

Strategies for Preventing Pseudomyxoma Peritonei After Resection of a Mucinous Neoplasm of the Appendix

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Abstract. *Background/Aim:* Considering the suspected link between mucinous neoplasm (MN) and pseudomyxoma peritonei (PMP), one option could be to propose prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) to selected patients in order to prevent the occurrence of PMP. *The aim of this study was to identify risk factors for developing PMP after curative surgery for a MN of the appendix. Patients and Methods:* All consecutive patients referred to our single tertiary care cancer center between September 1992 and March 2014 for MN of the appendix, initially without PMP, were retrospectively studied. Patients who had received prophylactic intraperitoneal treatment were excluded from the analysis. *Results:* Twenty-five patients with a median age of 51 (range=25-74) years were identified. At the initial appendectomy, 19 (76%) patients had a perforated MN. Nine of these patients (40%) exhibited disseminated-free acellular intraperitoneal mucin without PMP. Six (24%) patients had an unperforated MN without free intraperitoneal mucin. After a median follow-up of 50 months, 12 (52%) patients had developed PMP after a median time of 61 (range=13-121) months. Complete cytoreductive surgery plus HIPEC was possible in only seven (64%) out of these 12 patients. No factor reached statistical significance in predicting the occurrence of PMP but a trend was found in the case of perforated MN ($p=0.068$), associated with a 65% recurrence rate, compared to 17% without perforation. *Conclusion:* An appendicular MN cannot be considered a benign occurrence because PMP is common after resection and can occur up to 10 years after the initial appendectomy. Patients should be systematically followed up to detect PMP as early as possible. Patients with a perforated MN could be at higher risk of developing PMP.

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Pseudomyxoma peritonei (PMP) is a clinical syndrome related to the accumulation of mucin in the peritoneal cavity produced by a muco-secreting tumor (1). The estimated incidence of PMP is two cases per million per year (2). Since its first description by Spratt *et al.* in 1980, the combination of complete cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has become the treatment-of-choice for PMP, enabling a 15-year overall survival (OS) rate of 59% and a 5-year disease-free survival (DFS) rate of 55% in the latest series (3-5). The extent of the peritoneal disease is a major prognostic factor but it is also predictive of morbidity and mortality (5-7). The muco-secreting tumor at the origin of PMP is located in the appendix in more than 95% of cases (8). Appendiceal mucinous neoplasms (MN) are a group of epithelial neoplasms secreting gelatinous material which cause cystic dilation of the appendix due to an accumulation of mucin. Earlier referred to as a mucocele of the appendix, appendiceal MN was first described by Rokitsky in 1842 (9). The 'historical' rate of MN discovered after appendectomy has been estimated between 0.1% and 0.6%, and was confirmed in the largest retrospective study based on 24,697 patients, with a 0.2% rate of unexpected MN after appendectomy (10-14). A link between MN of the appendix and PMP is suspected and consequently one option could be to propose prophylactic HIPEC to selected patients operated on for an MN to prevent the occurrence of PMP.

The aim of the present study was to identify risk factors for developing PMP after curative surgery for appendiceal MN.

Patients and Methods

All consecutive patients who had undergone an appendectomy for a histologically proven appendiceal MN without PMP and had subsequently been referred to our single tertiary care cancer center between September 1992 and March 2014 were retrospectively studied. Patients who had received prophylactic intraperitoneal treatment (either HIPEC or early postoperative intraperitoneal chemotherapy) were excluded from the analysis. Patients with cystic dilatations of the appendix resulting from a non-neoplastic obstructing condition, such as appendicolith, endometriosis, extrinsic compression or an inflammatory disease causing luminal retention, were excluded

from the analysis. Patients for whom no initial pathological report was available were also excluded from the analysis. The patient files were retrospectively reviewed for preoperative demographic data, the diagnostic circumstances of the MN, treatment variables including the type of surgery, and for long-term outcomes, including subsequent treatment of PMP when applicable.

Definitions. Mucinous neoplasm: MN is a tumor of the appendix characterized by neoplastic villous or flat adenomatous changes of the epithelium associated with distension of the appendix lumen with secreted mucin. MN were retrospectively classified according to the 2010 WHO classification which recognizes three distinct categories: mucinous adenoma, low-grade appendiceal mucinous neoplasm (LAMN) and appendiceal mucinous adenocarcinoma (15, 16). In the case of adenoma with mucin, dissecting the appendiceal wall or perforating it, the lesion was reclassified in LAMN. This retrospective classification avoided the use of confusing terms such as cystadenomas, mucinous cystadenocarcinomas and mucocele.

Perforated mucinous neoplasm: Perforation of a MN was defined as either microscopic or macroscopic communication between the lumen of the appendix containing the mucin and the peritoneal serosal lining. Full mural tumor invasion was not considered as a perforation.

PMP and free intraperitoneal mucin: PMP was defined as disseminated intraperitoneal tumor cells with/without invasive peritoneal implants associated with free intraperitoneal mucin. Free intraperitoneal mucin, defined as mucinous ascites without tumor cells, was considered as contamination of the peritoneal cavity without actual PMP (16). Patients with free intraperitoneal mucin were included in the study and patients with PMP excluded.

Long-term follow-up. No standard follow-up method was used. Recurrences were diagnosed either clinically or radiologically and confirmed during a multidisciplinary team meeting without systematic histology. When surgery was subsequently performed for PMP, the peritoneal extent of the disease was measured using the Peritoneal Cancer Index (PCI) (17).

Statistical analysis. The cutoff date for survival analyses was August 1, 2014, for the censored data analysis. Categorical variables were compared within groups using Fisher's exact test. The survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. OS was computed from the date of the diagnosis to the date of death or the last follow-up. Time to recurrence was computed from the date of the primary tumor resection to the date of a distant recurrence. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA. Data were expressed as means \pm the standard error of the mean (SEM), unless otherwise stated. A p-value of less than 0.05 was considered significant.

Results

Demographics and initial disease. Twenty-five patients with an MN without PMP who had not received prophylactic intraperitoneal treatment were identified over this 22-year period. Their median age was 51 (range=25-74) years; 64% were females and 36% were males. At the time of initial surgery, 19 (76%) patients had a perforated MN. Among them, nine (36%) patients had free mucin located exclusively next to

the appendix and 10 (40%) patients had disseminated free acellular intraperitoneal mucin without PMP. In three patients, the perforation was due to perioperative mishandling. Six (24%) patients had an unperforated MN without free intraperitoneal mucin. No patient had free intraperitoneal mucin without perforation of the MN, either macroscopic or microscopic. Twenty-two (88%) patients had undergone an appendectomy and three (12%), a right colectomy. Laparoscopic procedures had been performed in 19 (86%) cases. The pathological analysis revealed a mucinous adenocarcinoma in one patient (4%), LAMN in 18 (72%) patients and a mucinous adenoma in six (24%) patients. For the three patients who had undergone a right colectomy, no invaded lymph nodes had been found among the 81 lymph nodes analyzed.

Long-term results and diagnosis of PMP. Two patients with a perforated MN were excluded from the long-term analysis because follow-up information was not available. After a median follow-up of 50 months, 12 (52%) patients had developed a PMP after a median of 61 (range=13-121) months. No other sites of recurrence were reported during the follow-up. For patients without a scheduled follow-up, the diagnosis of PMP had been made based on symptoms after a median of 72 (range=25-121) months. This interval was statistically shorter in patients who had been followed-up regularly; in their case, the diagnosis had been made after a median of 14 (range=13-46) months. In the univariate analysis, no factor reached statistical significance for the prediction of PMP. Nevertheless, a trend was found in the case of perforated MN ($p=0.068$; hazard ratio=8.294; 95% confidence interval=0.6972-470.4172). This was associated with a 65% recurrence rate compared to 17% in those without perforation.

Treatment of PMP. Among the 12 patients who had subsequently developed a PMP, 11 had been scheduled for CRS and one had been treated with systemic chemotherapy alone because of transdiaphragmatic tumor invasion. The median PCI at the time of surgery was 28 (range=8-39). Only seven (64%) patients had undergone a complete macroscopic resection (*i.e.* CC0/1) associated with HIPEC with a combination of oxaliplatin at the dose of 300 mg/m² plus irinotecan at a dose of 200 mg/m², at a temperature of 43°C during 30 min, associated with the administration of intravenous 5-fluorouracil at the dose of 400 mg/m² and leucovorin at the dose of 20 mg/m². For the remaining four patients, complete CRS had not been achieved either because of the extent of the peritoneal disease or due to poor general status related to their symptomatic PMP; HIPEC had not been performed in these patients. One patient had died postoperatively after complete CRS plus HIPEC on postoperative day 15. His peritoneal disease was extensive, with a PCI score of 28, and he had been operated on for a perforated mucinous adenocarcinoma with disseminated free acellular intraperitoneal mucin 8 years earlier.

Discussion

This study demonstrates that PMP may occur after MN resection at up to 10 years after the initial appendiceal surgery. This study failed to identify a subset of patients at risk of developing a PMP but a trend was found in the case of perforated MN, associated with a PMP rate of 65%, compared to 17% in the absence of perforation.

Complete CRS plus HIPEC is the treatment of choice for PMP. In 2006, an international panel of experts held a consensus conference where they stated that although PMP of MN origin is minimally invasive and rarely causes hematogenous or lymphatic metastases, the likelihood of long-term survival is limited, with no prospect of cure unless CRS and perioperative intraperitoneal chemotherapy are performed. These experts recommended CRS plus HIPEC as the standard of treatment for PMP (18). In the largest study from 16 specialized teams comprising 2,050 patients with PMP treated with CRS plus HIPEC, the median OS was 196 months and median PFS was 98 months. The 5-, 10- and 15-year OS rates were 74%, 63% and 59%, respectively (5).

Treating early disease is more efficient and less dangerous. The extent of the peritoneal disease, measured with the PCI, is an independent factor predictive of postoperative morbidity and poor survival (5). Currently, many teams consider that the best strategy for obtaining better long-term results after treating PMP is to treat the peritoneal disease as early as possible; no treatment would simply signify waiting for a more advanced stage in a weaker patient (1). This notion was demonstrated for the first time by Chua *et al.*, who reported a 77% 5-year OS rate with upfront CRS combined with perioperative intraperitoneal chemotherapy for PMP compared to only 37% when CRS combined with perioperative intraperitoneal chemotherapy was delayed after initial watchful waiting (19). The authors strongly recommended early referral to centralized treatment Centers to improve outcomes (19). In our study, we established a direct link between MN of the appendix and PMP, therefore with a possibility of being treated at the earliest stage with the lowest possible morbidity. With growing experience in specialized teams, CRS plus HIPEC-related mortality for PMP is currently 2% and major morbidity is 24% (5). Even better results could probably be expected if patients were treated at a pre-PMP stage but with an unknown risk of over-treatment.

Follow-up of patients after surgery for MN. Knowing the link between MN and PMP, the next challenge is to define how to follow-up patients in order to detect PMP as early as possible, taking into consideration the balance between repeated expensive imaging and the low risk of recurrence. A recent study on expectant observation strongly insisted on the need for a systematic follow-up based on imaging rather than on

symptoms in order to avoid making the diagnosis at an advanced stage. These results are confirmed by our data as patients with a scheduled follow-up were diagnosed with a PMP 5 years earlier than those with a symptom-based diagnosis, and systematically at a lower PCI. Nevertheless, the authors failed to recommend a specific imaging technique (20). The most sensitive technique for detecting early peritoneal metastases is currently second-look surgery with complete peritoneal examination but even if laparoscopy can reduce the associated morbidity, the invasiveness of the procedure still makes it an inappropriate approach for non-selected patients (21). Currently, the best non-invasive technique for detecting peritoneal metastases at an early stage seems to be magnetic resonance with breath-hold diffusion-weighted imaging (DWI-MRI) which improves the sensitivity, the accuracy and the specificity of detecting and depicting peritoneal metastases (22-24). This imaging method is very suitable for PMP because of the pseudoliquid contrast of the mucin (23, 24). There is no consensus regarding the adequate follow-up schedule after resection of an MN. In our study, the longest disease-free interval before the diagnosis of PMP was 10 years after the initial appendectomy. Ruiz-Tovar *et al.* reported the diagnosis of PMP after 6 years (25). In a recent study, Zhi *et al.* confirmed the very slow evolution of this disease, with the need for a very long follow-up (20). We recommend a follow-up examination with an abdominal DWI-MRI every 2 years for at least 10 years. The value of tumor markers in this situation is very difficult to determine but in our study, the diagnosis of PMP was based on an elevated cancer antigen 19-9 level in one patient with a perforated MN. Our study also shows that the absence of perforation does not absolutely rule out the risk of PMP, as observed in one of our patients. This should definitively banish the old non-evidence-based belief that unless a low-grade appendiceal MN is perforated in the peritoneum, it may be considered as a benign lesion with no risk of recurrence (26).

Prophylactic HIPEC. Some patients with MN could run a higher risk of PMP for which expectant observation may not be the most appropriate strategy. Even if no factor reached statistical significance in the prediction of PMP, a perforated MN was associated with a 65% recurrence rate after 50 months of median follow-up. Because the best strategy for obtaining the best long-term results is to treat PMP as early as possible, a systematic second-look surgery associated with HIPEC could be discussed for this subset of patients. We unfortunately cannot estimate the risk of overtreatment and the potential benefit of this invasive strategy. An indirect justification could nevertheless be drawn from our experience with watchful waiting in patients with a perforated MN: 65% developed PMP, 58% were operated on, and 54% of them underwent complete CRS plus HIPEC. One patient died postoperatively. We think this event could have been prevented with earlier treatment.

Prevention of MN rupture. In three of our patients, the ruptured MN was due to perioperative mishandling. Some authors when faced with an MN discovered at laparoscopy recommend converting the procedure into open surgery to avoid rupture and conduct a thorough examination of the peritoneum (27-31). Some surgeons consider that the resection can be safely performed laparoscopically and use a plastic bag when removing the MN from the abdomen to avoid iatrogenic rupture (32-34). There is no comparative study in the literature and most studies are case reports with a short follow-up, that probably underestimate the recurrence rate. The decision to convert to open surgery in fact only depends on the surgeon's confidence in their ability to remove the MN without rupturing it. With growing expertise in laparoscopic surgery, systematic conversion could be interpreted as over-treatment with undue postoperative morbidity. If a conversion is decided, the type of incision must be carefully thought-out because if the lesion ruptures during surgery, tumor cell spillage in the scar tissue could lead to a recurrence, which must be amenable to subsequent further surgery. If an unperforated MN is discovered perioperatively, we recommend that the surgeon continue the laparoscopy if they feel confident that the outcome will be successful. If the surgeon chooses to convert the procedure to open surgery, we recommend using a median laparotomy.

The importance of the operative and pathological reports. Whatever the technique used to remove the MN, a very detailed description of the extent of the peritoneal disease is mandatory for decision making regarding the best therapeutic strategy. Unfortunately, this information is frequently lacking when patients are referred. The surgeon should meticulously describe in detail the presence of free mucinous intraperitoneal fluid, or PMP and their location in the peritoneal cavity in the operative report. We recall that the majority of MN are resected either by elective incision (Mc Burney incision) or by laparoscopy, and surgeons should be aware that neither of these procedures allow adequate exploration of the peritoneal cavity. Whenever possible, adequate histological samples of the appendix and of the macroscopic peritoneal tumor implants should be obtained because the second mandatory element for appropriate decision making is an adequate pathological report. This report should systematically mention the search for perforation of the MN, the histological grade and whether all peritoneal samples were analyzed perioperatively. The presence of tumor cells, either in invasive peritoneal implants or in the free intraperitoneal mucin, signifies the existence of PMP and requires HIPEC with or without CRS. As for other rare tumor types, the pathological analysis can be difficult and a systematic reanalysis by an expert pathologist would be a useful adjunct to decision making (35).

The major limitation of this study is the very small number of patients because they such patients are usually only referred to expert centers at the PMP stage. Nevertheless, the patients included in our study were treated homogenously by an experienced team and had a long follow-up. Further information could be gathered only with the creation of a prospectively collected national database but it would probably take decades before results would be available. Until we have further data, after a multidisciplinary consensus, at our tertiary care center we decided to systematically propose second-look surgery plus systematic HIPEC to all patients referred for a perforated MN.

Conclusion

An appendicular MN cannot be considered as a benign occurrence because PMP is a common after resection and can occur up to 10 years after the initial appendectomy. Patients should be systematically followed-up to detect PMP as early as possible. Patients with a perforated MN could be at higher risk of developing PMP.

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Conflicts of Interest

The Authors have none to declare.

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