Review Article

Pseudomyxoma peritonei originating from appendix tumors

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A B S T R A C T

Background: Appendix tumors represent about 1\% of all gastrointestinal neoplasia, in other words they are quite rare. However, there is a specific type of appendiceal neoplasms (mucinous adenocarcinoma) that spreads to the peritoneum and in almost 20\% of the cases, resulting in a disease called pseudomyxoma peritonei. Although, it is a very rare condition, it is nonetheless a very severe one and therefore it is crucial to know how to correctly diagnose and treat it.

Objective: This study provides updated data on how to diagnose, classify and treat pseudomyxoma peritonei that originates from appendix tumors.

Methods: A bibliographic research was performed on PubMed database, including articles published since 2000, as well as, cross-referencing with the initial research.

Discussion: In the past, patients diagnosed with pseudomyxoma peritonei would only undergo palliative measures, so their overall survival rate was greatly reduced. Over the years pseudomyxoma peritonei treatment has evolved and patients are now undergoing treatment which is a combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. This new therapy has allowed an increase of survival chances of up to 5 years in those patients with values between 53\% and 88\%, depending on the type of tumor.

Conclusion: Despite the great progress we have witnessed in recent years, which have led to a large increase in survival rates, more research needs to be done, on what to do when the disease is in an unresectable stage. Finding a less aggressive therapy than cytoreductive surgery + hyperthermic intraperitoneal chemotherapy will be an important step forward.

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Pseudomixoma peritoneal 
Diagnóstico do cancro 
Cirurgia citoreductiva 
Quimioterapia hipertérmica intraperitoneal

Pseudomixoma Peritoneal com origem em Tumores do Apêndice

RESUMO

Introdução: As neoplasias do apêndice são bastante raras, representando atualmente cerca de 1% de todas as neoplasias gastrointestinais. O adenocarcinoma mucinoso é um dos subtipos de neoplasia do apêndice e caracteriza-se por metastizar para o peritoneu, em 20% dos casos, facto que se manifesta sob a forma de uma doença designada por Pseudomixoma Peritoneal. Apesar de ser uma condição muito rara, a sua extrema gravidade justifica a importância de a saber diagnosticar e tratar corretamente.

Métodos: Foi realizada uma pesquisa bibliográfica na base de dados PubMed, incluindo artigos publicados desde 2000 bem como artigos de pesquisa cruzada com os iniciais.

Discussão: No passado, os doentes diagnosticados com Pseudomixoma Peritoneal eram apenas submetidos a medidas paliativas, pelo que a sua sobrevida era muito reduzida. Ao longo dos anos o tratamento do Pseudomixoma Peritoneal foi evoluindo sendo agora os doentes submetidos a uma combinação de cirurgia citoreductiva e quimioterapia hipertérmica intraperitoneal. Esta nova terapêutica tem permitido aumentar a sobrevida aos 5 anos destes pacientes para valores entre os 53% e os 88%, dependendo do tipo de tumor.

Conclusões: Apesar dos grandes avanços que se têm verificado, e que culminaram com um grande aumento das taxas de sobrevivência, devem ser feitos mais estudos que encontrem novas abordagens para quando o tumor já é diagnosticado num estado irresssecível, bem como terapêuticas menos invasivas.

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Materials and methods

On April 10th, 2017, a bibliographic research on PubMed was initiated, using the following keywords: “appendix tumors”, “pseudomixoma peritonei” and “treatment”. The connector AND was applied among them. Two hundred and ninety-two articles were found in this search.

In order to verify if the articles met the criteria so as to be included in this research, all of the titles and abstracts were reviewed. A chosen criteria for the usage or exclusion of certain articles was that all the articles which did not have a full text available were immediately excluded. Cross-referenced studies from the chosen articles were also selected and used. Inclusion criteria consisted of analyzing experimental articles or reviews on how to approach and treat pseudomixoma peritonei with origin in appendix tumors, published after 2000, and written in English or in Portuguese.

Publications about pseudomixoma peritonei with only an extra-appendiceal origin were excluded. Articles without a full text available, case reports and comments were also not included in this review.

Introduction

Appendiceal neoplasms are very rare. In fact, they account for only 1% of lower gastrointestinal tumors and are found in less than 2% of the appendices which are surgically removed. There are two main types of appendiceal tumors, epithelial and non-epithelial. The most common are the carcinoid tumors, which represent about 50% of all appendiceal neoplasms, followed by adenocarcinomas.1

Adenocarcinomas of the appendix usually appear between the 6th and 7th decade of life and seem to be more common in males. Moreover, their annual incidence is 0.2/10,000 and about 40% of them are of mucinous type.2 The mucinos adenocarcinomas of the appendix can appear from an adenomatous polyp or from a serrated adenoma, and is the type of appendiceal neoplasms that is most frequently presented with pseudomixoma peritonei. This type of tumor has a wide spectrum of presentations, ranging from apparently benign tumors with slow progression and adenocarcinomas to high grade tumors with poor survival rates.1

Furthermore, adenocarcinomas can spread in three ways: hematogenous, peritoneal and lymphatic, the latter of which occurs only in 2% of the cases.1,2

When the appendiceal adenocarcinomas spreads into the peritoneum, what usually occurs after the drilling of the mucinous tumor, is named pseudomixoma peritonei (PMP).3 PMP has an indolent yet lethal behavior, and that is the reason why its treatment should be radical. However, in the past, peritoneal dissemination was considered a systemic disease and experts would only recommend palliative measures. Therefore 5.2–12.6 months was its median survival time.4 Nowadays, the paradigm has changed, and PMP is now considered a locoregional disease.5

PMP is the term used to refer to the accumulation of mucin within the secondary peritoneal cavity and the spread of mucinous neoplasia.2 94% of the times PMP develops from a mucinous tumor of the appendix and the other times it is a result of mucinous neoplasias from other locations like the ovaries, gall bladder, stomach, colorectum, pancreas, fallopian tubes, urachus, lungs and breasts.1,2 It commonly appears around the seventies, about four times more in women than
Moreover, experts estimate that 20% of mucinous adenocarcinoma of the appendix evolve to PMP.\textsuperscript{5,7}

One of the most distinctive features of PMP is its peculiar dissemination phenomenon. It starts with the drilling of the wall of the appendix into the peritoneal space. Then, the mucus and the cells follow the same pathway as the peritoneal fluid is redistributed into the lymphatic absorption sites that exist in the peritoneal cavity. Thus, the tumor cells end up depositing it in the omentum, pelvis, paracolic gutters and liver capsule.\textsuperscript{5} Such passive movement may be explained by the lack of adhesive characteristics of the cells’ surface.\textsuperscript{3} Furthermore, due to gravity, it is placed by cells in the cul-de-sac, also known as pouch of Douglas, the right retro hepatic space, the left abdominal gutter and in the space, that is created by the Ligament of Treitz. The absence of tumor cells in the small bowel is due to the almost constant peristaltic movement of this segment.\textsuperscript{8}

PMP can develop throughout months or even years without causing any symptoms. As the tumoral mucinous cells spread through the peritoneum the intra-abdominal pressure increases. Thereby explaining why one of the most common symptoms of PMP is the increment of the abdominal perimeter. The second most frequent symptom at least in men is the appearance of a hernia in which repairing it leads to discovering mucous fluid, whereas in women an ovarian mass is usually found on the right side. PMP may also make itself visible as an appendicitis, customarily after the rupture of the appendix.\textsuperscript{5} Commonly, the death of the patient derives from intestinal failure caused by the increase of intra-abdominal pressure, fistula formation or infection.\textsuperscript{4}

In the treatment of PMP, a more radical approach is now being adopted. Nowadays, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are combined and established as a treatment for PMP. However, the outcomes rely very much on the patient’s condition, therefore it is essential to accurately classify the disease for best results.\textsuperscript{5}

The aim of this article is to provide new information regarding the approach, classification and treatment of PMP exclusively originated from appendix tumors.

## Classification

Correct classification of PMP is extremely important for the therapy’s success. However, there is still no consensus on this matter. Carr and colleagues used a consensus method (Delphi Process) in order to standardize the terminology used for the classification of this disease. So, when there is mucin without epithelial cells the term “Acellular mucin” should be used. In this case, we only use the term PMP when accompanied by clinical features. When PMP presents a low-grade histologic feature the most consensual term to use is “Low-grade mucinous carcinoma peritonei” or “Disseminated peritoneal adenomucinosis (DPAM)”\textsuperscript{4}. Moreover, when PMP is presented with a high-grade histologic feature the terms “High-grade mucinous carcinoma peritonei” or “Peritoneal mucinous carcinomatosis (PMCA)” should be used. Finally, when there are signet ring cells the disease should be referred to as a “High-grade mucinous carcinoma peritonei with signet ring cells” or “Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)”.\textsuperscript{4}

On the other hand, Davidson et al. and Shetty et al. classified PMP into three different degrees according to the absence or presence of characteristics that confer a worse prognosis for the disease, such as destructive invasion, high cellularity, signet ring cells, perineural invasion, among others.\textsuperscript{15,16} DPAM is the subtype with the best prognosis. On the contrary, when PMP is found with signet ring cells invading tissue the prognosis worsens dramatically.\textsuperscript{15}

Noguchi and colleagues made a research about the differences between DPAM and PMCA’s molecular profiles. First, a higher frequency of KRAS mutations (about 60%) was found compared to other tumors with origin in the colon and rectum (40%). Yet the frequency of mutations in the KRAS gene in DPAM and PMCA was very similar. It is thought that RAS-MAPK pathway activation may be an eventual therapeutic target for PMP. There were also mutations in GNAS as frequent in DPAM as in PMCA. This mutation activates the PKA, which is responsible for regulating the activity of MUC2 and MUC5A. Consequently, this fact helps to clarify the etiopathogenesis of PMP. On the other hand, some mutations were identified more frequently in PMCA, namely in the genes TP53, PIK3CA and AKT1. Thus, the mutation in TP53 can be used as a biomarker of PMCA, while the remaining mutations, which interfere with the regulation of some cellular processes, may

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## Diagnosis

When there is a suspicion of appendix tumor that presents itself as a mass or already with PMP, imaging tests such as colonoscopy and CT scan should be performed in order to confirm the diagnosis and predict the success of the treatment. If the tumor presents itself as an appendicitis these tests will be done after the surgery.\textsuperscript{1}

Currently a PET scan and a CT scan of the chest, abdomen and pelvis are performed to diagnose and characterize the disease, as well as, to define the treatment.\textsuperscript{10} Some studies suggest a higher MRI’s sensitivity to stage the tumor than with the CT scan.\textsuperscript{11} Dineen and colleagues created a simplified preoperative assessment score for patients with low-grade mucinous adenocarcinoma of the appendix which is only based on the CT scan results and marks the disease severity.\textsuperscript{12}

In addition to the clinical and imaging evaluation, the tumor markers’ values should also be settled, in this case the carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA 19-9). Carmignani and colleagues have proven that both CEA and CA 19-9 provide accurate and inexpensive clinical information at the time of the diagnosis and have a practical role in the disease’s management. Moreover, CEA and CA 19-9 should be used together, as if they were a single marker. When the tumor is completely removed by cytoreductive surgery, a significant decrease in both markers is observed, which is associated with an excellent prognosis.\textsuperscript{13}

PMP is characterized by the overexpression of mucins, namely MUC2, MUC5AC and MUC5B, which deposit and accumulate in the peritoneal cavity as they cannot be degraded. However, the most specific mucin of this pathology is MUC2, so that it may serve as a marker thereof.\textsuperscript{14}
become therapeutic targets. Noguchi et al. found a new mutation in PDGFRα (p.P553L). The carriers of this mutation may benefit from treatment with imatinib.18

**Treatment**

Formerly, PMP patients underwent surgeries to reduce the size of the tumor (debulking surgery). Nonetheless, the purpose of the surgery was only to reduce the symptoms caused by the tumor, so there was not a prospect of long-term survival. Debubbling surgeries became more and more frequent as the disease progressed, and its results were less and less effective.4 In 1994, according to a study by Gough and colleagues, a 5-year survival rate was off 53% and a 10-year survival rate was off 32%. Then systemic chemotherapy was introduced, but still the disease continued to have a high recurrence rate.19

Currently the gold-standard treatment for PMP consists of CRS and HIPEC.20 After preoperative examinations the Peritoneal Cancer Index (PCI) should be estimated. It divides the abdomen and the pelvis into nine regions and a rating of 0 to 3 is assigned depending on whether or not there is a disease and its dimensions.21 Thus, the first phase of the CRS consists in evaluating the intraoperative PCI, since imaging tests may not give such accurate results. It is imperative to exclude extraperitoneal disease, namely the presence of liver metastases and the extent of lymph node involvement, to decide whether or not to progress with surgery.22 Menassal et al. identified that the infiltration of adipose tissue from the hepatoduodenal ligament and diffused involvement of the mesentery or/and the small bowel’s serosa are predictive signs of non-resectable.23

Both for DPAM and PMCA the main goal is to perform a complete resection (CC-0) however, when this is not possible a complete cytoreduction (CC-1) should be attempted, leaving the nodules smaller than 0.25 cm.24 The CRS begins with an incision from the xyphoid process to the pubis (xyphopubic), in order to expose the entire territory that may be affected by the tumor. Then, adhesiolysis is performed and mucinous ascites is removed in order to find out the PCI.24,25 When planning the surgery the surgeon should take into account the area where there is a greater risk of not being able to perform a complete resection, since that should be the area where the surgery should begin. If the tumor resection is not possible in that area, then the procedure should end.26 During CRS five peritonectomies should be performed, namely to the greater omentectomy-splenectomy, to the left and right subphrenic peritoneectomy, to the lesser omentectomy-cholecystectomy and to the pelvic peritoneectomy. The surgeon must also inspect certain areas where the tumor may be hidden, since they are difficult to visualize during surgery. These sites are the recess between the segment I of the liver and the inferior vena cava; the recess adjacent to the duodenojejunal flexure; the retroploric area and in women, to the retrouterine recess.27 There is the option of having the surgery performed in two stages, if it exceeds 10–15 h, if the blood loss is excessive or if the HIPEC cannot be performed.25 Moreover, if there is a need to remove the bowel at least 1.5 m of the small bowel should be kept. If there is a need to also perform a total gastrectomy more than 1.5 m of the small bowel should be preserved.28

As soon as the CRS ends, but before performing anastomosis, HIPEC is delivered. One of the advantages of this method is to keep systemic levels of the chemotherapy drugs low while regional levels remain high. In addition, before entering the bloodstream the drugs pass through the liver, which may even be more useful in cases of liver metastasis.29 CRS should precede the chemotherapy procedure since the maximum penetration of the chemicals into the tissue is 3–5 mm. The administered drug must reach the entire serosal peritoneal surface.29,30 Administer the HIPEC shortly after the cytoreduction aims to get the drugs into the tissues before the formation of post-surgical adhesions.31

Hyperthermia induces the destruction of malignant cells by a number of reasons: firstly, it promotes the formation of heat-induced lysosomes which confer the greater destructive capacity of the cells. Furthermore, the microcirculation of the tumor decreases in flow or stays in stasis. Hence, the cells resort to the anaerobic mechanism to gain energy which culminates with the accumulation of lactic acid within the cell. The cell acidity promotes the lysosomes’s activity, due to the fact that these have already increased in number in response to hyperthermia.29

HIPEC can be administered through two different techniques: open abdomen technique, the most commonly used method was created by Sugarbaker, and the closed abdomen technique. The infusion may take up to 30-90 min and continuous monitoring is required in order to ensure that all structures are exposed to chemicals. A pump pushes the fluid in the abdomen and then it is removed by draining at a rate of 1 L per minute. The chemotherapeutic fluid is perfused at about 44 °C, so that the intraperitoneal fluid is maintained at about 42 °C. This heat dissipation is greater when using the open abdomen technique, which constitutes one of its main disadvantages. On the other hand, in the closed abdomen technique the fluid is not equally distributed over all the anatomical structures, whereby the patient may be more likely to develop fistulas and bowel perforation. However, there still is not a study which shows that one of the techniques is the best.29 Nowadays the drugs used in HIPEC are Mytomycin C, which can be combined with 5-Flouracil, Oxaliplatin,4,29,30 Other drugs, such as cisplatin, may be used when there are special indications.33

Elias and colleagues made a study with 301 patients and 91% of these had PMP from an appendix tumor. Complete CRS was achieved in 73% of the patients. 85% were treated, then with HIPEC, while the rest were submitted to early postoperative intraperitoneal chemotherapy (EPIC). A 5-year survival rate is considered for all the patients, which accounts for 72.6%, but the truth is that there is a wide variation between the 5-year survival of patients with DPAM (85%) and PMCA (47%). In this study it was concluded that the extent of peritoneal invasion and the results of CRS are the factors with the greatest impact on this disease prognosis. Moreover, and although the authors suggested the possible existence of bias (EPIC was mostly used in the initial phase of the study), HIPEC appeared to be more effective than EPIC.34

Marcotte et al. also found (although their study had fewer patients) that 5-year survival rates were statistically different
for patients with DPAM and PMCA.\textsuperscript{35} In the study carried out by Austin and colleagues the patients’ lower survival rates (both for mean and 5-year survival rates) may be related to the fact that 38.7\% of all patients have previously undergone chemotherapy treatments. According to them, patients with a high-grade disease, lymph node involvement or already submitted to chemotherapy have a higher risk of death than those who do not have a high-grade disease, lymph node involvement or that have not been submitted to chemotherapy, respectively. It is also important to note that 61.3\% of the patients participating in this study had K-RAS’ mutation.\textsuperscript{36}

González-Moreno and Sugarbaker have shown in one of the studies which had the most patients to date, that survival in PMP is dependent (in a statistically significant way) of the presence of distant metastases. The presence of a second neoplasm, the peritoneal lesion morphology and the completeness of CRS are also factors that determine the chances of survival. This study has also shown that CRS with the right hemicolecctomy, a procedure used at the time, did not have a higher survival rate compared with a less aggressive approach (CRS with appendectomy, currently used).\textsuperscript{37} Thus, according to the authors, right hemicolecctomy should only be performed if necessary to achieve a complete cytoreduction, if the appendiceal or ileocolic lymph nodes are involved or if the tumor is histologically non-mucinous.\textsuperscript{37}

Jarvinen et al. compared the results of the previously used treatment (debulking surgery) with those used today (CRS + HIPEC). The 5-year survival rate was quite similar for both groups (67\% for the debulking group vs. 69\% for the HIPEC group) which led the authors to hypothesize that although this new approach does not increase dramatically short-term survival, its benefits should be more apparent over time, due to the slow evolution of the disease.\textsuperscript{38} Also Andrésson et al. observed the differences in outcomes between debulking surgery and CRS + HIPEC and concluded that although the latter is associated with greater morbidity it seems to be more efficient. Moreover, they believe that debulking surgery may be an option when the therapeutic goal is palliative, which is corroborated by Dayal and colleagues.\textsuperscript{39,40}

A retrospective multi-institutional study was carried out in 2012 that allowed data to be collected from 2298 patients with PMP from appendix tumors. A portion of this data had already been included in some previously published studies, so this study allows us to have an overview of the data that was released until 2012. Chua and colleagues concluded that advanced age, major post-operative complications, debulking surgery, previous chemotherapy treatments and the histological PMP’s subtype PMCA are independent predictors of poor outcomes. When the patient has DPAM the time between the diagnosis and CRS is also an important prognostic factor. The low morbidity observed in this study compared to the others was attributed to the surgeons’ experience.\textsuperscript{41} Although in this study the centers’ experience does not appear to interfere with the outcomes, there are studies where this does not occur.\textsuperscript{34,41}

Studies have been made in order to find out the learning curve (LC) of the procedures necessary for the PMP treatment and how many surgeries are necessary for the surgeon to make in order to have a better outcome. Kasamura and colleagues used a statistical tool (SPRT) that monitors the performance and safety of medical interventions. At their institution, they found out that approximately 140 CRS + HIPEC were needed to maximize the outcomes, but that this number could be minor, if more experienced surgeons taught the younger surgeons.\textsuperscript{42} More recently Polanco et al. published a study about their institution’s LC. They concluded that approximately 180 and 90 procedures were necessary to improve operative and oncologic outcomes, respectively.\textsuperscript{43} There are other published studies about this matter, however, not all of them note the existing bias caused by the other variables that may interfere with the outcomes.

A recent study by Ansari and colleagues has revealed not only lower morbidity, but also a better 5-year to 10-year survival rate in comparison to other studies. These results are attributed to the center’s experience and to the fact that the proportion of cases with resectable tumors is increasing. In this study the elevation of the tumor markers was found to be related to survival rates. In addition, older patients, patients with higher tumor markers or with PMCA are more likely to recur. Also included in this group are patients, who have to undergo distal gastrectomy and those, who require significant blood transfusions.\textsuperscript{44}

In case of recurrence Yan and colleagues showed that the patient should be re-operated and submitted to HIPEC again, since patients who repeat these procedures present greater survival rates than those who do not.\textsuperscript{45} Despite this, it is important to remember that recurrence of the disease is a poor prognosis factor. According to Lord et al. who conducted a study with 512 patients, approximately 1 in 4 patients developed recurrence of the disease after treatment with CRS + HIPEC.\textsuperscript{46}

In view of the excellent outcomes of CRS + HIPEC therapy, which shows a 5-year survival average between 60\% and 80\%, their morbidity and mortality rates are considered acceptable,\textsuperscript{47} although experts have been working on reducing these values.

However, and as noted above, not all patients can undergo surgery (CRS), as the disease may have already been unresectable. Although, there is still no great evidence about this matter, Pietrantonio and colleagues have studied the activity of chemotherapy with FOLFOX-4 (the name given to the combination of 5-Fluoracil and Oxaliplatin) in patients that are not surgical candidates. They have obtained a 20\% response rate and a 65\% disease control rate with a median overall survival of 26.2 months, so they have concluded that this regimen (FOLFOX-4) is active and promising and that more studies should be done, in order to establish a therapy for the unresectable disease.\textsuperscript{38} It is important to add that its toxicity is mostly reflected at hematological level, mostly as neutropenia.\textsuperscript{48}

Shortly afterwards emerged the hypothesis of joining biologic agents with chemotherapy in these patients’ treatment. Choe et al. submitted 65 patients to chemotherapy without a biologic agent and 65 with a biologic agent and concluded that the addition of an anti-VEGF (Bevacizumab) may be considered once they have reported, what seems to be an increase in overall survival and progression-free survival in patients submitted to that novel approach.\textsuperscript{49}
A group of experts have been working on the possibility of developing a less invasive treatment based on mucus lysis. Although, this hypothesis is still in initial testing, the in vitro results were quite encouraging. The idea of this treatment is to solubilize the mucinous mass lying in the abdominal cavity and remove it through a less invasive method, like a catheter, that would later be used to administer the chemotherapeutic agents. First, samples of the mucinous mass from 36 patients were collected and analyzed. Then, they were classified according to their hardness: soft, semi-hard and hard. It was found that soft mucins were more associated with DPAM than the remainder. Pillai and colleagues tried to solubilize the samples with a mixture by combining Bromelain and N-acetyl cysteine. In vitro, all samples with the soft variety of the mucins solubilized in total. The other samples only partially solubilized.50,51

**Conclusion**

PMP was for many years considered to be a terminal illness and therefore patients were only subjected to palliative measures. However, the paradigm has changed for the better.

First of all, it has become easier to diagnose and stage the disease thanks to the advances in imaging techniques. Moreover, the role of tumor markers (CEA and CA 19-9) in the diagnosis and surveillance of disease recurrence has become visible in several studies.

With regard to the disease's classification and nomenclature the controversy persists. It is important to note that its histological presentation does not only influence the treatment performed, but is also a predictive factor of its success, so it would be important to clarify this matter.

Moreover, regarding PMP's treatment various characteristics of the disease and the patient have already been identified as a predictor of its success. Thus, the patient's advanced age, previous chemotherapy, high-grade disease, failure to achieve complete CRS and the development of major post-operative complications are factors that predict therapeutic failure. Nowadays, the gold-standard treatment is CRS plus HIPEC which has significantly increased the patients' overall survival, but has high morbidity. Concerning the drugs used in HIPEC there were no differences in the outcomes, so there is not a standard formula for it. Formerly 5-Fluouracil was more used, but now the centers are using Mytomycin C or Oxaliplatin more often.

There still is not great evidence on what to use when the disease is not resectable, however the use of chemotherapy in this case may be beneficial and is now advocated by some experts. In addition, when the surgical approach is only for palliative purposes debulking surgery may be used, which were previously used as first-line treatment for PMP.

Despite the excellent progress that has been made in this area, we believe that more research should be done on what to do when the disease is unresectable. Finding a less aggressive therapy than CRS + HIPEC would also be an important step forward.

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