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REVIEW ARTICLE

Proactive Management for Gastric, Colorectal and Appendiceal Malignancies: Preventing Peritoneal Metastases with Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Abstract An integrated treatment strategy using peritonectomy procedures plus hyperthermic intraperitoneal chemotherapy (HIPEC) is now a clinical standard of care in selected patients with peritoneal metastases and primary peritoneal tumors. This comprehensive approach can offer many patients, who hitherto had no hope of cure, a good quality of life and survival despite limited morbidity. The increasingly successful results and chance of interfering in the natural history of disease has prompted research to develop for some clinical conditions a therapeutic strategy designed to prevent malignant peritoneal dissemination before it becomes clinically evident and treat it microscopically (tertiary prevention). The main factor governing successful cytoreductive surgery and predicting outcome is the extent of peritoneal spread assessed with the peritoneal cancer index (PCI). In peritoneal metastases from colorectal and gastric cancer the PCI score acquires a specific role acting as the cut-off between patients who can undergo curative surgery or palliation. Long-term results show that the only group enjoying favorable results are patients with limited disease (a statistical minority). By applying to appropriately selected patients with primary malignancies a proactive management strategy including HIPEC we can treat patients with microscopic peritoneal dissemination and therefore at PCI 0. Among treated conditions pseudomyxoma peritonei enjoys the best results. But a major future advance comes from identifying among lesions at major risk of pseudomyxoma.

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Until the 1980s consensus considered endoperitoneal spread from an intraabdominal neoplasm and a primary tumor developing within the peritoneum conditions for which no therapy existed apart from palliative procedures able to guarantee only a few months of life [1]. Thanks to Paul Sugarbaker's pioneering efforts [2, 3], advances over the past 30 years now offer these patients a standardized integrated (multimodal therapy) combining cytoreductive surgery (CRS) (peritonectomy procedures) with hyperthermic intraperitoneal chemotherapy (HIPEC), an approach that has in selected cases allowed hitherto unhoped for survival [4–8]. Owing to these results the previously used term carcinomatosis, which implies a terminal condition, has been abandoned and cancer spread into the peritoneal space is now referred to as peritoneal metastases, a term that more intuitively implies a chance for cure similar to that for disease in other currently treatable localizations, such as hepatic and lung metastases [9]. At the 9th International Congress on Peritoneal Surface Malignancies the Peritoneal Surface Oncology Group International (PSOGI) guidelines recommend CRS combined with HIPEC as the preferred treatment for pseudomyxoma peritonei, for appendiceal neoplasia with peritoneal metastases and for selected patients with peritoneal mesothelioma or peritoneal metastases with moderate spread from colorectal cancer. Although this strategy may be helpful also in patients who have ovarian or advanced peritoneal metastases from gastric cancer, additional evidence is needed from ongoing collaborative studies at experienced treatment centers [10]. Collectively the literature to date suggests that the currently generalized use of proper selection criteria, advanced surgical techniques and lack of substantially new drugs in the pipeline argue, at least in the short term, against a further improvement

in the results for the aforementioned peritoneal dissemination or in the available therapeutic strategies. For this reason, research in this field seems now to move in two different directions. The first consists in using these integrated procedures to treat peritoneal spread from cancers hitherto left untreated (-breast, small bowel, and endometrial cancer) [11–13].

The second research direction, on which this review focuses, concerns developing proactive management for peritoneal metastases for specific primary malignancies (gastric, colorectal and appendiceal tumors). Consensus opinion among those who treat these diseases affirms that the good results obtained with integrated treatment (CRS + HIPEC) for peritoneal metastases from gastric and colorectal cancer correlate closely with the extent of peritoneal spread. The higher the peritoneal cancer index (PCI) [14] the less likely are we to achieve a good therapeutic outcome and acceptable long-term results. In these cases, the amount of peritoneal spread negatively influences the patient's outcome to such an extent that the PCI score seems to acquire a specific role as a cut-off value for selecting candidates for CRS plus HIPEC [7, 15–18]. Ample evidence shows that in these patients whether we can intervene to interrupt a frequently unfortunate clinical history depends exclusively on applying the same therapeutic procedures used to treat peritoneal spread but intervening at an earlier time-point, when peritoneal spread remains microscopic (tertiary prevention). The preventive approach originated from the concept originally expressed by Benjamin Franklin "An ounce of prevention is worth a pound of cure" and later underlined by Paul Sugarbaker in a well-known article that expresses the underlying therapeutic rationale right from the title "It's what the surgeon does not see that kills the patient" [19]. Analogously, though in another clinical setting, others adapted the concepts for "proactive management" to treat appendiceal neoplasms in preventing pseudomyxoma peritonei (PMP). PMP is a clinical condition caused by mucin accumulating within the peritoneum secondary to mucinous epithelial neoplasia. Mucinous neoplastic epithelium most often spreads to the peritoneum from a low-grade appendiceal mucinous neoplasm (LAMN) or mucinous adenocarcinoma [20]. In about 20 % of the patients with a mucinous tumor in the appendix PMP subsequently develops. Even though multimodal treatment (CRS + HIPEC) for peritoneal metastases obtains its best results in PMP, several investigators in recent years suggest that using proactive management on a presumably initial lesion such as an appendiceal mucinous neoplasm tumor could prevent PMP from developing [21, 22].

Proactive Management for Peritoneal Metastases from Gastric Cancer

An estimated 951,600 new gastric cancer cases and 723,100 deaths occurred in 2012 worldwide. Even though the incidence of gastric cancer has steadily declined in the more developed countries in Northern America and Europe since the mid-20th century, these data suggest that treatment results remain disappointing [23]. From 5 to 20 % of patients already have peritoneal metastases at diagnosis and metachronous peritoneal metastases onset during a 5-year follow-up in a percentage ranging from 29 to 38 % of the patients who underwent resection with curative intent [24–26]. Even though the past 10 years have witnessed advances in systemic chemotherapy and novel targeted drugs, no phase III study has yet proved that any therapeutic regimen has really benefitted disease progression [27]. As in other clinical conditions characterized by peritoneal metastases, our literature review identified several studies reporting the results obtained with CRS + HIPEC (usually always preceded by systemic or endoperitoneal neoadjuvant chemotherapy or both) in gastric cancer [6, 18, 28, 29] (Table 1). Among these, the study conducted by Yang et al. [6] – one of the few randomized control studies focusing on cytoreductive surgery for peritoneal metastases – has shown that in patients with peritoneal spread from gastric cancer CRS + HIPEC achieves better results than CRS alone.

In general, therefore, outcomes after integrated treatment for peritoneal metastases from gastric cancer, though better than those after systemic chemotherapy alone, remain exceedingly disappointing. Ample data confirm as the main independent factors indicating a worsening prognosis, a PCI >6 and the presence of metachronous peritoneal metastases [6, 18]. These observations clearly support a proactive approach to peritoneal metastases in advanced gastric cancer so as to treat microscopic endoperitoneal spread before it becomes clinically evident. In gastric carcinoma lengthy debate questions whether the various diagnostic techniques can reliably ascertain a positive endoperitoneal cytologic finding, what this means for prognosis and how it influences the therapeutic strategy [30, 31]. A systematic review published in recent years confirms that the various diagnostic techniques have intrinsic limitations related to reliability, to the cost-benefit ratio and last to the time needed to obtain a response able to influence therapeutic strategies [32]. The limitations of the perioperative cytological diagnosis have prompted many, almost exclusively Asian investigators, to conduct numerous studies addressing HIPEC understood as hyperthermic perioperative adjuvant chemotherapy done with curative intent in patients with no signs indicating peritoneal spread but with gastric carcinoma invading the serosa. Three meta-analyses conducted in recent years show that this strategy especially when combined with R0 resection can reduce the onset of peritoneal recurrence more efficiently than standard treatment and improve the outcome without increasing morbidity [33–35]. Although these results remain important even today, perioperative chemotherapy regimens still need standardizing especially given the systemic or endoperitoneal neoadjuvant

Table 1 Cytoreduction + HIPEC in gastric cancer with peritoneal metastases

Gastric cancer with peritoneal metastases					
Results of cytoreduction + HIPEC					
Author/year	n/pts	Morbidity %	Mortality %	Survival	
				Median (mo)	Survival rate %
Glehen 2010	159	20	6.5	9	23
Yang 2011	34	14.7	–	11	15
Canbay 2014*	152	23.6	3.9	15.8	10.7
Magge 2014	22	52	4.3	9.5	18

*Bidirectional neoadjuvant chemotherapy prior to surgery

chemotherapy regimens that patients often undergo. Besides, these studies typically conducted in Asian countries receive scarce support from those in Western countries where stomach cancer also owing to its low epidemiological incidence finds it hard to fit into a homogenous therapeutic organization.

Proactive Management of Peritoneal Metastases from Colorectal Cancer

Colorectal cancer is one of the leading causes of cancer death in developed countries. Despite recent advances in understanding the molecular pathogenesis and improvements in diagnosis and treatment, more than 1,2 million new cases and 600,000 deaths occur annually worldwide and cure rates remain low for patients with metastatic or recurrent disease [36]. According to reports from the National Cancer Institute, colon cancer is a highly treatable disease, and when confined to the bowel is often curable. Primary treatment, surgery, results in a cure in about 50 % of the patients. A major problem, however, and often the ultimate cause of death, is recurrence after surgery [37]. Recurrence remains a frequent cause of mortality after the surgical treatment of colorectal cancer with curative intent. Epidemiological studies show that the site involved by recurrent disease (liver, lung, locoregional sites) can vary according to the site of the primary tumor and its stage [38, 39]. Specifically for colorectal cancers a cumulative analysis addressing disease recurrence is made more complex, especially for locoregional recurrence, by the different approaches used in treating rectal tumors and colon tumors. In this scenario, major influential factors are the primary tumor site (colon vs. *rectum*) and treatment variables. In the past, survival was from 5 % to 10 % higher for colon than for rectal cancer [40, 41]. Over the decades the widespread usage in rectal surgery of total mesorectal excision (TME) procedures popularized by Heald and Ryall [42], together with neoadjuvant chemoradiotherapy protocols in advanced cases, have lowered local recurrence rates and improved survival [43–45]. Similar trends remain unobserved in colon cancer, and patients with colon cancer now have a worse prognosis than those with rectal cancer even though they more frequently undergo adjuvant chemotherapy [46–49]. Cancer statistics in the United States as well as in Europe show that in the past 20 years the survival rates for rectal cancer have overtaken those for colon cancer [50, 51]. Yet the criteria for defining and quantifying endoperitoneal recurrence in colon cancer remain unclear, some proposed classifications that leave the problem unsolved [52] and some investigators surprisingly considered peritoneal seeding or ovarian involvement after colonic resection as distant metastases [53]. If we accept the term “locoregional recurrence” in resected colonic cancer defined in an aspecific way, data from 27,000 patients resected for cure yield a recurrence rate ranging between from 5.6 to 12.8 % of the cases [54–63] (Table 2). Conversely, when published data refer specifically to peritoneal metastases (and in these cases include also those from rectal cancer) the rates for metachronous spread approach the previously cited figures. The rate for metachronous peritoneal spread increases in pT3/pT4 tumors, namely 60–70 % of the patients usually treated in surgical centers. Equally important, metachronous spread rates would be even higher if they referred only to patients with colonic cancer [64–66] (Fig. 1). Strategies for treating locoregional recurrence in colon cancer are disappointing for two reasons: first because only 30 % of patients can be surgically treated and second because from this 30 % only 30 % survive 5 years, leaving only 10 % of patients with a chance of being cured [67]. For the aforementioned reasons, the results of surgical treatment for these patients are difficult to analyze because some papers specifically report the results obtained for so-called locoregional recurrence whereas others refer to cytoreductive surgery (usually combined with intraoperative chemotherapy) for peritoneal metastases insofar as the two clinical conditions usually coexist. Two of the largest series describing attempted salvage surgery for locoregional recurrences from colon cancer reported by the Memorial Sloan Kettering Cancer Center and by the Netherland Cancer

Table 2 Rate of locoregional recurrence in colon cancer patients resected for cure

27,111 Colon cancer patients resected for cure		
Study	PTS (N)	Locoregional recurrence (%)
Manfredi s. (54)	2657	12,8
Stockholm colorectal cancer study group (55)	1856	11,5
Color trial (56)	1076	8
Netherlands cancer registry (57)	2282	6,4
Classic trial (58)	413	5 LEFT 14,7 RIGHT
Digestive cancer registry cote d'or (59)	3375	8,2
German research group oncology of gastrointestinal tumor (60)	904	8,4
Danish colorectal cancer group (61)	9333	12,2
Korean national cancer center (62)	1632	4,1 LEFT 8,5 RIGHT
Japanese society for colorectal cancer (63)	3583	5,6

Registry [57, 68], showed a Kaplan-Meier 5-year survival rate between 25 and 40 %.

Peritoneal spread from colorectal cancer has long been regarded as a terminal condition carrying a dismal prognosis. Only during the past 10 years has a new approach combining CRS + HIPEC yielded encouraging results [7, 69, 70]. A French multicenter study [7] showed that in the surgical approach to colorectal peritoneal metastases the determinant factor in predicting the likelihood of achieving optimal cytoreduction and a major prognostic indicator is the PCI. When the PCI is low, long-term results and postoperative morbidity improve. The PCI score is a critical issue in evaluating patients to undergo CRS and HIPEC for peritoneal metastases from colorectal cancer. Some suggest that 20 is a limit over which the surgical approach should be excluded [71]. Yet even if the Uppsala group report that treatment for high–volume peritoneal disease (PCI >20) seldom results in long-term survival [72], in their multivariate analysis Goéré et al. found as the only independent factor predicting cure a PCI of 10 or less (73): the median PCI in long-term survivors was 4, a value we rarely find in our clinical practice.

Among the first to suggest using preventive perioperative intraperitoneal chemotherapy in colorectal cancer were Jayne et al. several years ago [74]. Various investigators have reproposed this strategy particularly in patients with free endoperitoneal cancer cells [75, 76]. In 2014 Sloothaak et al. [77] published a systematic review evaluating the main experiences in preventing endoperitoneal spread in advanced colorectal cancer with proactive endoperitoneal chemotherapy. Unfortunately the various studies evaluated used different selection criteria, drugs and timing for intraperitoneal therapy. Despite these drawbacks, collectively these studies suggest that proactive intraperitoneal chemotherapy (including HIPEC) after primary resection is feasible, well-tolerated

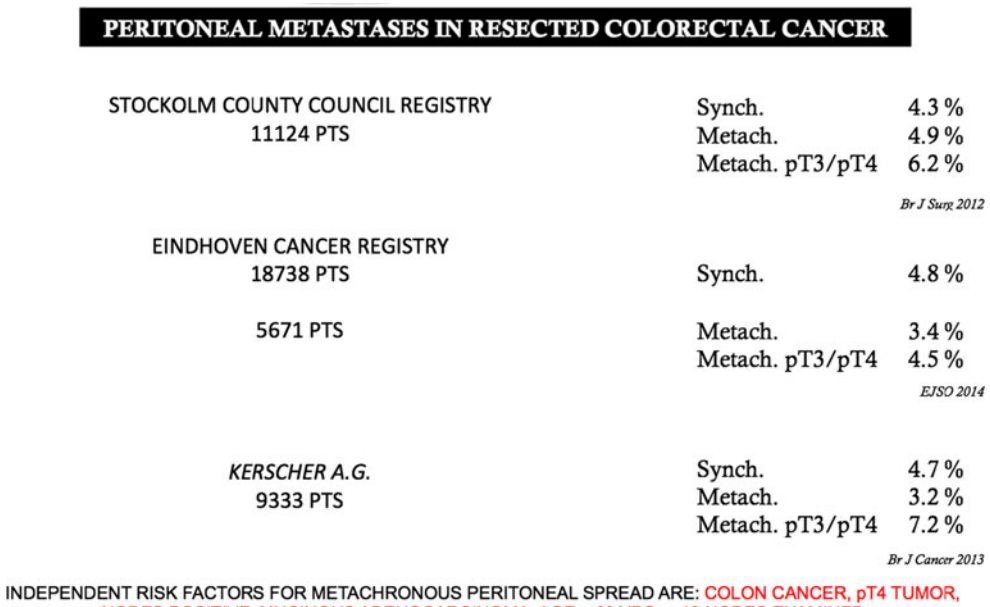


Fig. 1 Peritoneal metastases in resected colorectal cancer

and possibly reduces metachronous peritoneal spread. What we now need are data from well-designed randomized control trials addressing two fundamental issues: which patients these trials should include and the optimal timing for HIPEC. Published studies so far focus their efforts in preventing peritoneal metastases in colorectal cancer on second-look surgery plus HIPEC, a strategy proposed by Elias et al. [78]. Based on these preliminary results, a multicenter randomized trial was designed in France in 2010 (Prophylochip) [71] comparing, in asymptomatic patients at high risk of colorectal peritoneal metastases, systematic second-look + HIPEC (oxaliplatin intraperitoneally + intravenous 5-FU) with standard surveillance. Patient accrual for this trial has recently completed (Fig. 2). This trial nevertheless raises questions regarding patient selection because the main study group comprises patients whose malignancies had already spread to the peritoneum at the first operation, hence were incorrectly defined as "patients at risk of peritoneal spread" [79]. A trial more closely addressing the concept of proactive management is the COLOPEC trial started last April in The Netherlands and involving nine Dutch HIPEC centers. The target is patients with colon cancer pT4 any N M0 selected before or after primary surgery with HIPEC (oxaliplatin +5-FU) given simultaneously or eventually delayed in the immediate postoperative period. The trial randomizes 88 patients per arm to receive adjuvant systemic chemotherapy only versus adjuvant HIPEC plus adjuvant systemic chemotherapy. At 18 months staging laparoscopy is done in both treatment arms in patients considered disease-free [80] (Fig. 3). Even though the rationale underlying the decision to limit preventive measures to avoid peritoneal recurrence only to patients with pT4 tumors seems correct, in clinical practice identifying pT4 tumors preoperatively with the current diagnostic tools seems an almost impossible task. Multidetector computed tomography (MDCT) is highly accurate in distinguishing pT1–2 from pT3–4 tumors, but differentiating between pT3 and pT4 tumors remains a challenging task [81–84]. A correct differential diagnosis between pT3 and pT4 tumors is even difficult macroscopically unless tumor filtrates clearly into adjacent organs, and often requires a thorough pathologic assessment [85]. These observations underline that because correctly identifying pT4 tumors preoperatively and perioperatively remains difficult, patients selected for the COLOPEC trial will inevitably undergo a two-stage procedure, primary resection followed by HIPEC. Equally important, pathology studies also showed that, as in lung cancer [86], pT3 tumors invading the peritoneal elastic lamina (30 % of the cases) and pT4 cancers have the same outcome [87–90]. Studies designed to decide on the therapeutic strategy before the definitive pathological assessment are therefore unable to consider pT3 and pT4 tumors separately. For this reason, the FOXTROT trial, aimed to investigate the feasibility, safety and efficacy of preoperative systemic chemotherapy for locally-advanced but operable colon cancer, considered pT3 (with extramural depth > 5 mm) and pT4 tumors together [91]. Based on previous studies conducted in our Institution [92, 93], a new trial (PROMENADE trial) will start next year in four high-volume centers for colon cancer surgery in Italy. The target is patients with pT3, pT4 tumors any N, M0, selected by MDCT (in patients with suspected systemic disease combined with functional positron-emission tomography (PET)), who will be randomized (153 patients in each arm) to undergo standard surgical treatment versus proactive management (standard surgery plus complete greater omentectomy, appendectomy, resection of the round ligament of the liver and, in postmenopausal women, a bilateral adnexectomy) including

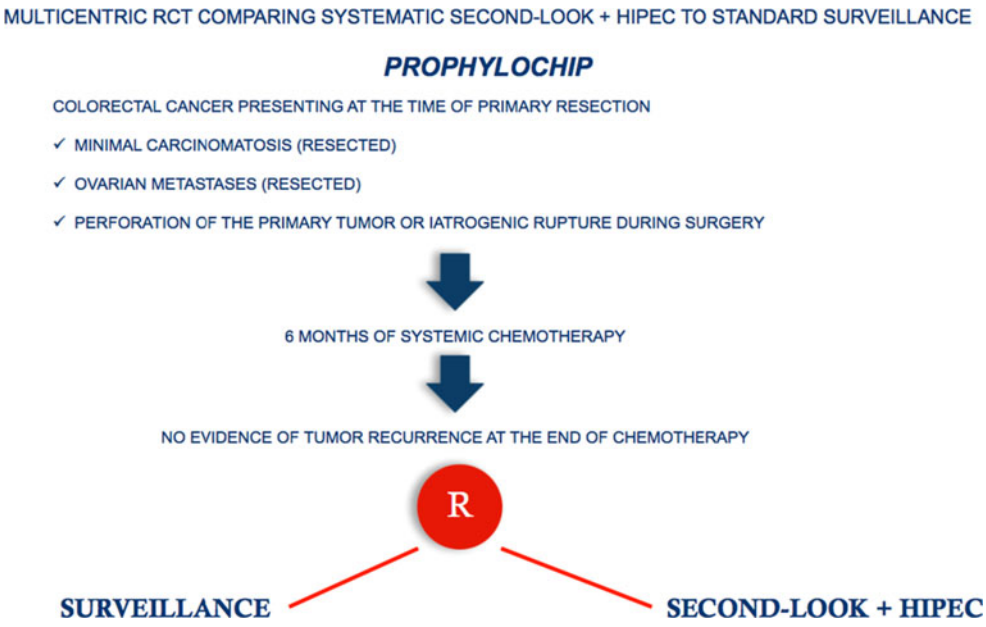
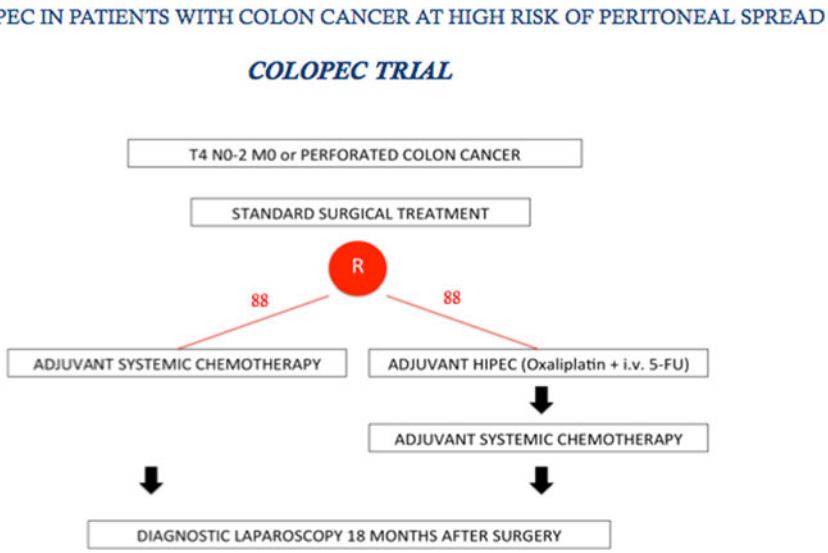


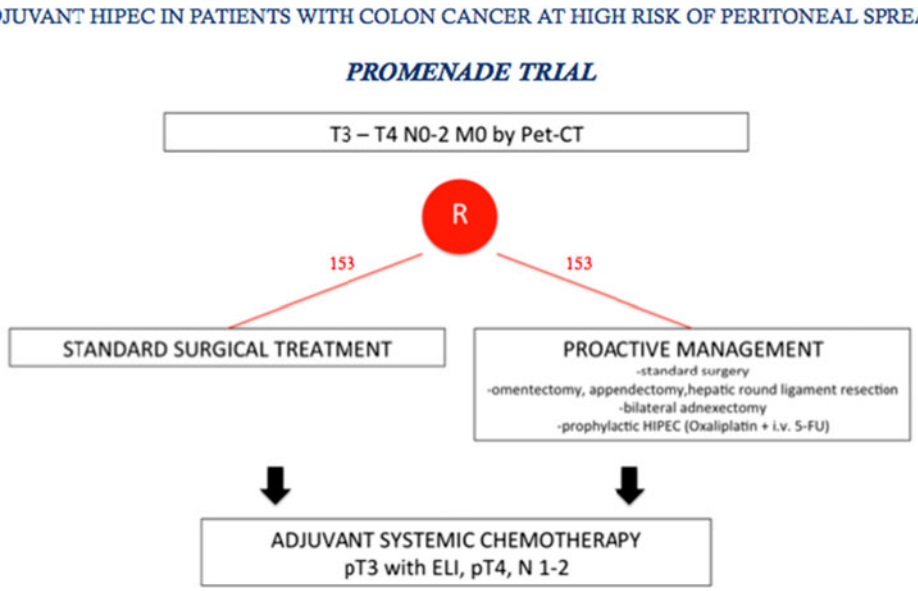
Fig. 2 PROPHYLOCHIP trial

Fig. 3 COLOPEC trial



HIPEC (oxaliplatin +5 FU). In both groups adjuvant systemic chemotherapy will be given in patients with pT3 tumors invading the peritoneal elastic lamina, in pT4 tumors and in patients with lymph node metastases (Fig. 4). Even though the COLOPEC and PROMENADE trials have almost the same primary and secondary endpoints (including rate of metachronous peritoneal spread and outcome) other factors in the two trials differ. In the PROMENADE trial we include patients with pT3 tumors and have several reasons for doing so. First consensus experience from surgeons treating peritoneal metastases from colorectal cancer suggests that peritoneal spread correlates with the same rate in pT3 and in pT4 tumors [65, 74, 94]. Second, correctly assessing serosal invasion in colorectal cancer is difficult and can require extensive tissue sampling. The studies conducted by several far eastern authors show that the subserosal elastic lamina is an anatomic landmark for stratifying pT3 colorectal cancer. When a pT3 tumor invades the subserosal elastic lamina, as it does in 30 % of the cases currently classified as pT3, the clinical outcome almost matches that in patients with pT4 cancer [87–90]. Other differences involve the timing for HIPEC, the decision as to whether to include other surgical procedures and last, including in the trial surgical quality measures. The PROMENADE trial foresees compulsory HIPEC given as soon as the surgical procedure ends whereas COLOPEC – because they use it only in patients with pT4 tumors and definitive histopathological findings – often waits for some days after surgery. Another difference is that unlike COLOPEC the PROMENADE trial envisages ancillary surgical procedures such as omentectomy and adnexectomy. The COLOPEC investigators [80] underline that no evidence exists to justify these procedures especially in patients who

Fig. 4 PROMENADE trial



undergo HIPEC, a procedure explicitly aimed to eradicate microscopic residual disease. Even though we might agree that no clinical evidence exists for justifying these ancillary resections we underline that removing these anatomic structures known at high risk of harboring tumor cells (omentum or appendix) is included in the guidelines for staging initial ovarian cancers [95]. Hence these procedures might seem reasonable in patients presenting with a large colon tumor infiltrating the peritoneal serosa despite HIPEC. Last, in designing study protocols for preventing locoregional or diffuse peritoneal recurrence our experience suggests that we need to establish criteria for surgical quality intended to leave uninfluenced the meaning of the awaited results. For this reason, we consider that the PROMENADE trial should include only patients resected with curative intent and whose surgical specimen contains, according to the criteria stated by the American Joint Committee on Cancer Staging (7th edition), a congruent lymph node count established in our protocol as a minimum number of 12 [96, 97].

Proactive Management of Peritoneal Metastases from Appendiceal Tumors

PMP has an estimated incidence of 1–2 in a million [98] and is listed by the National Organization for Rare Disorders as a rare disease [99]. Appendiceal mucinous neoplasms are considered equally rare tumors with an age-adjusted incidence of 0–12 cases per 1 million individuals per year [100]. As many as 50 % of these patients present with mucinous ascites. The main clinical and pathological prognostic factors for PMP developing are stage at diagnosis and pathologic features of primary tumor [101]. Data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) showed that the overall incidence of PMP and disease diagnosis in younger patients increased and survival improved from 1973 to 2006 mainly because patients with appendiceal mucinous tumors with advanced stage disease underwent CRS + HIPEC [102]. The finding that three-quarters of the patients with appendiceal mucinous tumors presented with symptoms of acute appendicitis or right iliac fossa pain suggests that many attend general surgical services. Hence at least at disease onset most of these patients are managed by non-specialist centers who lack the necessary know-how and technical equipment needed for CRS + HIPEC. And notwithstanding an interesting contribution showing that among patients who present to a general hospital with symptoms of acute appendicitis, criteria exist that raise a suspicion of appendiceal cancer (patient's age, disease onset with perforation) [103], most cases are diagnosed only after anatomopathological operative specimen analysis. Hence the onset of PMP can be preventively managed only as second-look surgery [22]. Of great interest in this regard is the study conducted by McDonald et al. at Manchester University, UK, who reviewed patients who had a LAMN and disease limited to the appendix or immediate peri-appendiceal tissues, and identified two LAMN subtypes, LAMN I (disease confined to the appendiceal lumen) and LAMN II (mucin or neoplastic epithelium or both in the appendiceal submucosa, wall or peri-appendiceal tissue or both, with or without perforation) that differed in pathological features and risk for dissemination towards PMP [21]. Patients with LAMN II lesions are therefore at increased risk for dissemination and even those with no clinical signs of spread should undergo second-look with preventive HIPEC. In their series, second-look disclosed mucin in the peritoneum or microscopic spread in 47 % of the patients [21]. Identifying a LAMN class at risk therefore opens the way to minimal access laparoscopic CRS combined with HIPEC [104].

Closing Remarks

The idea of preventing peritoneal metastases before they arise is now among the most interesting though speculative concepts in this fascinating oncologic surgical field. Tertiary prevention, to which proactive management is inter-connected, is ideally suited to advanced colorectal and gastric M0 tumors for which the treatment of metachronous peritoneal spread fails to achieve satisfactory results. In these patients, the ideal therapeutic aim is to treat microscopic peritoneal spread (PCI = 0), a clinical condition that is probably frequently present in patients with advanced tumors, but is exceedingly hard to diagnose. Of fundamental importance in establishing which patients should undergo proactive management are selection criteria, criteria that still today rely on anatomopathological features. Further studies, above all concerning genetic data able to illustrate the changing molecular dynamics underlying malignant progression, are indispensable to integrate present knowledge [105]. In other conditions such as appendiceal tumors, most being low-grade lesions, the decision to undertake proactive management for PMP (for these patients second-look) depends on how the histopathological features of the primary lesion are interpreted. Interpretative variability can run the risk of undertreatment or overtreatment.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

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