World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i39.5489

World J Gastroenterol 2012 October 21; 18(39): 5489-5494
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options

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Received: March 11, 2012 Revised: May 31, 2012
Accepted: June 8, 2012
Published online: October 21, 2012

Abstract

Peritoneal carcinomatosis (PC) is one manifestation of metastatic colorectal cancer (CRC). Tumor growth on intestinal surfaces and associated fluid accumulation eventually result in bowel obstruction and incapacitating levels of ascites, which profoundly affect the quality of life for affected patients. PC appears resistant to traditional 5-fluorouracil-based chemotherapy, and surgery was formerly reserved for palliative purposes only. In the absence of effective treatment, the historical prognosis for these patients was extremely poor, with an invariably fatal outcome. These poor outcomes likely explain why PC secondary to CRC has received little attention from oncologic researchers. Thus, data are lacking regarding incidence, clinical disease course, and accurate treatment evaluation for patients with PC. Recently, population-based studies have revealed that PC occurs relatively frequently among patients with CRC. Risk factors for developing PC have been identified: right-sided tumor, advanced T-stage, advanced N-stage, poor differentiation grade, and younger age at diagnosis. During the past decade, both chemotherapeutical and surgical treatments have achieved promising results in these patients. A chance for long-term survival or even cure may now be offered to selected patients by combining radical surgical resection with intraperitoneal instillation of heated chemotherapy. This combined procedure has become known as hyperthermic intraperitoneal chemotherapy. This editorial outlines recent advancements in the medical and surgical treatment of PC and reviews the most recent information on incidence and prognosis of this disease. Given recent progress, treatment should now be considered in every patient presenting with PC.

Key words: Colorectal cancer; Peritoneal carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Chemotherapy; Prognosis

Peer reviewers: Dr. Marek Bebenek, MD, PhD, Department of Surgical Oncology, Regional Comprehensive Cancer Center, pl. Hirszfelda 12, 53-413 Wroclaw, Poland; Jai Dev Wig, MS, FRCS, Former Professor and Head, Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Klaver YLB, Lemmens VEPP, Nienhuijs SW, Luyer MDP, de Hingh IHJT. Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options. *World J Gastroenterol* 2012; 18(39): 5489-5494 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i39/5489.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i39.5489

INTRODUCTION

Peritoneal carcinomatosis (PC) secondary to colorectal

cancer (CRC) is characterized by the development of solid tumor deposits on the peritoneal surface[1]. Cell shedding from the primary tumor is thought to be responsible for these peritoneal deposits, which may occur spontaneously or as a result of spillage during surgical procedures. Attachment of tumor cells to peritoneal mesothelial cells involves neoangiogenesis and is mediated by several growth factors[2]. Tumor implantation and growth may lead to invasion of any organ or structure that is covered by peritoneum.

Common sites for peritoneal implants are the omentum, mesentery, bowel surface, pouch of Douglas, right paracolic gutter, and diaphragm[3,4]. Patients initially present with nonspecific symptoms such as abdominal discomfort, nausea, weight loss, cachexia, and fatigue; however, these symptoms are often indistinguishable from more general features of malignant disease. The tumor growth on intestinal surfaces and associated fluid accumulation eventually result in signs of bowel obstruction[5] and incapacitating volumes of ascites[6,7]. Previously, providers were reluctant to treat these patients because of their extremely poor prognosis and invariably fatal outcomes[8-10]. Therefore, PC resulting from CRC had received little attention from oncologic researchers. Hence, data was lacking regarding incidence, clinical disease course, and accurate treatment evaluation for patients with PC.

Since the 1980s, PC research has attracted renewed interest because of the observation that a subgroup of patients presents solely with peritoneal tumor implants without systemic metastases[11,12]. This finding spurred the development of aggressive surgical treatment modalities which combined radical cytoreductive surgery with intraperitoneal chemotherapy[13-17]. With this approach, prolonged overall survival and even disease cure have been reported[8,18-26]. Here, we will discuss the recent advances in the characterization and treatment of these patients.

INCIDENCE OF PC

The extent of peritoneal disease is frequently underestimated by imaging modalities[27], and the presence of peritoneal involvement often remains unknown until a laparotomy is performed. This uncertainty in preoperative diagnosis results from the low sensitivity and specificity of imaging techniques such as abdominopelvic ultrasound and computed tomography. The small size of tumor deposits (typically less than 1 cm) negatively affects sensitivity[27-30]. Furthermore, peritoneal spread of tumor cells characteristically follows the anatomic outline of normal abdominal structures, making radiologic detection more challenging.

Underestimation of PC due to poor preoperative imaging diagnostics, combined with the aforementioned lack of interest, likely explains the virtual absence of data on PC incidence. Most available data were retrieved from single hospital-based studies that reported incidence of PC encountered during laparotomy. In the largest study, which included 2756 patients with CRC, 214 (8%) patients were diagnosed with synchronous PC and 135 (5%) with metachronous disease[10]. Two older studies, also single hospital-based, reported that 10% to 15% of patients with colon cancer presented with PC[9,31]. Recently, two population-based studies reported the incidence of synchronous PC in The Netherlands (4.8%) and in Sweden (4.3%)[32,33]. Risk factors for developing PC include right-sided tumor, advanced T-stage, advanced N-stage, poor differentiation grade, and younger age at diagnosis.

In clinical studies, metachronous PC is reported in 4% to 12% of patients following curative resection for colon cancer and in 2% to 19% of patients following curative resection for rectal cancer[34]. In patients undergoing repeat procedures for CRC following primary curative resection, 21% to 44% of patients are diagnosed with peritoneal tumor deposits[35,36]. In autopsy studies, PC is found in up to 40% of patients who die from colorectal carcinoma[37,38]. On a population level, 4.2% of Swedish patients with CRC developed metachronous PC following initial treatment[33]. Risk factors for developing metachronous PC are similar to those for synchronous PC, but also include initial emergency procedures and non-radical initial tumor resection[33].

TREATMENT

Systemic treatment

Few studies have been published describing the effectiveness of systemic chemotherapy in patients with PC. Due to an inability to accurately measure tumor load and treatment response, patients with peritoneal tumors usually do not meet the inclusion criteria for randomized trials[39]. The few studies describing chemotherapeutic treatment response focus on systemic 5-fluorouracil (5-FU) and leucovorin using retrospective analysis. The results invariably show a disappointing response to systemic treatment and a poor prognosis compared to other metastatic sites. A French prospective multicenter study of 118 patients with PC of colorectal origin showed a median survival of only 5.2 mo[40]. In a large series of CRC patients, which included 392 patients with peritoneal involvement, Jayne *et al*[10] showed a median survival of 7 mo. Chu *et al*[9] reported a median survival of 6 mo in a series of 45 patients who were treated primarily with 5-FU and leucovorin. A sub-analysis by Köhne *et al*[41] of patients with PC treated with 5-FU-based therapy showed a median survival of 7.7 mo. Slightly better results were reported by Bloemendaal *et al*[8], who described 50 patients with PC but without hematogenous metastases who were treated with systemic chemotherapy and palliative surgery. Their overall median survival was 12.6 mo, with a 2-year survival rate of approximately 18%[8,24]. However, selection bias probably explains these findings, because these patients were initially referred for hyperthermic intraperitoneal chemoperfusion (HIPEC)-

treatment but eventually randomized to the study control group. It is conceivable that these patients were healthier and their PC disease was more limited compared to the average PC patient.

A few studies have aimed to describe the effect of newer chemotherapeutic combinations, such as oxaliplatin plus irinotecan[8,42,43]. Results are conflicting and require careful interpretation. Many of these studies were performed to compare systemic treatment with surgical treatment. Selection bias may play a role in these studies because only patients in good condition with limited disease and without systemic metastases were eligible. Nevertheless, the median survival of 23 mo, as described by Elias *et al*[18] and obtained with modern systemic chemotherapy, is remarkable and dispels the notion that PC is chemotherapy-resistant. A similar conclusion may be drawn from the only population-based study to investigate this topic thus far. From 1995 to 2008, the administration of chemotherapy to patients with PC gradually increased, from 16% to 46% ($P = 0.001$), with the treatment rate rising to 64% for younger patients[41]. However, a survival benefit was only apparent after 2005 when modern chemotherapy schedules were introduced[44].

Introduction of targeted therapies, including monoclonal antibodies specifically targeted to epidermal growth factor receptor and vascular endothelial growth factor, has resulted in a significantly increased survival among patients with metastasized CRC[41,45,46]. Although these agents are now routinely included in the treatment of patients with stage Ⅳ disease, only one small retrospective study has evaluated the effect of adding targeted therapies in patients with PC; a survival of 22.4 mo was observed when biologicals were added to first line of treatment in this patient group[47].

Cytoreductive surgery and intraperitoneal chemotherapy

The observation that some patients present with PC in the absence of systemic metastases has led to the hypothesis that PC results from locoregional spread rather than systemic metastasis. This belief has encouraged surgical oncologists to examine possibilities for locoregional therapies. In the 1980s and 1990s, physicians and researchers developed new treatment strategies consisting of aggressive cytoreductive surgery plus intraperitoneal chemotherapy, often combined with hyperthermia.

Surgical procedures invariably start with a careful and systematic abdominal exploration and registration of the extent of peritoneal disease. The abdomen is divided in 13 regions and for each region, the number and size of tumor deposits are assessed and recorded. The sum of these scores represents the peritoneal cancer index (PCI), which ranges from 0 to 39. For PC resulting from CRC, a PCI score of 15 or more is generally accepted as exclusion criterion for HIPEC. In The Netherlands, the simplified PCI (sPCI) is commonly used to describe the PC involvement of 9 regions of the abdomen[24]. The PCI and sPCI are well-known predictive outcome indices for patients undergoing cytoreductive surgery and perioperative chemotherapy[48,49].

During cytoreductive surgery, surgeons attempt to remove all visible tumor deposits from the peritoneal surface. To achieve a radical resection, resection of grossly involved organs may be required. Additionally, peritonectomy may be performed[15]. Resection completeness is recorded using the completeness of cytoreduction score (CCR). A CCR-0 score indicates that no macroscopic peritoneal tumor remains following cytoreduction. A CCR-1 score occurs when tumor nodules less than 2.5 mm persist following cytoreduction. Residual disease measuring 2.5 mm to 2.5 cm is scored as CCR-2. A CCR-3 score indicates the presence of tumor nodules greater than 2.5 cm, or a confluence of unresectable tumor nodules at any site within the abdomen or pelvis[50]. Alternatively, the R1-R2a-R2b scoring system classifies R1 as no macroscopic residual tumor, R2a as macroscopic residual disease less than 2.5 mm, and R2b as tumor deposits greater than 2.5 mm[24]. Treatment outcomes are poorer in the presence of residual tumor following optimal cytoreduction, particularly for residual tumor diameters exceeding 2.5 mm. It is hypothesized that 2.5 mm is the maximum penetration depth of chemotherapeutic agents[48].

After macroscopically complete cytoreduction, intraperitoneal chemotherapy is administered to eradicate microscopic disease. This chemotherapy can be administrated immediately following surgery in the operating room, usually in combination with HIPEC or on postoperative days 1 to 5 (early postoperative intraperitoneal chemotherapy). HIPEC perfusion may be performed with a closed abdomen, or with an open "coliseum technique". Chemotherapeutic agents and doses vary widely between centers worldwide, with mitomycin C and oxaliplatin being the most frequently used agents.

Only one completed phase Ⅲ randomized trial investigating the outcome of surgical intraperitoneal treatment has been published to date. Verwaal *et al*[24,25,51] reported a significant increase in median overall survival among patients treated with cytoreductive surgery and HIPEC, as compared to patients receiving standard palliative care using systemic 5-FU and leucovorin. The promising outcomes observed in this study have convinced many surgeons to accept this technique as standard of care for selected patients with PC, and HIPEC treatment is now offered in specialized centers all over the world. However, this study was heavily criticized for not including a control group of patients receiving cytoreductive surgery only. Therefore, it remains unclear whether cytoreductive surgery and HIPEC are both required to improve survival, or if the observed benefit was due to a single component[52]. Ideally, these questions should be addressed in randomized trials. However, this type of study has proven difficult to implement, as demonstrated by a phase Ⅲ trial in France that failed to enroll enough patients due to patient dissatisfaction

with randomization[53]. Recently, investigations of cytoreductive surgery and HIPEC in PC animal models have provided a sound scientific rationale for the application of intraperitoneal chemotherapy in conjunction with cytoreductive surgery[54-56], although the additional value of hyperthermia is questionable[54].

The best available clinical evidence now comes from multi-institutional registries[18-23]. These data require careful interpretation, as surgeon experience, technique and perioperative care differs widely between institutions[57]. However, reported median survival rates of up to 63 mo following cytoreductive surgery and HIPEC with limited postoperative morbidity and mortality[58,59] suggest that treatment should be considered in all patients with PC secondary to CRC.

In conclusion, PC of colorectal origin was formerly considered untreatable, with an extremely poor prognosis. Recent treatment advances using modern systemic chemotherapy or cytoreductive surgery combined with HIPEC have improved patient outcomes. In our opinion, treatment should be considered for every patient presenting with PC due to CRC. However, further understanding of PC pathogenesis, optimal diagnostics and treatment requires ongoing experimental and clinical research.

REFERENCES

1 **Ceelen WP**, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol* 2009; **10**: 72-79

2 **Jayne DG**. The molecular biology of peritoneal carcinomatosis from gastrointestinal cancer. *Ann Acad Med Singapore* 2003; **32**: 219-225

3 **Gerber SA**, Rybalko VY, Bigelow CE, Lugade AA, Foster TH, Frelinger JG, Lord EM. Preferential attachment of peritoneal tumor metastases to omental immune aggregates and possible role of a unique vascular microenvironment in metastatic survival and growth. *Am J Pathol* 2006; **169**: 1739-1752

4 **Meyers MA**. Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. *Am J Roentgenol Radium Ther Nucl Med* 1973; **119**: 198-206

5 **Ketcham AS**, Hoye RC, Pilch YH, Morton DL. Delayed intestinal obstruction following treatment for cancer. *Cancer* 1970; **25**: 406-410

6 **Tamsma J**. The pathogenesis of malignant ascites. *Cancer Treat Res* 2007; **134**: 109-118

7 **Tamsma JT**, Keizer HJ, Meinders AE. Pathogenesis of malignant ascites: Starling's law of capillary hemodynamics revisited. *Ann Oncol* 2001; **12**: 1353-1357

8 **Bloemendaal AL**, Verwaal VJ, van Ruth S, Boot H, Zoetmulder FA. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol* 2005; **31**: 1145-1151

9 **Chu DZ**, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; **63**: 364-367

10 **Jayne DG**, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; **89**: 1545-1550

11 **Sugarbaker PH**. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. *Semin Surg Oncol* 1998; **14**: 254-261

12 **Sugarbaker PH**. Management of peritoneal-surface malignancy: the surgeon's role. *Langenbecks Arch Surg* 1999; **384**: 576-587

13 **Esquivel J**, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R, Baratti D, Bartlett D, Barone R, Barrios P, Bieligk S, Bretcha-Boix P, Chang CK, Chu F, Chu Q, Daniel S, de Bree E, Deraco M, Dominguez-Parra L, Elias D, Flynn R, Foster J, Garofalo A, Gilly FN, Glehen O, Gomez-Portilla A, Gonzalez-Bayon L, Gonzalez-Moreno S, Goodman M, Gushchin V, Hanna N, Hartmann J, Harrison L, Hoefer R, Kane J, Kecmanovic D, Kelley S, Kuhn J, Lamont J, Lange J, Li B, Loggie B, Mahteme H, Mann G, Martin R, Misih RA, Moran B, Morris D, Onate-Ocana L, Petrelli N, Philippe G, Pingpank J, Pitroff A, Piso P, Quinones M, Riley L, Rutstein L, Saha S, Alrawi S, Sardi A, Schneebaum S, Shen P, Shibata D, Spellman J, Stojadinovic A, Stewart J, Torres-Melero J, Tuttle T, Verwaal V, Villar J, Wilkinson N, Younan R, Zeh H, Zoetmulder F, Sebbag G. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Ann Surg Oncol* 2007; **14**: 128-133

14 **Katz MH**, Barone RM. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. *Surg Oncol Clin N Am* 2003; **12**: 673-688

15 **Sugarbaker PH**. Peritonectomy procedures. *Ann Surg* 1995; **221**: 29-42

16 **Sugarbaker PH**, Schellinx ME, Chang D, Koslowe P, von Meyerfeldt M. Peritoneal carcinomatosis from adenocarcinoma of the colon. *World J Surg* 1996; **20**: 585-591; discussion 592

17 **Sugarbaker PH**. Carcinomatosis--is cure an option? *J Clin Oncol* 2003; **21**: 762-764

18 **Elias D**, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goéré D, Bonastre J. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; **27**: 681-685

19 **Kecmanovic DM**, Pavlov MJ, Ceranic MS, Sepetkovski AV, Kovacevic PA, Stamenkovic AB. Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy. *Eur J Surg Oncol* 2005; **31**: 147-152

20 **Pilati P**, Mocellin S, Rossi CR, Foletto M, Campana L, Nitti D, Lise M. Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from colon adenocarcinoma. *Ann Surg Oncol* 2003; **10**: 508-513

21 **Piso P**, Dahlke MH, Ghali N, Iesalnieks I, Loss M, Popp F, von Breitenbuch P, Agha A, Lang SA, Kullmann F, Schlitt HJ. Multimodality treatment of peritoneal carcinomatosis from colorectal cancer: first results of a new German centre for peritoneal surface malignancies. *Int J Colorectal Dis* 2007; **22**: 1295-1300

22 **Schneebaum S**, Arnold MW, Staubus A, Young DC, Dumond D, Martin EW. Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996; **3**: 44-50

23 **Shen P**, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA, Levine EA. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol* 2004; **11**: 178-186

24 **Verwaal VJ**, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; **21**: 3737-3743

25 **Verwaal VJ**, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; **15**: 2426-2432

26 **Chua TC**, Yan TD, Morris DL. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: the Australian experience. *J Surg Oncol* 2009; **99**: 109-113

27 **Koh JL**, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2009; **16**: 327-333

28 **Franiel T**, Diederichs G, Engelken F, Elgeti T, Rost J, Rogalla P. Multi-detector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. *Abdom Imaging* 2009; **34**: 49-54

29 **Jacquet P**, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 1993; **72**: 1631-1636

30 **Esquivel J**, Chua TC, Stojadinovic A, Melero JT, Levine EA, Gutman M, Howard R, Piso P, Nissan A, Gomez-Portilla A, Gonzalez-Bayon L, Gonzalez-Moreno S, Shen P, Stewart JH, Sugarbaker PH, Barone RM, Hoefer R, Morris DL, Sardi A, Sticca RP. Accuracy and clinical relevance of computed tomography scan interpretation of peritoneal cancer index in colorectal cancer peritoneal carcinomatosis: a multi-institutional study. *J Surg Oncol* 2010; **102**: 565-570

31 **Golfinopoulos V**, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007; **8**: 898-911

32 **Lemmens VE**, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; **128**: 2717-2725

33 **Segelman J**, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2012; **99**: 699-705

34 **Koppe MJ**, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; **243**: 212-222

35 **Gunderson LL**, Sosin H, Levitt S. Extrapelvic colon--areas of failure in a reoperation series: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1985; **11**: 731-741

36 **Tong D**, Russell AH, Dawson LE, Wisbeck W. Second laparotomy for proximal colon cancer. Sites of recurrence and implications for adjuvant therapy. *Am J Surg* 1983; **145**: 382-386

37 **Gilbert JM**, Jeffrey I, Evans M, Kark AE. Sites of recurrent tumour after 'curative' colorectal surgery: implications for adjuvant therapy. *Br J Surg* 1984; **71**: 203-205

38 **Russell AH**, Pelton J, Reheis CE, Wisbeck WM, Tong DY, Dawson LE. Adenocarcinoma of the colon: an autopsy study with implications for new therapeutic strategies. *Cancer* 1985; **56**: 1446-1451

39 **Assersohn L**, Norman A, Cunningham D, Benepal T, Ross PJ, Oates J. Influence of metastatic site as an additional predictor for response and outcome in advanced colorectal carcinoma. *Br J Cancer* 1999; **79**: 1800-1805

40 **Sadeghi B**, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, François Y, Vignal J, Gilly FN. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; **88**: 358-363

41 **Köhne CH**, Cunningham D, Di Costanzo F, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Baron B, Pignatti F, Schöffski P, Micheel S, Hecker H. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; **13**: 308-317

42 **Folprecht G**, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer; in Peritoneal carcinomatosis. United States: Springer, 2007: 425-440

43 **Pelz JO**, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL, Maeder U, Germer CT, Kerscher AG. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer* 2010; **10**: 689

44 **Klaver YL**, Lemmens VE, Creemers GJ, Rutten HJ, Nienhuijs SW, de Hingh IH. Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy. *Ann Oncol* 2011; **22**: 2250-2256

45 **Meulenbeld HJ**, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 2008; **19**: 1600-1604

46 **Chua TC**, Morris DL, Saxena A, Esquivel J, Liauw W, Doerfer J, Germer CT, Kerscher AG, Pelz JO. Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. *Ann Surg Oncol* 2011; **18**: 1560-1567

47 **Klaver YL**, Leenders BJ, Creemers GJ, Rutten HJ, Verwaal VJ, Lemmens VE, de Hingh IH. Addition of Biological Therapies to Palliative Chemotherapy Prolongs Survival in Patients With Peritoneal Carcinomatosis of Colorectal Origin. *Am J Clin Oncol* 2012 Feb 6; Epub ahead of print

48 **Verwaal VJ**, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004; **91**: 739-746

49 **Chua TC**, Morris DL, Esquivel J. Impact of the peritoneal surface disease severity score on survival in patients with colorectal cancer peritoneal carcinomatosis undergoing complete cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2010; **17**: 1330-1336

50 **Jacquet P**, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996; **82**: 359-374

51 **Verwaal VJ**, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; **12**: 65-71

52 **Khatri VP**. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer: a panacea or just an obstacle course for the patient? *J Clin Oncol* 2010; **28**: 5-7

53 **Elias D**, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, Giovannini M, Lasser P. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; **11**: 518-521

54 **Klaver YL**, Hendriks T, Lomme RM, Rutten HJ, Bleichrodt RP, de Hingh IH. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. *Br J Surg* 2010; **97**: 1874-1880

55 **Klaver YL**, Hendriks T, Lomme RM, Rutten HJ, Bleichrodt RP, de Hingh IH. Intraoperative versus early postoperative intraperitoneal chemotherapy after cytoreduction for

colorectal peritoneal carcinomatosis: an experimental study. *Ann Surg Oncol* 2012; **19** Suppl 3: S475-S482
56 **Klaver YL**, Hendriks T, Lomme RM, Rutten HJ, Bleichrodt RP, de Hingh IH. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study. *Ann Surg* 2011; **254**: 125-130
57 **Sommariva A**, Pilati P, Rossi CR. Cyto-reductive Surgery combined with Hyperthermic Intra-peritoneal Chemotherapy for Peritoneal Surface Malignancies: current treatment and results. *Cancer Treat Rev* 2012; **38**: 258-268
58 **Chua TC**. Progress in the combined modality management of peritoneal carcinomatosis. *J Surg Oncol* 2010; **102**: 728-729
59 **Klaver YL**, Chua TC, de Hingh IH, Morris DL. Outcomes of elderly patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal cancer peritoneal carcinomatosis. *J Surg Oncol* 2012; **105**: 113-118

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