

Second-look surgery plus hyperthermic intraperitoneal chemotherapy for patients with colorectal cancer at high risk of peritoneal carcinomatosis: Does it really save lives?

Delia Cortes-Guiral, Dominique Elias, Pedro Antonio Cascales-Campos, Alfredo Badía Yébenes, Ismael Guijo Castellano, Ana Isabel León Carbonero, José Ignacio Martín Valadés, Jesus Garcia-Foncillas, Damian Garcia-Olmo

Delia Cortes-Guiral, Alfredo Badía Yébenes, Ismael Guijo Castellano, Damian Garcia-Olmo, Department of General Surgery (Peritoneal Surface Surgical Oncology), Fundación Jiménez Díaz Hospital, 28050 Madrid, Spain

Dominique Elias, Department of Surgical Oncology, Institut Gustave Roussy, 94805 Villejuif, Cédex, France

Pedro Antonio Cascales-Campos, Department of General Surgery (Peritoneal Surface Surgical Oncology), Virgen de la Arrixaca, 30120 Murcia, Spain

Ana Isabel León Carbonero, José Ignacio Martín Valadés, Jesus Garcia-Foncillas, Department of Medical Oncology, Fundación Jiménez Díaz Hospital, 28050 Madrid, Spain

Author contributions: Cortes-Guiral D wrote this paper; Elias D, Cascales-Campos PA, Badía Yébenes A, Guijo Castellano I, León Carbonero AI, Martín Valadés JI, Garcia-Foncillas J and Garcia-Olmo D reviewed this article.

Conflict-of-interest statement: Cortes-Guiral D declares no conflict of interest in relation to this publication.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Delia Cortes-Guiral, MD, Department of General Surgery (Peritoneal Surface Surgical Oncology), Fundación Jiménez Díaz Hospital, Avda. Reyes Católicos 2,

28050 Madrid, Spain. delia.cortes.guiral@gmail.com
Telephone: +34-651-924994

Received: August 27, 2016

Peer-review started: August 28, 2016

First decision: October 20, 2016

Revised: November 2, 2016

Accepted: November 15, 2016

Article in press: November 16, 2016

Published online: January 21, 2017

Abstract

The treatment of peritoneal carcinomatosis (PC) of colorectal origin with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has a 5-year recurrence-free or cure rate of at least 16%, so it is no longer labeled as a fatal disease, and offers prolonged survival for patients with a low peritoneal carcinomatosis index. Metachronous PC of colorectal origin is so predictable that there is a model which has been used to successfully determine the individual risk of each patient. Patients at risk are clearly identified; those with the highest risk have small peritoneal nodules present in the first surgery (70% probability of developing PC), ovarian metastases (60%), perforated tumor onset or intraoperative tumor rupture (50%). Current clinical, biological and imaging techniques still lack sufficient sensitivity to diagnose PC in its initial stages, when CRS plus HIPEC has a greater impact and a higher cure rate. Second-look surgery with HIPEC or prophylactic HIPEC at the time of the first intervention have been proposed as means of preventing and/or anticipating clinical or radiological relapse in at-risk patients. Both techniques have shown

a significant decrease in peritoneal relapses and should be considered essential weapons in the management of colorectal cancer.

Key words: Second-look surgery; High-risk patients; Peritoneal carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Colo-rectal cancer

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Metachronous peritoneal carcinomatosis of colorectal origin is so predictable that at-risk patients can be clearly identified. Treating peritoneal carcinomatosis in its early stages, when the peritoneal carcinomatosis index is as low as possible, is vitally important to get the maximum benefit from cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). Second-look surgery with HIPEC or prophylactic HIPEC at the time of the first intervention have been proposed as means of preventing and/or anticipating clinical or radiological relapse in at-risk patients. Both techniques have shown a significant decrease in peritoneal relapses and should be considered essential weapons in the management of colorectal cancer.

Cortes-Guiral D, Elias D, Cascales-Campos PA, Badía Yébenes A, Guijo Castellano I, León Carbonero AI, Martín Valadés JI, García-Foncillas J, García-Olmo D. Second-look surgery plus hyperthermic intraperitoneal chemotherapy for patients with colorectal cancer at high risk of peritoneal carcinomatosis: Does it really save lives? *World J Gastroenterol* 2017; 23(3): 377-381 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i3/377.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i3.377>

INTRODUCTION

The treatment of peritoneal carcinomatosis (PC) of colorectal origin through a multimodal approach (cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy) means it is no longer labeled as a fatal disease. Median survival is about 6 mo without treatment. Nowadays it would seem unacceptable to offer these patients a palliative approach (palliative surgery and systemic chemotherapy with/without biologics) with a survival rate of about 24 mo. The multimodal approach with curative intent achieves survivals of up to 64 mo with a mean 5-year survival of 51% in patients receiving a completeness of cytoreduction (CCR)-0^[1] and a disease-free survival at 5 years of 16%^[2].

Surgeons and oncologists accept R0 resection plus systemic treatment with curative intent as the standard therapy for colorectal cancer liver metastases, this offers 5-year survival rate of 36.5%. This survival curve runs parallel to the curve for PC patients treated with CRS + HIPEC, which has a survival rate of 38%,

as reflected in the retrospective study presented by Elias in 2015^[3]. In fact analysis of this work confirmed that PC patients with a low peritoneal carcinomatosis index (PCI) (between 1 and 5) treated with CRS + HIPEC, with a 3-year survival of 89%, have a better prognosis than those with liver metastases. These data are confirmed in Huang *et al*^[4] review of 60 patients with a PCI of less than or equal to 5 which observed a median survival of 80.6 mo, a 5-year survival rate of 54.7% and no mortality.

Therefore it is very important to treat PC while the PCI is as low as possible. Less aggressive surgery is required for lower PCI values and is also more likely to achieve CCR-0; both PCI and CCR-0 are repeatedly the two factors with the highest prognostic significance in the treatment of PC^[5-6].

However, early PC (when PCI is ≤ 5) cannot be detected with clinical, biological or radiological methods. It can only be detected through a surgical approach (this is the basis for second-look surgery). On the other hand, when the symptoms, biological abnormalities and/or radiological signs of PC are detectable, then patients usually present a high PCI and CRS + HIPEC offers a poor outcome^[7].

This locoregional colorectal cancer relapse and the perception that it can probably be prevented or treated in high-risk patients at an early stage, unfortunately when it is still clinically and radiologically undetectable, is an issue that has concerned surgeons for many years. In 1948, Wagensteen performed second-look laparotomy in asymptomatic patients with lymph node involvement in the surgical specimen extracted from the first colorectal resection. He followed the hypothesis that early surgery in the incipient stages of relapse would increase survival in these patients and in 1962 he published a series on 98 asymptomatic patients, of which 36 patients had a positive second-look (36.7%), and 6 subjects in this group (17%) never experienced recurrence^[8]. Wagensteen also published a series on 47 symptomatic second-look patients of which 15% became long-term survivors after several interventions.

Several works with different selection criteria involving patients undergoing second-look surgery were published in the 1980s. Gunderson *et al*^[9-10] published a very noteworthy paper that investigated second-look surgery performed within 6 to 12 mo after resection of the primary tumor in 60 patients with pT4 tumors or positive lymph nodes; relaparotomy yielded positive findings positive in 42% of asymptomatic patients.

All these studies placed particular interest in the morbidity and mortality rates associated with reoperation and the increased survival rates for patients whose relapse was diagnosed at an early stage. However, despite treating relapse before it was symptomatic or radiographically detectable, the suboptimal treatment offered to these patients meant recurrence was the norm.

Table 1 Risk of recurrence in function of clinical and histopathological characteristics of tumors

	Estimated incidence of peritoneal metastases observed in follow-up
Clinical characteristic	
Peritoneal nodules detected during primary cancer resection	70%
Ovarian metastases	60%
Perforation through the primary cancer	50%
Adjacent organ or structure invasion	20%
Signet-ring histology	20%
Fistula formation	20%
Obstruction of primary cancer	20%
Histopathological characteristic	
Positive resection margin	80%
Positive cytology before or after resection	40%
Positive imprint cytology	40%
Positive lymph nodes at or near resection margin	20%
T3/T4 mucinous cancer	40%

Appreciation of the need for quality cancer surgery changed the techniques used in colorectal resection forever: total mesorectal excision and mesocolic excision were introduced and their impact on survival was quantified^[11]. These techniques were universalized, as were resections with safety margins and extensive lymphadenectomies. However, local relapse, and especially recurrence in the form of peritoneal carcinomatosis, emerged as an issue pending resolution in the treatment of colorectal cancer.

LOOKING FOR HIGH RISK PATIENTS: EVIDENCE FROM CLINICAL TRIALS

The titanic work of Honoré *et al.*^[12] defined patients at risk of developing peritoneal carcinomatosis and classified those with small peritoneal nodules present in the first surgery (70% probability of developing PC), ovarian metastases (60%), and perforated tumor onset or intraoperative tumor rupture (50%) as being high risk. Positive cytology (pre- or post-surgical resection), the imprint of a positive tumor and T3-T4 mucinous tumors have a risk of 30% to 40%.

According to Sugarbaker^[13], the risk of recurrence is determined by the clinical and histopathological characteristics of the tumor, as shown in Table 1.

In fact, metachronous peritoneal carcinomatosis of colorectal origin is so predictable that Segelman developed an individualized prediction model to estimate each patient's risk^[14-15]. In her review the development of metachronous PC was associated independently with tumors located in the right colon ($P < 0.002$), emergency surgery ($P < 0.001$), non-R0 surgery ($P < 0.001$), pN2 with lymphadenectomy with less than 12 nodes examined ($P < 0.001$), and pT4 ($P < 0.001$). <http://www.imm.ki.se/biostatistics/calculators/pcrisk>

Logically this led to the conclusion that second-

look surgery for patients at risk of developing PC could provide a means of anticipating clinical or radiological relapse and treating carcinomatosis in its early stages, culminating in the remarkable work by Elias *et al.*^[16]. Their study comprised a prospective series from 1999 to 2009 in which second-look laparotomy was indicated for 47 patients considered at very high risk of developing carcinomatosis: 28 patients with minimal peritoneal nodules resected at the time of the first intervention, 8 patients with synchronous ovarian metastases and 11 patients who had a perforated tumor at onset. All patients underwent appropriate oncological surgery with extensive lymphadenectomy, negative margins and completed adjuvant therapy according to current standard-of-care regimens (FOLFOX or FOLFIRI). After systemic chemotherapy extension study was subsequently performed and those patients who had no clinical, biological or radiological signs of disease underwent (within 12 mo of the first intervention) second-look laparotomy, revealing macroscopic carcinomatosis in 49% of patients with an average PCI of 7. In a group of 24 macroscopic PC-free patients, 18 received HIPEC, of which only one (5.5%) presented peritoneal recurrence, while the other six did not receive HIPEC, of which three (50%) suffered peritoneal relapse. Of all patients treated with HIPEC only 17% experienced a peritoneal relapse. This approach achieved a 5-year survival of 90% of the series with a disease-free survival at 5 years of 44%. These results underlined the tremendous impact of second-look surgery plus HIPEC in this group of asymptomatic patients and therefore emphasize the unavoidable responsibility of professionals treating colorectal cancer to be aware of each patient's risk of recurrence and current early treatment and prevention options. It is important to note that all patients in the above study had firstly undergone oncological R0 colectomy with adequate lymphadenectomy and adjuvant therapy; so, despite establishing optimal surgical and chemotherapeutic treatment to prevent peritoneal relapse or treat it in its early stages, a strategy that includes regional intensification therapy is required for high risk patients, in other words HIPEC.

Two approaches can be used to treat patients at risk of recurrence. One is the realization of second-look surgery plus HIPEC, unavoidable in patients at very high risk, *i.e.*, with a positive resection margin, tumor perforation, ovarian metastases, or implants in the first intervention. For these patients the treatment sequence is oncological colorectal surgery, adjuvant therapy for 6 mo and, if the extension study is negative, second-look laparotomy with risk-reducing surgery and HIPEC. Another option to avoid delay of the second-look is to administer systemic chemotherapy for 3 mo, followed by a laparotomy and HIPEC, and then complete the remaining 3 mo of systemic chemotherapy. The selection criteria and second-look algorithm proposed by Sugarbaker^[17] in 2011 have become the worldwide reference.

The second approach for at-risk patients is considered to be ideal by many units of peritoneal surgery and is offered to all patients at risk of peritoneal relapse (1 to 12). It is performed simultaneously with resection of the primary tumor, risk-reducing surgery and prophylactic HIPEC (which is as well-known as upfront HIPEC), followed by 6 mo of systemic chemotherapy and regular follow-ups^[13].

Accepted exclusion criteria^[17] for the second-look approach are unresectable liver (more than 4 lesions) or lung metastases, over 75 years (although this varies between different units) or the presence of significant comorbidities (performance status > 2, renal failure with creatinine > 3, cardiac failure with ejection fraction < 50%).

Sammartino *et al.*^[18] applied this proactive approach in 25 patients at risk of peritoneal recurrence (pT3/T4 and mucinous or signet-ring cell), performing risk-reducing surgery with prophylactic resection of organs which are frequently affected by carcinomatosis (omentectomy, removal of the round ligament, appendectomy and bilateral oophorectomy in postmenopausal patients) and HIPEC. The results were analyzed and compared with 50 controls (treated in another unit) and then re-analyzed 48 mo after closing the study. Morbidity in both groups was comparable, but with a 4% incidence of carcinomatosis development in the HIPEC treated group vs 28% in the control group ($P < 0.03$) and a disease free survival ($P < 0.05$) and overall survival (OS) ($P < 0.04$) significantly higher in the group with prophylactic treatment.

In 2013 Tentes *et al.*^[19] published a prospective study comparing the adjuvant setting in patients with pT3 or pT4 colorectal cancer receiving systemic chemotherapy (40 patients) vs intraperitoneally by HIPEC with mitomycin (41 patients). There were no recurrences in the peritoneum in the group treated with HIPEC vs 3 cases of PC in the systemic chemotherapy group; the 5-year survival was 100% in the HIPEC group vs 72% in the conventional group without reaching statistical significance ($P = 0.0938$).

Phase III studies were initiated in light of these results in order to assess the impact of a second-look protocol or HIPEC performed at the time of surgery of the primary tumor to avoid cell implantation as a result of surgical trauma.

The PROMENADE trial NCT02974556 in Rome led by Sammartino randomizes patients with T3/T4 colorectal cancer into two arms, one for conventional surgery of the primary tumor followed by adjuvant systemic chemotherapy vs surgery of the primary tumor with risk-reducing surgery (omentectomy, appendectomy, removal of the round ligament and bilateral oophorectomy in postmenopausal patients) and HIPEC followed by adjuvant therapy.

Also for high-risk patients with pT4 or perforated tumors, the Dutch trial COLOPEC^[20] randomizes these patients to receive treatment with conventional surgery followed by systemic adjuvant therapy vs

surgery of the primary tumor and administration of HIPEC (intraperitoneal oxaliplatin and intravenous 5-FU) during the intervention or within 5 to 8 wk after the intervention. At 18 mo, an exploratory laparoscopy will be performed in all patients. This study presents a strategy that combines the advantages of prophylactic HIPEC with second-look laparoscopy to detect relapse; a promising strategy that may be useful in very high risk patients or help to detect treatment resistance. The French RENAPE group is finishing a prospective study (COELIOCHIP) which compares the performance of a laparoscopic approach against that of a laparotomic approach: all patients receiving second-look surgery will undergo a careful initial exploration by laparoscopy followed by the usual laparotomy.

Also, for radiologically identified T4, the HIPEC-T4 study in Spain will evaluate the impact of prophylactic HIPEC with mitomycin at the time of first intervention.

The ProphylloCHIP NCT01226394 Phase III trial led by Elias seeks to analyze the impact of second-look laparotomy with HIPEC (intraperitoneal oxaliplatin and intravenous 5-FU) in 150 patients with a very high risk of peritoneal relapse (ovarian metastases, perforated tumors or small number of implants resected with the primary tumor) within 12 mo after the first intervention and with negative extension tests vs conventional follow-up, both groups receiving systemic adjuvant therapy. They have finished recruiting and collecting data; analysis will be completed in June 2019.

CONCLUSION

While awaiting the results of these Phase III trials, the evidence from studies published to date impels us to acknowledge the existence of groups at risk of developing carcinomatosis among our patients with colorectal cancer. We must also be very conscious of the potential benefits of cytoreductive surgery plus HIPEC in patients with a very low PCI where the chances of cure or preventing any future relapses are maximized.

So the aim is to treat patients with the lowest possible PCI, ideally between 1 and 5, but these early stages are beyond the sensitivity of current clinical, biological and imaging techniques. Therefore these patients must receive this treatment before any detectable signs of relapse manifest. Thus prophylactic HIPEC at the time of the first intervention or second-look laparotomy with HIPEC during or after a course of adjuvant systemic chemotherapy are the means available to achieve this goal. The most common approach is second-look laparotomy because most colorectal cancer interventions are performed in centers where HIPEC is unavailable and high-risk patients are referred to specialized units for assessment.

For patients at risk of peritoneal relapse, optimal surgical treatment at the first intervention followed by systemic chemotherapy is not enough to prevent or provide early treatment of peritoneal metastases.

Therefore a strategy including a regional intensification treatment is required, *i.e.*, up-front HIPEC or second-look surgery plus HIPEC. This approach achieves a decrease in peritoneal relapse from 50%-70% to 6%-17% in high-risk patients and from 30%-40% down to 0%-4% in other at-risk patients. We can therefore conclude that this course of action will save many lives by preventing the development of peritoneal carcinomatosis or enabling successful treatment of carcinomatosis before it is clinically or radiologically detectable while yielding the maximum benefit from cytoreductive surgery and HIPEC.

Patients have the right to know their risk of developing PC and the possibilities of prevention and early treatment currently available.

If we want to offer our patients the best treatment, we must be aware that second-look surgery with HIPEC, prophylactic HIPEC or both have become essential weapons in the management of colorectal cancer.

REFERENCES

- 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 [PMID: 19103728 DOI: 10.1200/JCO.2008.19.7160]
- Goéré D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, Maggiori L, Dumont F, Ducreux M, Elias D. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Ann Surg* 2013; **257**: 1065-1071 [PMID: 23299520 DOI: 10.1097/SLA.0b013e31827e9289]
- Elias D, Faron M, Iuga BS, Honoré C, Dumont F, Bourgain JL, Dartigues P, Ducreux M, Goéré D. Prognostic similarities and differences in optimally resected liver metastases and peritoneal metastases from colorectal cancers. *Ann Surg* 2015; **261**: 157-163 [PMID: 24509197 DOI: 10.1097/SLA.0000000000000582]
- Huang Y, Alzahrani NA, Chua TC, Liauw W, Morris DL. Impacts of low peritoneal cancer index on the survival outcomes of patient with peritoneal carcinomatosis of colorectal origin. *Int J Surg* 2015; **23**: 181-185 [PMID: 26361862 DOI: 10.1016/j.ijsu.2015.08.078]
- Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010; **116**: 5608-5618 [PMID: 20737573 DOI: 10.1002/cncr.25356]
- Passot G, Vaudoyer D, Cotte E, You B, Isaac S, Noël Gilly F, Mohamed F, Glehen O. Progression following neoadjuvant systemic chemotherapy may not be a contraindication to a curative approach for colorectal carcinomatosis. *Ann Surg* 2012; **256**: 125-129 [PMID: 22580942 DOI: 10.1097/SLA.0b013e318255486a]
- Dromain C, Leboulleux S, Auperin A, Goere D, Malka D, Lumbroso J, Schumberger M, Sigal R, Elias D. Staging of peritoneal carcinomatosis: enhanced CT vs PET/CT. *Abdom Imaging* 2008; **33**: 87-93 [PMID: 17632751 DOI: 10.1007/s00261-007-9211-7]
- Gilbertsen VA, Wangenstein OH. A summary of thirteen years' experience with the second look program. *Surg Gynecol Obstet* 1962; **114**: 438-442 [PMID: 13898554]
- 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 [PMID: 3980270]
- Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following curative surgery for adenocarcinoma of the rectum. *Cancer* 1974; **34**: 1278-1292 [PMID: 4424091 DOI: 10.1002/1097-0142(197410)34: 4]
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-1482 [PMID: 2425199]
- Honoré C, Goéré D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. *Ann Surg Oncol* 2013; **20**: 183-192 [PMID: 23090572 DOI: 10.1245/s10434-012-2473-5]
- Sugarbaker PH. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. *World J Gastroenterol* 2014; **20**: 9286-9291 [PMID: 25071322 DOI: 10.3748/wjg.v20.i28.9286]
- Segelman J, Akre O, Gustafsson UO, Bottai M, Martling A. Individualized prediction of risk of metachronous peritoneal carcinomatosis from colorectal cancer. *Colorectal Dis* 2014; **16**: 359-367 [PMID: 24410859 DOI: 10.1111/codi.12552]
- Segelman J, Akre O, Gustafsson UO, Bottai M, Martling A. External validation of models predicting the individual risk of metachronous peritoneal carcinomatosis from colon and rectal cancer. *Colorectal Dis* 2016; **18**: 378-385 [PMID: 26588669 DOI: 10.1111/codi.13219]
- Elias D, Honoré C, Dumont F, Ducreux M, Boige V, Malka D, Burtin P, Dromain C, Goéré D. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2011; **254**: 289-293 [PMID: 21709543 DOI: 10.1097/SLA.0b013e31822638f6]
- Sugarbaker PH. Second-look surgery for colorectal cancer: revised selection factors and new treatment options for greater success. *Int J Surg Oncol* 2011; **2011**: 915078 [PMID: 22312530 DOI: 10.1155/2011/915078]
- Sammartino P, Sibio S, Biacchi D, Cardi M, Mingazzini P, Rosati MS, Cornali T, Sollazzo B, Atta JM, Di Giorgio A. Long-term results after proactive management for locoregional control in patients with colonic cancer at high risk of peritoneal metastases. *Int J Colorectal Dis* 2014; **29**: 1081-1089 [PMID: 24980687 DOI: 10.1007/s00384-014-1929-4]
- Tentes AAK, Kakolyris S, Pallas N, Korakianitis O, Mavroudis C, Zorbas G, Sarlis P. Preliminary results with the use of hyperthermic intraperitoneal intraoperative chemotherapy or systemic chemotherapy in high-risk colorectal cancer patients. *Transl Gastrointest Cancer* 2013; **2**: 6-10 [DOI: 10.3978/j.issn.2224-4778.2012.10.02]
- Klaver CE, Musters GD, Bemelman WA, Punt CJ, Verwaal VJ, Dijkgraaf MG, Aalbers AG, van der Bilt JD, Boerma D, Bremers AJ, Burger JW, Buskens CJ, Evers P, van Ginkel RJ, van Grevenstein WM, Hemmer PH, de Hingh IH, Lammers LA, van Leeuwen BL, Meijerink WJ, Nienhuijs SW, Pon J, Radema SA, van Ramshorst B, Snaebjornsson P, Tuynman JB, Te Velde EA, Wiezer MJ, de Wilt JH, Tanis PJ. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. *BMC Cancer* 2015; **15**: 428 [PMID: 26003804 DOI: 10.1186/s12885-015-1430-7]

P- Reviewer: Koda K, Lakatos PL S- Editor: Qi Y

L- Editor: A E- Editor: Liu WX





Published by Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>



ISSN 1007-9327

