# Comprehensive treatment algorithms of the Swiss Peritoneal Cancer Group for peritoneal cancer of gastrointestinal origin

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**Keywords** Peritoneal carcinomatosis, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, HIPEC, gastrointestinal cancer, pressurized intraperitoneal chemotherapy, PIPAC

Manuscript: 4’430; abstract 264 words

## Summary

### Objective

Peritoneal cancer (PC) is a dooming finding, yet in selected patients, long-term survival is possible. Complete cytoreductive surgery (CRS), mostly together with modern combination chemotherapy, is essential to achieve cure. Hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC) are increasingly added to the multimodal treatment. The present treatment algorithms offer guidance for interdisciplinary care of patients with PC of gastrointestinal origin.

### Methods

The Swiss Peritoneal Cancer Group (SPCG) is an interdisciplinary working group of clinicians with an interest and expertise in the treatment of patients with PC. The Board of the SPCG includes medical and surgical oncologists and it is representative of the Swiss practice in the care of PC. It has formalized the present comprehensive treatment algorithms that are endorsed by virtually every Swiss clinician routinely involved in the multimodal care of patients with PC of gastrointestinal origin.

### Results

Comprehensive treatment algorithms for patients with PC from pseudomyxoma peritonei, peritoneal mesothelioma, gastric cancer, and colorectal cancer were written. They include straight surgical resection, multimodal neoadjuvant treatment, and referral to palliative care. The requirement, indication for, and results of CRS HIPEC and PIPAC in light of the current literature were discussed. Institutional volume and clinical expertise to achieve best outcomes were underlined, while inclusion of patients considered for CRS HIPEC and PIPAC in the nationwide SPCG clinical registry is strongly advised. The present recommendation are in line with current international guidelines and provides the first comprehensive treatment proposal for patients with PC including intraperitoneal chemotherapy.

### Conclusion

The SPCG comprehensive treatment algorithms provide evidence-based guidance for contemporary multimodal care of patients with PC of gastrointestinal origin.

## Introduction

Peritoneal cancer (PC) comprises a heterogeneous group of primary peritoneal tumours and metastatic disease from various origin. Common characteristics are late diagnosis, a limited response to systemic therapy, and hence a dismal prognosis (1, 2). New treatment modalities and multimodal strategies have improved prognosis considerably over the last decade and cure has become possible for selected patients. Complete cytoreductive surgery (CRS) with or without heated intraperitoneal chemotherapy (HIPEC) provides best outcomes for most entities but entails risks for postoperative complications and a long recovery period (3-6). While the intent of CRS is to remove all visible disease, intraperitoneal (ip) chemotherapy addresses microscopic residual disease, so as the maximize benefit of an extensive surgical resection. PC occurs frequently in colorectal and gastric cancers. Indeed, up to 25% of relapsing colorectal cancer patients develop metastatic disease restricted to the peritoneum, while around 8% of patients present with isolated PC at primary resection (7-9). In gastric cancer, isolated PC is found in 5-20% of patients who undergo surgical exploration for potentially curative resection (5). In infrequent cancers such as pseudomyxoma peritonei and peritoneal mesothelioma, CRS HIPEC is a standard of care, whenever a patient is fit for major surgery (4, 6, 10-16). Thus, in expert centres providing CRS HIPEC, cure rates above 80% are reported for pseudomyxoma peritonei (6, 10, 17-19).

Conversely, the debate is ongoing for colorectal and gastric cancers that represent the vast majority of patients affected by PC, who are largely treated by palliative care. Indeed, it is estimated that more than 90% of these patients only receive a systemic chemotherapy and a biological agent, whereas about 5% may be treated in a multimodal approach, including CRS HIPEC (20). This is unfortunate and unfair to our patients as the evidence in favor of cytoreductive surgery is strong, with a controversy limited to the additional value of HIPEC on top of a complete cytoreduction. Several international registries as well as phase 2 and phase 3 randomized controlled trials have underlined the benefit of a curative approach taking advantage of CRS HIPEC in PC of gastric and colorectal origin (21-27), with a single, although most recent, randomized controlled trial not concluding in favour of HIPEC in colorectal cancer (22). Beyond PC originating from gastrointestinal cancers, another large European multicentric randomized controlled trial demonstrated a remarkable overall survival benefit of one year in women with stage III ovarian cancer who underwent HIPEC in addition to CRS (28). Nonetheless, morbidity and resource utilization remain a concern when considering the true value of CRS HIPEC. Indeed, the nationwide Dutch CRS HIPEC prospective registry reported a mortality rate of 3% for a major morbidity of 34% and a length of stay of 16 days, which is similar to clinical outcomes of most major oncological

procedures. Importantly, numerous studies have demonstrated that CRS HIPEC, including the addition of HIPEC to CRS is worth the trouble in the patients' perspective with acceptable to high quality of life reported within few months after CRS HIPEC (29-34).

Recently, the surgical administration of intraperitoneal chemotherapy evolved further to include pressurized intraperitoneal aerosol chemotherapy (PIPAC) administered laparoscopically (35). Phase I and II studies have reported safety and efficacy of PIPAC for a variety of cancers (36-38), including low morbidity and preservation or improvement of quality of life (39-42). Moreover, iterative laparoscopy when performing PIPAC allows for repeat biopsy and objective assessment of tumor regression with a validated grading system to guide multimodal treatment (43). Hence, both CRS HIPEC and PIPAC now belong to the advanced armentarium of an efficient multimodal approach to peritoneal cancer.
Today, clinicians and tumor boards that advice treatment for patients with PC are confronted with a large and dynamic body of literature in a rapidly evolving, highly specialized clinical context. However, RCT or prospective comparative studies are rare for most clinical situations. The aim of the present comprehensive treatment algorithms by the Swiss Peritoneal Cancer Group (SPCG) is therefore to propose a standardized and pragmatic approach for multimodal treatment of PC of gastrointestinal origin

## Methods

The SPCG was founded in 2012 as a working group within the society of Swiss Visceral Surgeons. Since inception, a medical oncologist with an academic practice has been a member of its executive board and instrumental in securing a true interdisciplinary vision.

This practice consensus was elaborated as follows:

1. Thorough review of the literature and drafting of comprehensive treatment algorithms

Pertinent literature and current guidelines on the treatment of PC of gastrointestinal origin were scrutinized by the core team from Lausanne. The literature search focused on pseudomyxoma, mesothelioma, and PC of gastric and colorectal origin. The best available evidence was collated giving priority to RCTs, comparative prospective studies, large-scale retrospective studies and clinical registry data. Well-performed systematic reviews and meta-analysis were considered and searched for further references. Opinion statements, editorials, and expert opinion were not considered. Hence, 4 working algorithms with accompanying text were drafted.

2. Internal validation of the Lake of Geneva algorithms

The 4 treatment algorithms and their accompanying text were submitted for internal review to surgical and medical oncologists involved in the treatment of PC patients at the university hospitals of Lausanne and Geneva. Substantial modifications of the algorithms were discussed and implemented during a 4-month working period including 3 on-site meetings.

3. Final validation of the SPCG algorithms

The Lake of Geneva algorithms were presented to the board of the SPCG and thoroughly reviewed. The literature was cross-checked and updated, the algorithms were complemented by in-depth discussion and alignment to nationwide clinical practice in Swiss expert centres until a consensus was reached and unanimously endorsed by the board of the SPCG. Last, the present SPCG comprehensive treatment algorithms for PC of gastrointestinal origin were presented to the international audience and faculty of the SPCG symposium and validated during the general assembly of the SPCG on September 3, 2021.

The SPCG treatment algorithms are endorsed by all Swiss institutions routinely offering extensive cytoreductive surgery with multivisceral resection and HIPEC or PIPAC. They are intended as representative guidance for interdisciplinary tumorboards and clinicians taking care of patients with PC and not as formal guidelines. This practice consensus intends to

standardize multimodal care of patients with PC in Switzerland and promote nationwide inclusion in the prospective SPCG registry.

PC of gynecologic origin is not covered in the present treatment algorithms, yet a similar approach is currently underway by the respective working group of the SPCG.

## Results

### Pseudomyxoma peritonei

Pseudomyxoma peritonei is a rare cancer originating from a ruptured low grade mucinous neoplasia of the appendix (LAMN) with an estimated incidence of 2-4 / million (44-46). Rarely, it may also arise from the colon, the pancreas, or the ovary. It is often an incidental finding either upon radiologic examination or when performing an abdominal procedure, including appendectomy for suspected appendicitis. Left untreated, mucinous tumor cells accumulate by gravity at the sites of peritoneal fluid uptake, in the pelvis, along the rima coli and the greater and lesser omentum, and under the diaphragm. Deep infiltration of organs is not happening in the early course of the disease and the small bowel tends to be spared. Accumulation of mucus causes slowly progressive abdominal distension and organ dysfunction, including intestinal obstruction, cachexia, and ultimately death. Metastatic disease outside the abdomen is uncommon.

Surgical treatment is the only curative option, yet cure necessitates a complete cytoreduction. Cytoreduction typically includes a right colectomy, radical omentectomy, cholecystectomy, pelvic peritonectomy, bilateral parietal and diaphragmatic peritonectomy, and in women hysterectomy with salpingo-oophorectomy. Additional peritonectomy (liver capsule, mesentery), splenectomy and bowel resection are performed when infiltration is suspected. Complete cytoreduction is essential and it proceeds irrespective of the peritoneal cancer index, with the remaining small bowel length and preservation of vital organ function being the only technical limitation. Extensive surgery is challenging for the patient and the surgeon alike, frequently lasting 6 to 12 hours. Yet, when supplemented with HIPEC, long-term cure rate above 80% can be achieved (6, 10, 17-19, 47).

Neoadjuvant treatment is not generally recommended, owing to poor response rate. Adjuvant chemotherapy is, however, advisable in selected cases with high recurrence risk, e.g. incomplete resection, high grade pseudomyxoma, and increasing peritoneal cancer index (48). Measurement of the tumor markers CEA, CA 19-9, and CA 125 is often elevated and if so, it may prove useful in the follow-up.

About a quarter of the patients treated with optimal CRS HIPEC recur (48, 49). Of those who qualify for a repeat CRS HIPEC, long-term survival and morbidity is similar to the figures observed in primary CRS HIPEC patients (48-50). A large registry study totalizing 1’924 patients with pseudomyxoma peritonei treated until December 2017 compared patients treated with cytoreductive surgery alone to the conventional CRS HIPEC regimen: it showed

better overall survival and reasonable morbidity in patients treated with CRS HIPEC. Hence, the SPCG recommends CRS HIPEC for patients deemed fit for extensive surgery who present with a pseudomyxoma peritonei. The treatment algorithm proposed by the SPCG is illustrated in Figure 1. These recommendations are consistent with the current guidelines of the Peritoneal Surface Oncology Group International (PSOGI) and with most national guidelines (51).

Performing a laparoscopic staging allows to customize treatment according to the histology at hand (52): in presence of localized mucin without epithelial cells, simple laparoscopic follow-up without CRS HIPEC may be offered; conversely high-grade with signet-ring histology tumors may receive neoadjuvent systemic treatment, followed by CRS HIPEC .

Pressurized intraperitoneal aerosol chemotherapy (53, 54) is the latest addition to the interdisciplinary armentarium for the treatment of PC. PIPAC may also be considered in patients with pseudomyxoma peritonei, in particular in presence of unresectability (53). However, clinical experience in this context is still limited and no firm recommendation for PIPAC can be made at present.

**Peritoneal mesothelioma**

Malignant mesothelioma is affecting the serosal membranes of the pleura, peritoneum, pericardium or tunica vaginalis testis. The peritoneum is the second most frequent site following the pleura. It is a rare and highly lethal cancer with an incidence of about 0.7-3 per million people (55, 56). It has been linked to asbestos exposure, yet association is weaker than with pleural mesothelioma and no sex predominance exists. Patients present with abdominal distension/pain, weight loss/anorexia, while bowel obstruction is a manifestation of advanced disease. Diagnosis relies on percutaneous core needle biopsy or explorative laparoscopy with biopsy, rather than on cytological examination of serosal effusion or fine needle biopsy (12). It is adviseable to place all laparoscopic trocars along the midline, so as to allow for a straightforward resection at laparotomy and minimize port site metastasis. Expert pathology review is recommended to differentiate histological subtypes (epithelioid, sarcomatoid, or biphasic) and estimate clinical course. Measurement of the tumor marker CA 125 is recommended in addition to cross-sectional imaging and laparoscopy (12).

Two main subtypes show different behavior: the rarer well-differentiated papillary mesothelioma progresses slowly and metastasizes late, the more frequent diffuse malignant

peritoneal mesothelioma shows an aggressive behavior and responds poorly to chemotherapy (57). In patients of both subtypes fit for surgery, CRS HIPEC is a curative approach. Watchful waiting is an alternative approach in the frail patient with a well-differentiated papillary peritoneal mesothelioma with treatment escalation when progressive disease is detected. In presence of an epithelioid subtype, exploratory laparoscopy is advised to assess the true extent of disease, as no imaging modality is able to reliably assess resectability of PC of any origin. Some centers advise to take advantage of exploratory laparoscopy to initiate intraperitoneal chemotherapy with administration of a first PIPAC. Indeed, neoadjuvant PIPAC has been shown to be effective and of low morbidity, in particular when performed ahead of any major surgery or associated with neoadjuvant systemic chemotherapy (58, 59). Neoadjuvant therapy is required whenever initial evaluation reveals a high risk peritoneal mesothelioma (peritoneal cancer index > 17, Ki-67>9%, sarcomatoid histology, nodal positive status, incomplete resection CC score >1) and/or borderline resectability. Following a course of neoadjuvant systemic chemotherapy, re-evaluation is performed, including another explorative laparoscopy – which again may be supplemented by a PIPAC with the purpose to improve resectability (60). Once a patient is deemed resectable and fit for surgery, CRS HIPEC is offered.

In recurrent peritoneal mesothelioma following curative CRS HIPEC, another CRS HIPEC is rarely offered but palliative systemic chemotherapy, which again may be supplemented by palliative PIPAC. Similarly, non-resectable mesothelioma is treated by systemic chemotherapy and/or PIPAC (53, 57, 61, 62). The treatment algorithm proposed by the SPCG is illustrated in Figure 2. These recommendations are consistent with the 2021 published guidelines of the Peritoneal Surface Oncology Group International (12) and with the Chicago consensus on peritoneal surface malignancies (16).

**Gastric cancer**

In Western countries, gastric cancer often presents in symptomatic, late stages of disease and it is hence often incurable. It is, however, a common cancers ranking 13$^{th}$ with an incidence of 8.1 per 100’000 people in Europe (5.1/100’000 in Switzerland) and a cure rate of 37.5% (63).

The European Society of Medical Oncology recommends multimodal treatment for patients with stage ≥ IB resectable gastric and gastroesophageal junction cancers, including laparoscopic staging, neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy (64,

65). Tumor staging includes computer tomography (CT) and frequently endoscopic ultrasound, which may provide more accurate locoregional staging than CT, as well as biopsy. Laparoscopy completes tumor staging and provides direct visualization of peritoneal surfaces and local lymph nodes, as well as biopsy of any suspicious lesions. Often, PC is diagnosed during laparoscopic staging and/or peritoneal washing. Again, no diagnostic imaging can rule out PC so that laparoscopic staging is advised in most curative situations. Indeed, PC is detected in 15-53% of gastric cancers treated in curative intent (66, 67). Measurement of the tumor markers CA 19-9 and CEA have a prognostic value and can be used in the follow-up, while HER2 and microsatellite status can be sought after as a biomarker with therapeutic implications.

In presence of PC, whenever the patient is deemed resectable and presents a peritoneal cancer index not greater than 7, we advise for standard neoadjuvant chemotherapy which may be supplemented by 2 concomitant PIPAC to optimize resectability and cure rate (60). The additional benefit of performing neoadjuvant PIPAC is the dynamic laparoscopic evaluation, including histology of the tumor regression as a refined evaluation of the response and potential resectability of the primary cancer and PC. CRS and HIPEC, including D2 lymphadenectomy and peritonectomy then follow, completed by adjuvant chemotherapy as mentioned in European guidelines (64, 65). Prospective cohort series and randomized trials in Asian patients have shown a survival advantage for CRS HIPEC in gastric cancer patients presenting with PC (68, 69), whereas a large French multicentric study reported a median survival of 15 months and a 5-year overall survival of 23% (5). Conversely, when a patient is deemed unresectable or progresses during neoadjuvant chemotherapy, palliative systemic chemotherapy is offered, which can also be supplemented with PIPAC for optimal response and quality of life with conversion to resectability reported in few cases (37, 70). PIPAC is also a valuable option for control of ascites and other symptoms in patients refractory to systemic treatment (37, 39, 54, 61, 70).

The treatment algorithm proposed by the SPCG is illustrated in Figure 3. It is important to note that supplementing perioperative chemotherapy and surgery with CRS HIPEC allows for a 5-year overall survival of up to 27% in metastatic patients who would most likely have died earlier otherwise (5, 26, 27, 69, 71-74). Also, neoadjuvant PIPAC has been successfully assessed in many specialized centres (58, 59, 75) and it is currently investigated in a dedicated trial (76).

**Colorectal cancer**

Colorectal cancer is the third most common cancer with an incidence of 30.4 per 100'000 people in Europe (22.3/100'000 in Switzerland) and a cure rate of 59.5%% (63). At the time of diagnosis, up to 10% of patients with colorectal cancer have synchronous PM and more than half of the patients with recurrent disease will present with metachronous PM (77-79). Of the 3 histological subtypes of colorectal cancer (adenocarcinoma (85-90%), mucinous adenocarcinoma (10-15%), signet ring cell carcinoma (1%)), PM occur predominantly in mucinous and signet ring histologies (80), while adenocarcinoma preferably metastasize to the liver. When PM is left to conventional palliative chemotherapy, median overall survival does not exceed 16 months (81). Recent developments in the management of advanced colorectal cancer include total neoadjuvant chemotherapy, targeted therapies, and refinements in the indication and practice of CRS HIPEC. Yet, the fate of patients with PM from colorectal cancer is grim as no systemic chemotherapy including biologic agents can offer any prospect of cure (1, 81, 82), as opposed to complete cytoreductive surgery – possibly supplemented with intraperitoneal chemotherapy. A large body of literature, including multicentric prospective clinical registries, suggest a survival benefit when complete cytoreductive surgery is achieved and HIPEC is performed (4, 18, 24, 83-85), which has led to inclusion of CRS HIPEC in several national guidelines. As conventional imaging performs poorly for the early detection of PC, diagnostic laparoscopy may be offered in colorectal cancer patients at high recurrence risk within 6-12 months of the primary bowel resection or when the tumor marker CEA rises during follow-up with no obvious metastatic disease in radiological staging.

Two randomized controlled trials have assessed CRS HIPEC compared to CRS alone. The first and smaller trial (n=105) found a benefit for CRS HIPEC performed with Mitomycin C (21). The second, larger (n=265) and recent trial (PRODIGE-7) found no survival benefit for CRS HIPEC performed with oxaliplatin ip and 5-FU/leucovorin iv, but for a subgroup of patients with a peritoneal cancer index of 11-15 (22), consistent with prior finding suggesting that patients with a peritoneal cancer index up to 16 and/or limited small bowel involvement benefit most from CRS HIPEC (86-89). Much has been written on the strength and weakness of the PRODIGE-7 trial, which was first presented in June 2018 at the American Society of Clinical Oncology meeting and included contemporary systemic chemotherapy and targeted therapy. Complete cytoreduction was confirmed as the cornerstone of a curative approach in PC with an overall survival of 41.7 months for CRS HIPEC and of 41.2 months for CRS alone, and a recurrence-free survival of 13.1 vs 11.1 months, respectively. While survival and 30-day morbidity did not differ significantly, 60-day morbidity was significantly higher in the CRS HIPEC arm compared to CRS alone (24.1% vs 13.6%). Potential causes for the late

morbidity were heavily preoperative systemic treatment for 6 months and an aggressive course of ip/iv intraoperative chemotherapy with maximal dosage of ip oxaliplatin (460mg/$m^2$) and hyperthermia (43°C) that may ultimately have made CRS HIPEC patients more vulnerable to late medical complications (90). Indeed, routine perioperative administration of a 6-month course of oxaliplatin-based systemic chemotherapy is not common practice across countries, neither is the aggressive HIPEC regimen of PRODIGE-7. A Dutch randomized trial (CAIRO6) currently near completion may shed light soon on the benefit of perioperative systemic chemotherapy in patients who undergo CRS HIPEC.

Signet ring cell histology is an independent defavorable prognostic factor, regardless of the treatment approach. Data from the nationwide Dutch cancer registry have shown that the relative survival gain of CRS HIPEC is comparable for adenocarcinoma, mucinous adenocarcinoma and signet ring histology, while systemic therapy improved survival in all histological subtypes (91). Since patients with signet ring histology are often young, CRS HIPEC may thus be offered in highly selected patients with an absolute survival gain of up to 18 months, when compared to supportive care only (91). The Biological score of peritoneal metastasis (BIOSCOPE) was recently proposed to help patient assessment and selection. It takes into account peritoneal cancer index, nodal status, differentiation grading, and KRAS/BRAF mutations and allows categorization of patients into 4 survival groups with a prediction perfomance of 0.70 (development/validation area under the curve). It underlined that RAS/RAF mutations impair survival after CRS HIPEC, independently of the use of current targeted therapy (92). Tumor biology is a key element to factor in when choosing intensity and sequence of therapies.

As of Summer 2021, German (93), French (https://www.snfge.org/content/4-cancer-colorectal-metastatique ), British (94), American (95) and Canadian (96) practice guidelines stated that CRS HIPEC can be considered in experienced centers for selected patients. Selection amounts to fitness for major surgery and completeness of cytoreduction, both of which are mandatory. Also, the extension of PC of colorectal origin matters beyond mere resectability with a threshold peritoneal cancer index of 20 and below most commonly reported. Indeed, many expert centers today set the bar for CRS HIPEC at a peritoneal cancer index of 16 (86-89, 97, 98) to maximize cure, while avoiding large resection of small bowel to prevent a short bowel syndrome. Peritoneal recurrence after CRS HIPEC is common with a median time to recurrence of 33 months (99-101). Repeat CRS HIPEC can be offered in highly selected patients with similar results as for a primary procedure, once extraperitoneal metastases have been excluded (50, 102).

The treatment algorithm proposed by the SPCG is illustrated in Figure 4. Upfront diagnostic laparoscopy is recommended to assess the diagnosis of PC and resectability, thus overcoming the limitations and low reliability of PC imaging (103). It may include a first PIPAC to initiate treatment of PC (58). In presence of resectable PC, systemic chemotherapy is performed, followed by repeat staging and CRS HIPEC, pending objective response is confirmed. Additional systemic chemotherapy follows CRS HIPEC, whenever a full regimen has not been given prior to CRS HIPEC.

When, however, diagnostic laparoscopy reveals a borderline resectable situation, in particular a peritoneal cancer index greater than 15 in a patient otherwise fit for surgery (104), a maximal approach includes neoadjuvant systemic therapy combined with 2 further PIPAC. Indeed, published prospective series and clinical experience of Swiss centres speak for safety and effectiveness of joint systemic and PIPAC chemotherapy as a means to optimize response and select the patient with a chance for cure (58, 60). Repeat staging follows and final selection either for a curative approach including CRS HIPEC as of above or for a palliative approach is done.

Last, when a patient is deemed unresectable, palliative systemic chemotherapy may be enhanced by iterative PIPAC, including ascites control and relief. The development of extraperitoneal metastatic disease or tumor progression during neoadjuvant systemic chemotherapy are further grounds to opt for a palliative approach.

## 4. Discussion

Peritoneal carcinomatosis is affecting a significant number of patients with cancers of gastrointestinal origin. Treatment options are evolving rapidly and the prospect of a cure is realistic for selected patients who are willing and able to undergo a demanding multimodal treatment in specialized cancer centres. CRS HIPEC is a key element in this context and a complete cytoreduction is the cornerstone of every curative approach. The addition of intraperitoneal chemotherapy to complete cytoreduction is a logical step, as peritoneal relapses are frequent and driven by non visible/non resectable PC against which chemotherapy is best active when administered in situ. Repeat ip chemotherapy has been tested and deemed effective, yet it encompassed prolonged intraabdominal tubing (in- and effluent of chemotherapy) or repeat laparotomies, both of which prone to morbidity. Iterative PIPAC combines the ease of a minimally invasive approach, including repeat biopsy to objectively monitor tumor response, and the advantage of repeat ip administration of chemotherapy. More than 215 publications document the effectiveness of PIPAC in the treatment of PC and multiple clinical trials include PIPAC in the multimodal approach to PC (105). The combination of systemic chemotherapy and PIPAC is a further evolution in the treatment of PC (106) and an integral part of the present SPCG comprehensive treatment algorithms that builds up on multiple current oncologic guidelines. The present treatment algorithms reflect the forefront thinking and practice of specialized Swiss centres. They complement existing recommendations by including PIPAC in their standard of care, which is a reimbursed procedure in Switzerland since 2016 (104). They are intended as an outline for interdisciplinary discussion at tumorboards.

Providing contemporary treatment of advanced malignancies requires specialized knowledge of all involved caregivers, including medical and surgical oncologists, nutritional support and intensive care physicians. Best practice for perioperative management of patients with CRS HIPEC have been established (107). Patient care is at its best when clinicians monitor own outcomes prospectively and participate to translational and clinical research. Hence, the SPCG has initiated in 2021 a dedicated, nationwide prospective clinical registry for all patients considered for CRS HIPEC and/or PIPAC. The SPCG registry allows clinical research and facilitates participation to clinical trials. All Swiss institutions providing CRS HIPEC and PIPAC services are either board members of the SPCG or have confirmed their participation to the SPCG registry, so that a nationwide coverage is warranted. Beyond morbidity, mortality, length of hospital stay, recurrence-free and overall survival, the SPCG registry monitors the rate of complete cytoreduction, the multimodal treatment protocol followed, and the case load of each institution. The Dutch and the Brits have reported their

nationwide experience in standardization and specialization of care in dedicated centres for the treatment of peritoneal surface malignancies, while a minimal case load of 10 CRS HIPEC per surgeon/institution and year have been proposed as a threshold to maintain proficiency (6, 108, 109). In our experience, meeting such a threshold requires a catchment area of half a million, whereas a larger referral zone of one million and an institutional volume of 20 CRS HIPEC are advisable. Looking at three metrics from the nationwide Dutch experience (960 CRS HIPEC patients) allows for performance benchmarking: the reported rate of complete cytoreduction was 80% for a median hospital stay of 16 days and a mortality rate of 3%. In terms of survival, median overall survival was 33 months (95% CI 28-38 months) for colorectal cancer and 130 months (95% CI 98-162 months) for pseudomyxoma patients) (109, 110). These outcomes are realistic figures that have been met and exceeded by specialized Swiss centres (92, 111).

## Conclusion

The cornerstone of a curative approach in the treatment of PC is completeness of cytoreduction, which requires a high surgical expertise and routine in the care of multivisceral resections. The addition of ip chemotherapy supports completeness of cytoreduction by eliminating unseen tumor clusters prone to relapse. PIPAC is a much needed and validated addition to the treatment of PC: its inclusion to the present recommendations supports a quest for excellence by repeat delivering chemotherapy in situ and providing an objective response grading to guide multimodal treatment. The inclusion of all patients treated with CRS HIPEC and PIPAC in Switzerland in the prospective SPCG registry allows for performance benchmarking and supports clinical research. It is hoped that the present comprehensive treatment algorithms will provide guidance for interdisciplinary discussion at tumorboard and help for optimal and tailored care for patients with PC of gastrointestinal origin.

## Disclosure statement

There are no funding sources for this initiative. The authors declare that there are no conflicts of interest regarding the content of this paper.

## Acknowledgements

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## Figures

**Figure 1. Treatment algorithm for pseudomyxoma peritonei**

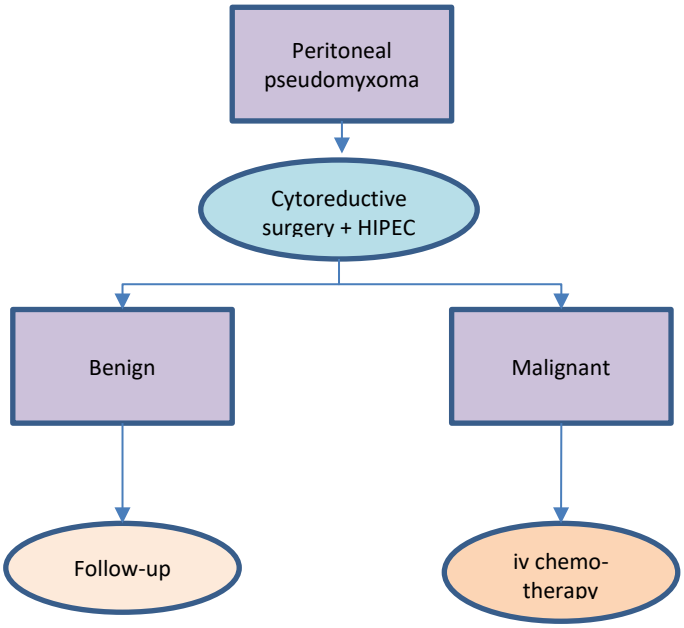

**Figure 2. Treatment algorithm for peritoneal mesothelioma**

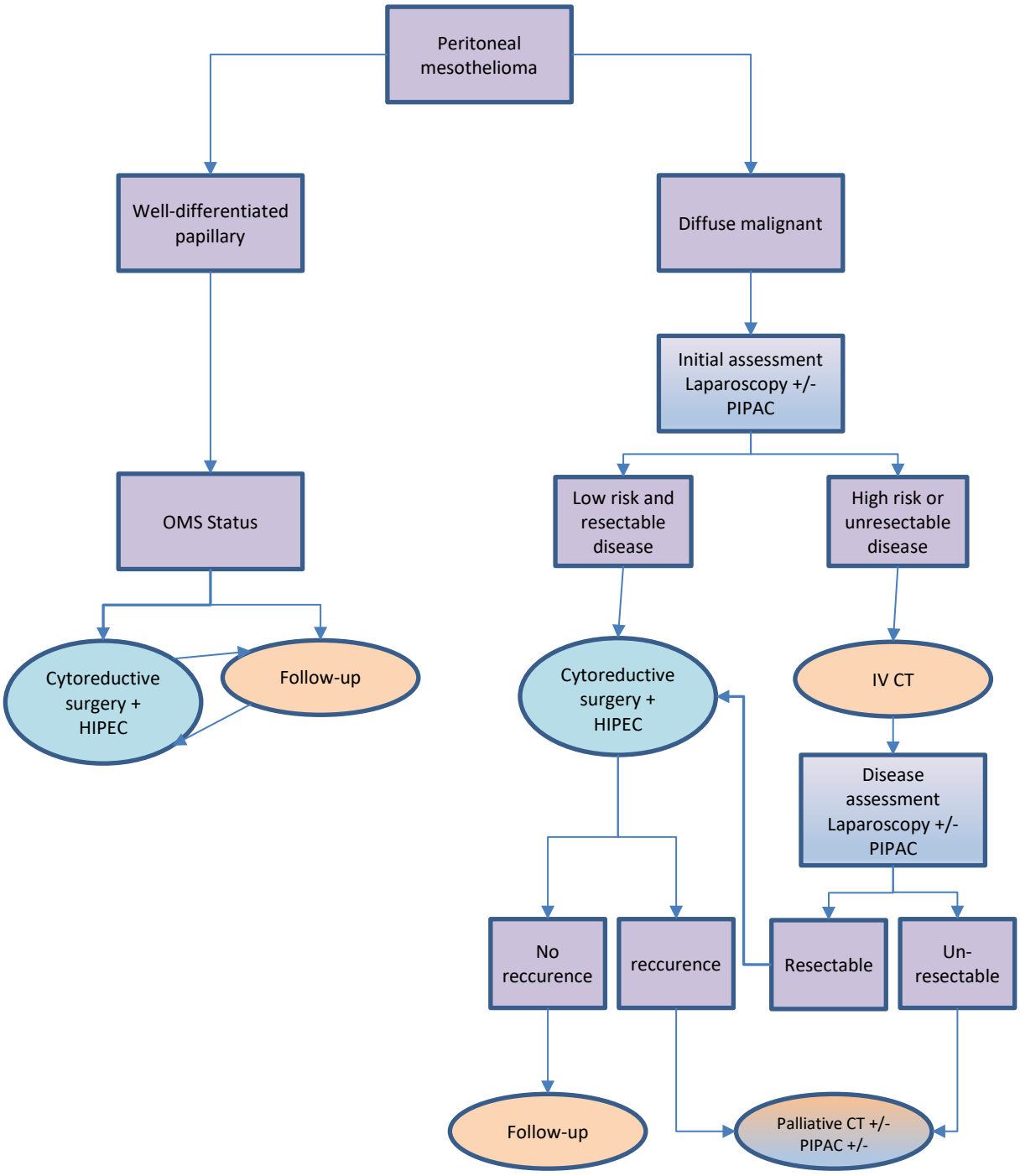

**Figure 3. Treatment algorithm for gastric cancer**

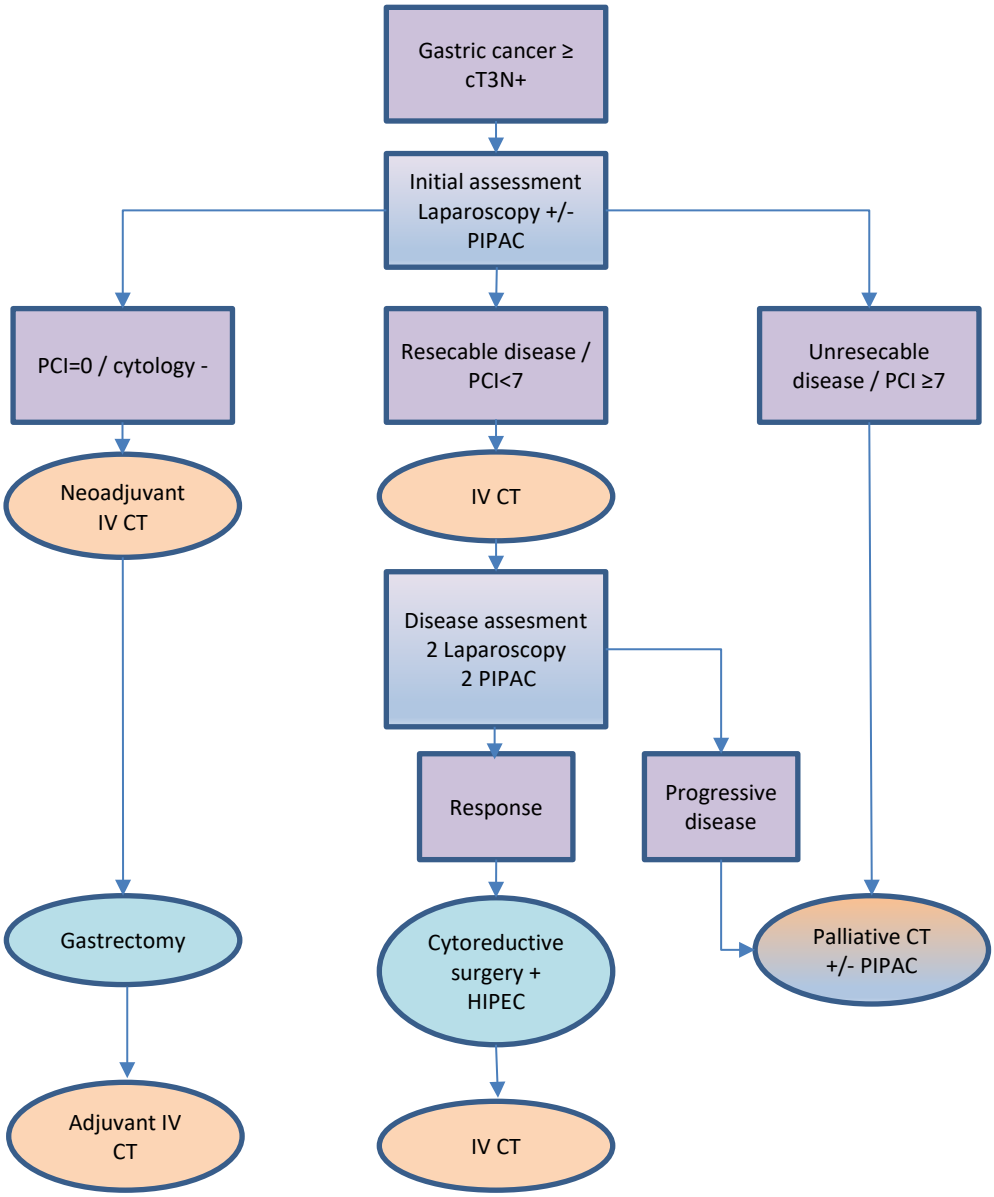

**Figure 4. Treatment algorithm for colorectal cancer**