the expertise from two high-volume centers for this procedure. In our cohort of patients with primary LAMN, as determined through reviewed pathology, we showed that most recurrences happen within 3 years after complete CRS-HIPEC. Because no recurrence was detected after 5 years, the role of routine surveillance after that time point may be limited. We also report that a higher PCI score was independently

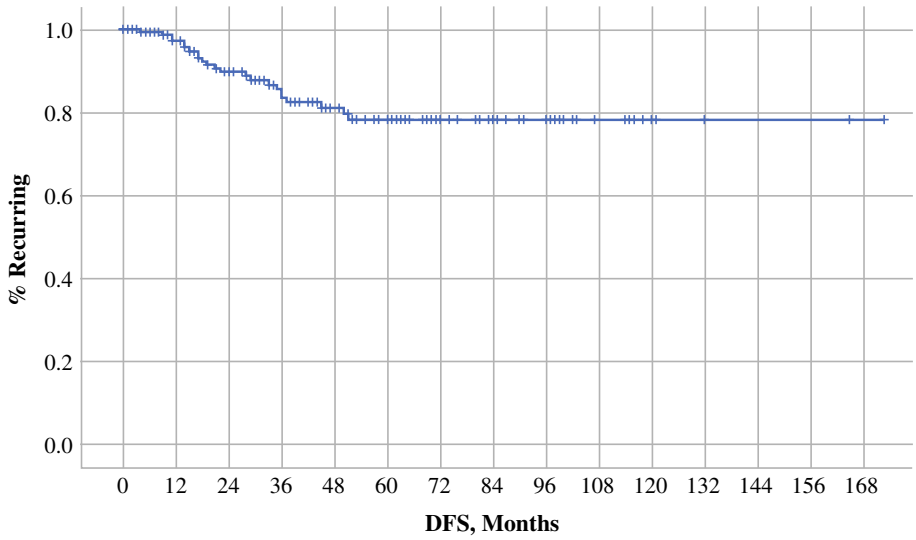

FIG. 2 Kaplan Meier curve demonstrating disease free survival following CRS/HIPEC in the study population. *DFS* disease-free survival

TABLE 2 Uni- and multivariate Cox regression analyses showing predictors of earlier recurrence

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value[a]	HR	95% CI	*P* value[a]
Age	.989	0.954–1.025	0.550			
Gender, Female	.555	0.243–1.265	0.161			
ASA score	1.219	0.611–2.434	0.574			
Preoperative CEA	1.003	1.001–1.006	0.012			
Preoperative CA-125	1.003	1.000–1.005	0.032			
PCI	1.114	1.064–1.166	< 0.001	1.105	1.050–1.162	< 0.001
CC score (0)	.313	0.138–0.710	0.005	.458	0.708–1.762	0.347
Anastomosis	1.451	0.597–3.527	0.411			
Peritoneal Carcinomatosis, AJCC grading	1.291	0.560–2.975	0.549			

HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiology; CEA, carcinoembryonic antigen; CA-125, carbohydrate antigen 125; PCI, peritoneal carcinomatosis index; CC, completeness of cytoreduction; AJCC, American Joint Commission on Cancer

[a]Results are considered statistically significant at $p < 0.05$

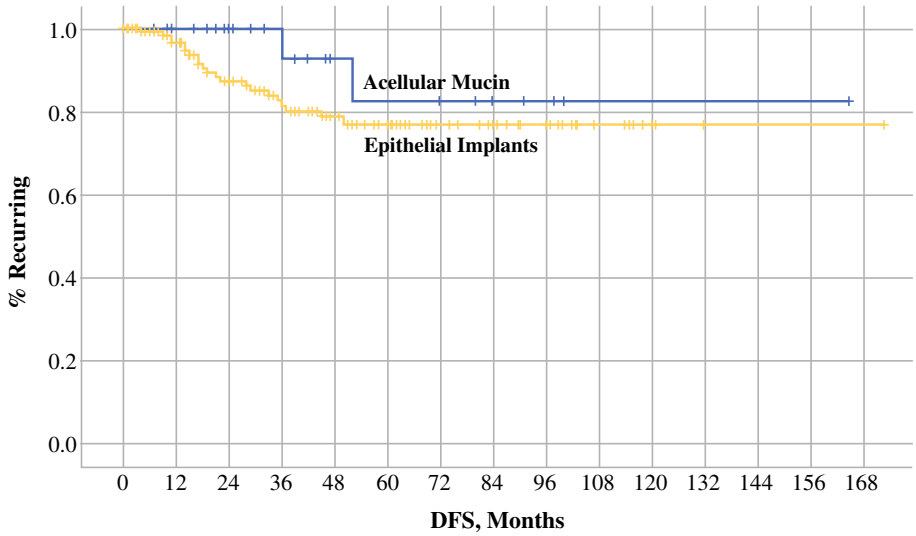

FIG. 3 Kaplan Meier curves comparing disease free survival following CRS/HIPEC in patients with acellular mucin implants and epithelial implants (G1/2/3)

associated with earlier recurrence, whereas CC0 cytoreduction and lower levels of CEA and CA-125 predicted lower likelihood of recurrence in the univariate analysis.

The classification of mucinous neoplasms and the resulting PMP are controversial. Multiple recently developed staging systems exist, but none of these have been uniformly adopted across institutions. Using an international modified Delphi consensus process, a classification for both primary appendiceal neoplasms and PMP was proposed in 2016 by the Peritoneal Surface Oncology Group International (PSOGI) expert panel.[6,18]

The PSOGI has defined LAMNs as tumors with low-grade cytology lacking overt infiltrative epithelium, confined by the muscularis propria, and including any of the following features: loss of muscularis mucosae, fibrosis of submucosa, undulating or flattened epithelial growth, "pushing invasion," dissection of acellular mucin in the wall, or mucin and/or neoplastic cells outside the appendix.[6] In the AJCC classification, these tumors can be categorized as well-differentiated (G1) and are mostly included in the in situ T category, or alternatively as T3, T4a, and T4b when mucin is found beyond the muscularis propria.[19]

The lack of a standardized, widely adopted classification system for appendiceal neoplasms reflects negatively on preoperative assessment, perioperative treatment (e.g., neoadjuvant treatment inappropriately administered), and ultimately, oncologic outcomes. Overinterpretation of results was reported in a previous study by Valasek et al.[20] which found a discordance rate of 28.3% in a comparison of reports from outside institutions at which the appendiceal primary was resected and internal pathology was reviewed. This phenomenon is likely reflected in our series as well, in which 11 patients were administered

chemotherapy preoperatively. Albeit both of our institutions routinely use the AJCC classification, conference calls, and discussion among surgeons and pathologists involved in the study in order to include patients in a uniform manner and avoid overinterpretation. This led to a thorough review of pathologic reports and tissues slides, and any case presenting higher-grade features or evidence of epithelial invasion of the primary tumor was excluded from the analysis.

Of all the patients initially categorized as low-grade (G1) appendiceal neoplasms, only 68% were confirmed LAMNs after pathologic review, mostly due to exclusion of well-differentiated MACAs. The latter tumors behave differently from LAMNs, recurring in 56% of cases after CRS-HIPEC according to recently published data.[21] We believe our effort to achieve a homogeneous population of patients represents a major strength of this study.

Limited literature exists regarding the oncologic outcomes for patients with LAMN-PMP undergoing CRS-HIPEC, likely because most patients undergoing this procedure at high-volume centers had their primary tumor removed externally. For example, the largest series on CRS-HIPEC performed for PMP of appendiceal neoplasms did not report data on the histology of the primary tumor.[13] Therefore, only limited data were available for comparison with our recurrence rates after CC0/1 CRS-HIPEC.

In their study, Reghunathan et al.[21] analyzed and discussed histologic predictors of progression after CRS-HIPEC for PMP secondary to appendiceal neoplasms. Review of the appendiceal primary according to the PSOGI criteria resulted in most patients presenting with LAMN pathology (44%, 33/75). The most frequent peritoneal histology among LAMN primaries was low-grade mucinous carcinomatosis peritonei (66.7%) followed by acellular mucin (21.2%). Among the 33 patients with LAMNs, 11 had recurrence (33.3%), more than we found in our study. Likely, a larger study population and exclusion of patients who underwent incomplete cytoreduction may account for this difference in progression rates. All recurrences happened within 5 years, and the median PFS was not reached. In their series, PCI score, CC score, and CEA levels were significant predictors of progression in the univariate analysis. Except for higher progression rates, their results are close to our findings in terms of Cox regression analysis and timing of recurrence. Finally, the authors also noted that recurrence may be better predicted by peritoneal histology than by primary histology. This also has been demonstrated by a previous study reporting worse outcomes when comparing patients with and without epithelial cells in cytoreductive specimens.[22]

In our study population, only two patients with acellular mucin had recurrence after CRS-HIPEC, and although there is a trend toward longer DFS for patients with acellular implants versus patients with epithelial implants, we failed to detect a significant difference. Our findings confirm the biologic complexity of LAMN-PMP, in which the histology of both primary and metastatic tumor cells interact and have an impact on oncologic outcomes in a heterogeneous and often unpredictable fashion.

Some studies on surveillance after resection of non-metastatic primary tumors have reported extremely limited data on recurrences after CRS-HIPEC for PMP secondary to LAMNs. Foster et al.[23] reported the outcomes for 22 patients with a diagnosis of LAMN according to PSOGI criteria, showing that five patients from their series experienced PMP. All four patients treated with CRS-HIPEC were disease-free during a median follow-up period of 50 months. An additional patient who received CRS alone experienced recurrence after 24 months, underwent a second CRS, and was disease-free at the follow-up assessment.

In another paper on surveillance strategies after resection of LAMN primaries, during a median follow-up period of 58 months, 2 (5.5%) of 36 patients had recurrence peritoneally and were offered CRS-HIPEC.[24] Regarding stages 2 and 3 colorectal cancer, the NCCN recommends a postoperative surveillance period of 5 years[25] despite the fact that about 5% of the patients may experience recurrence beyond that time.[26] A cutoff of 5 years also has been recommended for stage 4 CRC.

In cases of non-metastatic appendiceal tumors, the development of PMP is reported to occur within 2 years, with only isolated cases of long latency.[5,27] Similarly, in a study of patients who underwent resection of appendiceal neoplasms from a nationwide database, Smeenk et al.[5] recommended a minimal follow-up period of 5 years for detection of PMP. In our population of patients who underwent CRS-HIPEC for LAMN-PMP and experienced recurrence, the majority of cases were detected within 3 years as well, with only 17% of the patients experiencing recurrence later. Because no recurrences were detected after 5 years, we believe that appropriate surveillance should include tumor markers (both CEA and CA-125) and appropriate imaging methods (CT or, alternatively, MR) at least every 6 months during the first 3 years, with annual surveillance thereafter up to 5 years. Because surveillance after 5 years may have limited impact, closer or longer surveillance may be considered for patients deemed at high risk for recurrence (e.g., high PCI or CC scores).

Our study had several limitations. Our limited follow-up period of 45 months was a major limitation. However, 59 patients (38%) were followed up longer than 5-years and did experience recurrence, supporting our conclusions. Due to the retrospective nature of this study, data on perioperative levels of CA 19-9 were inconsistent, and this marker was not included in the analysis. Finally, the reason why

some patients received perioperative treatment was often unclear because the treatment frequently was administered at outside institutions.

CONCLUSION

For patients with LAMN-PMP who underwent CRS-HIPEC, most recurrences were identified within 3 years after the procedure, and none were identified after 5 years. Our findings support intensive surveillance with tumor markers and imaging methods during the first 3 years, and annual surveillance thereafter, with follow-up evaluation after 5 years yielding limited benefit.

DISCLOSURE There are no conflicts of interest.

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