

Bases of oncologic surgery for peritoneal disease



Pr Marc Pocard

INSERM U 1275 : CaP Paris - Tech : CArcinomatosis Peritoneum Paris Technology

Oncological surgical unit = Lariboisière's Hospital, Paris, France

International Society for the study of Pleura and Peritoneum









Links of interest – Pr Marc Pocard

- 2014 2019:
- Honorary:

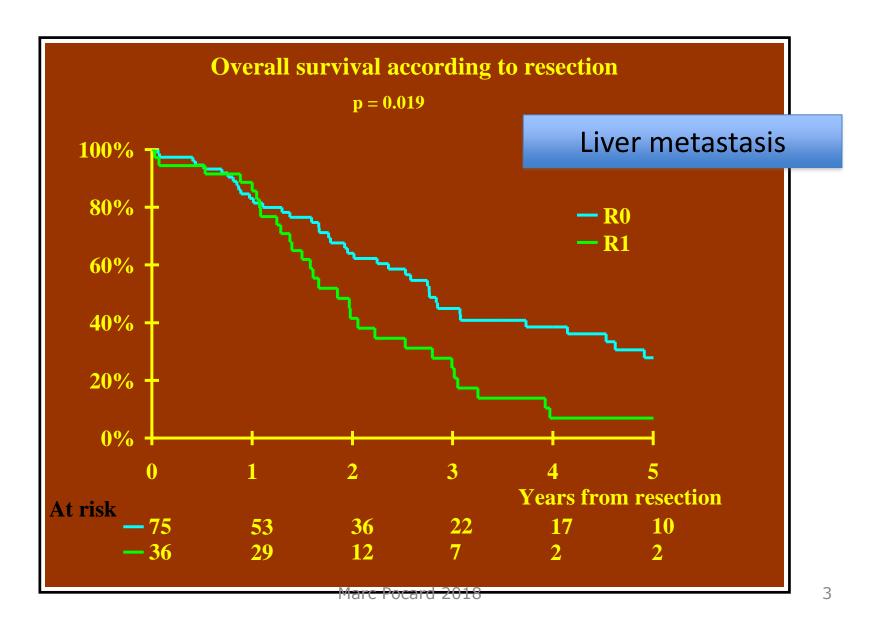
Gamida, Léo-Pharm, Sanofi, Roche

Award – congress – laboratory research grant:

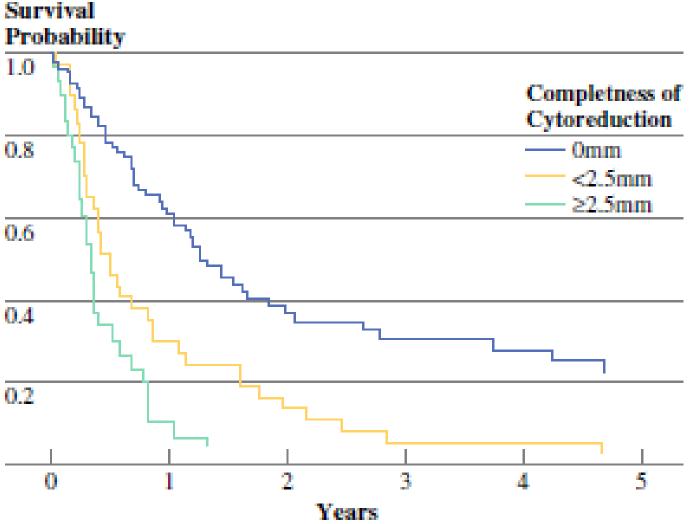
Capnomed, Clerad, Ethicon, Fujinon, Gamida, INSERMTransfert, Plasma-jet, Roche, Sanofi, Soframédical, STAGO, Storz, Rand

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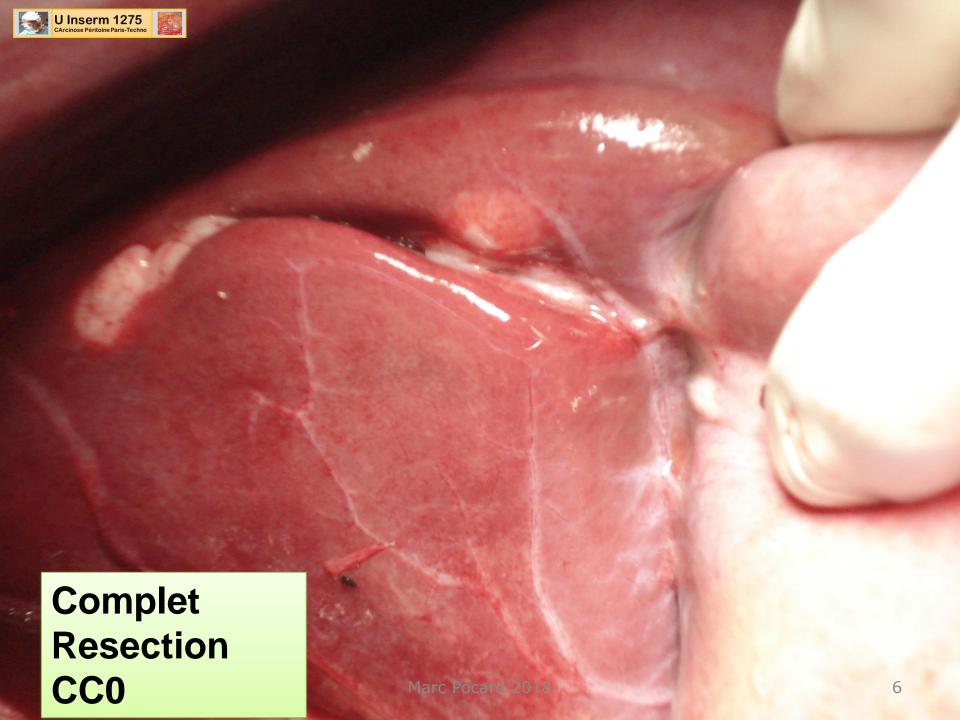


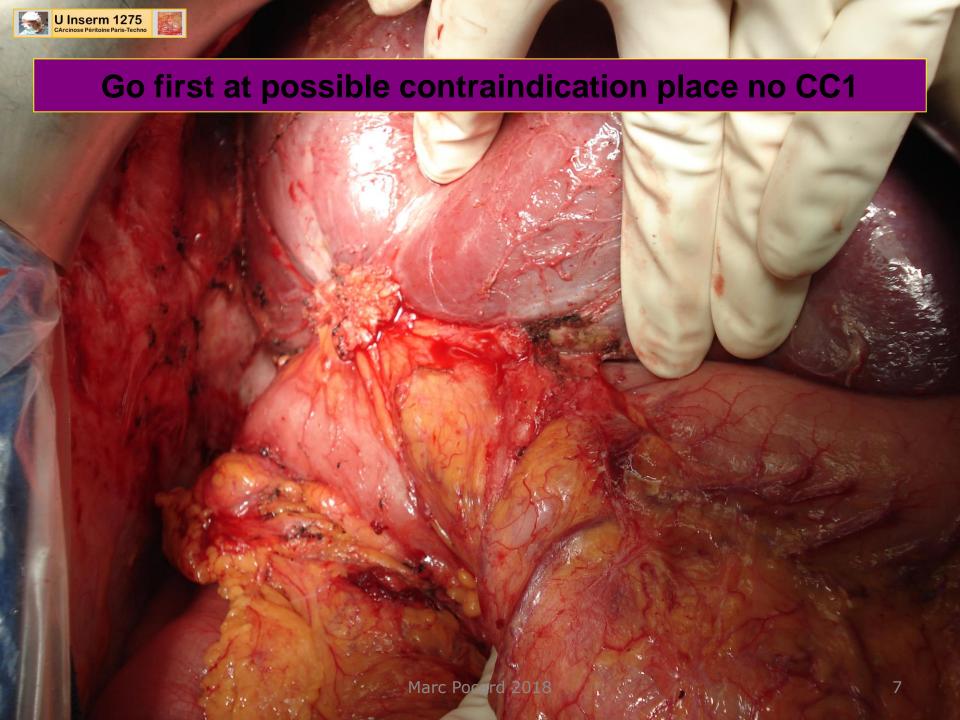
Peritoneal Carcinomatosis from Gastric Cancer: A Multi-Institutional Study of 159 Patients Treated by Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy

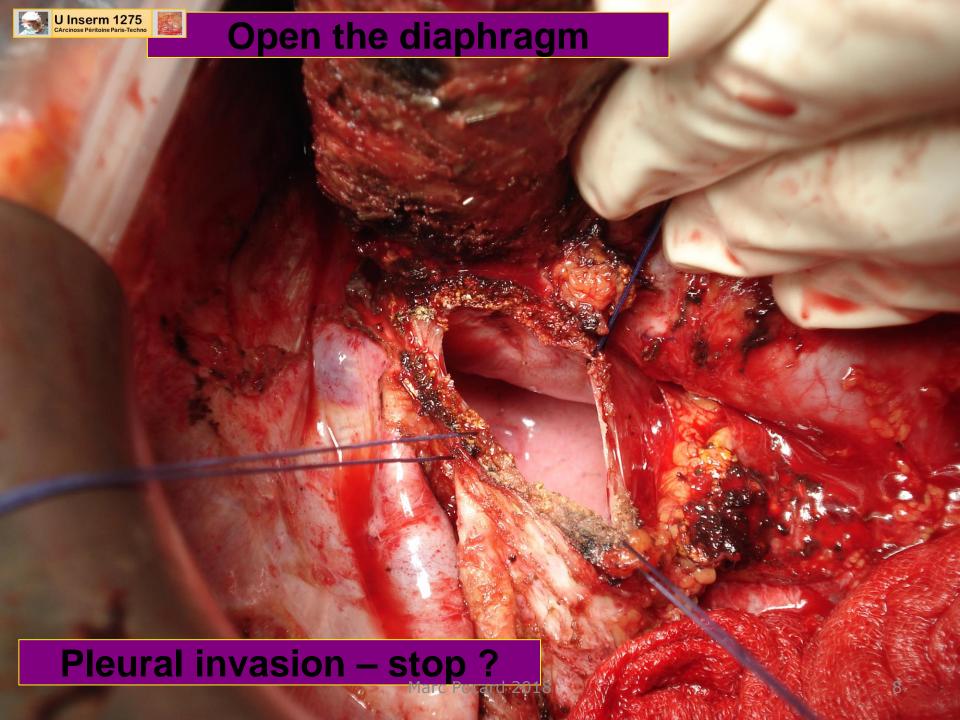
Ann Surg Oncol (2010) 17:2370-2377 DOI 10.1245/s10434-010-1039-7



- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery









- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- But for peritoneal disease there is no margin So you can not perform a RO resection

Use intra peritoneal chemotherapy to perform a CC0 resection

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Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia With Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin

Dominique Elias, Jérémie H. Lefevre, Julie Chevalier, Antoine Brouquet, Frédéric Marchal, Jean-Marc Classe, Gwenaël Ferron, Jean-Marc Guilloit, Pierre Meeus, Diane Goéré, and Julia Bonastre

J Clin Oncol 2008 27:681-685

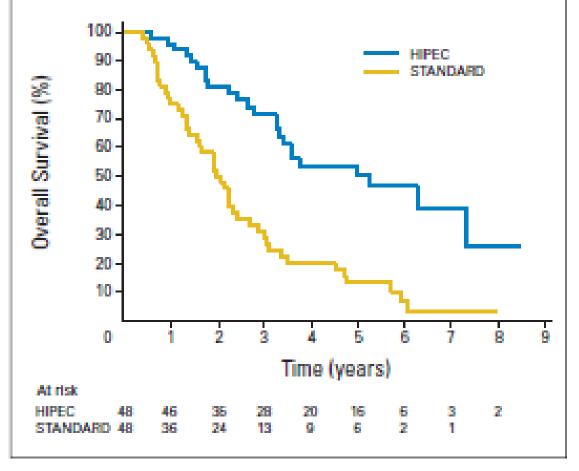


Fig 1. Overall survival of group receiving cytoreductive surgery, hyperthermic intraperitoneal oberpotherapy (HPEC), and systemic treatment versus those receiving standard treatment.



- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- But for peritoneal disease there is no margin So you can not perform a RO resection

Use intra peritoneal chemotherapy to perform a CC0 resection

- Select patient with limited metastatic disease
 - You need to evaluate the extension of the metastatic process

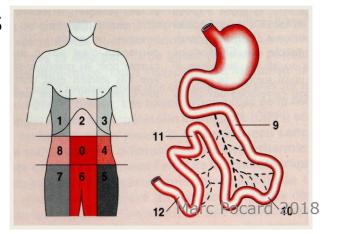


- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- But for peritoneal disease there is no margin So you can not perform a RO resection

Use intra peritoneal chemotherapy to perform a CCO resection

- Select patient with limited metastatic disease
 - You need to evaluate the extension of the metastatic

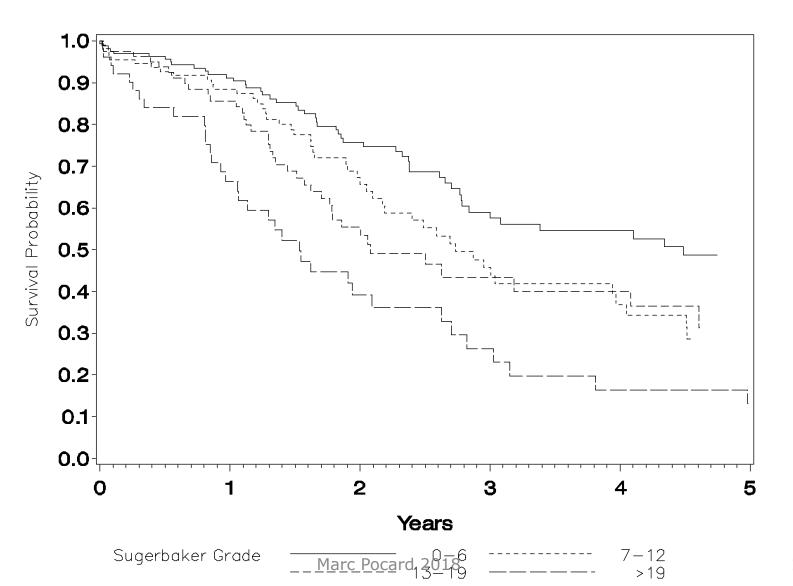
process



P C I
Peritoneal cancer index



440 patients after CC0 and intraperitoneal chemo ip : colon – rectum – small bowel and appendice





Lariboisière's exclusion criteria in case of colon peritoneal metastasis

Major criteria:

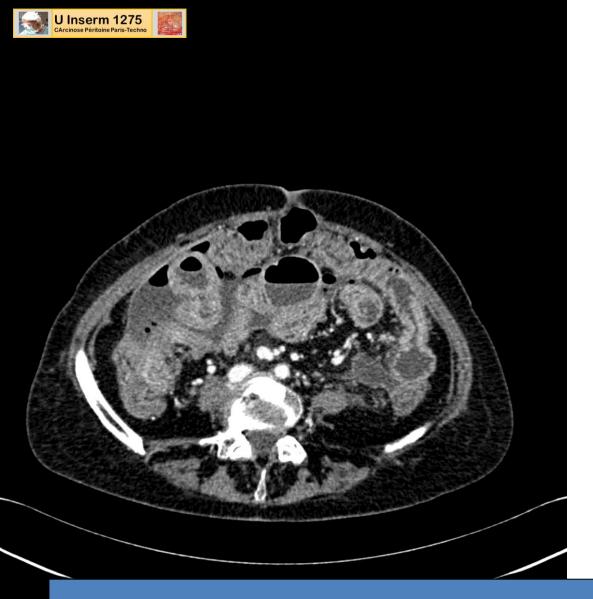
- Physiological age of 75 years
- Multiple liver metastases and bilobar
- OMS 2 or more (performance status)
- Serious medical history (neurological, renal failure, cirhossis)
- Clinical worsening under IV chemotherapy
- malnutrition
- Diffuse lung metastases



Lariboisière's exclusion criteria in case of colon peritoneal metastasis

minor criterion (indication need to be debated)

- Increased markers chemotherapy
- Obesity (BMI> 40)
- Extended scanner carcinomatosis or clinically significant
- ascites
- occlusion
- Para-aortic lymph node metastases

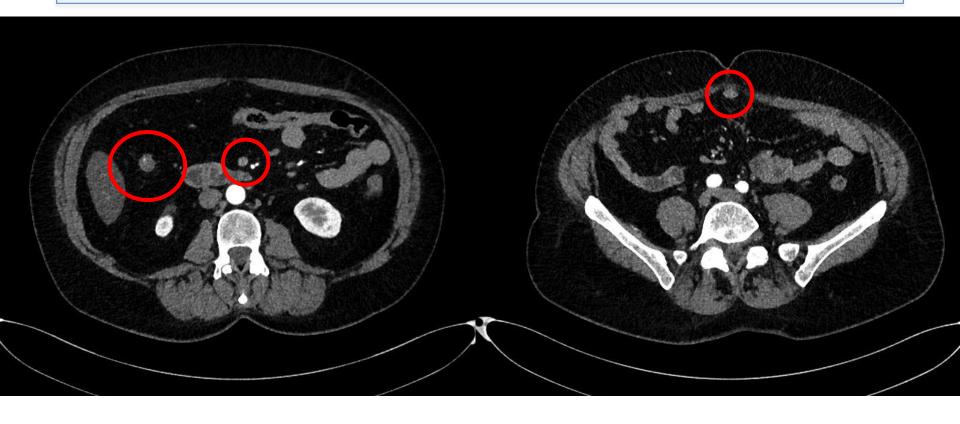


Not for extended peritoneal carcinomatosis



High selection and exhaustive evaluation

Limited peritoneal carcinomatosis





Peritoneal metastasis for gastric cancer

- In medical day care
- General status ++++
- Laparoscopic evaluation of peritoneal metastasis

1.00

• If PCI < 7

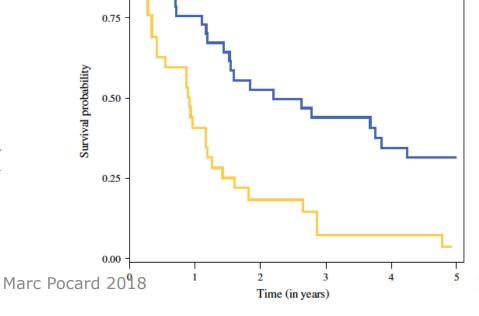
Discussion for HIPEC?

• If PCI > 7

Chemo and PIPAC?



Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is Cure a Possibility?



PCI<7 PCI>=7



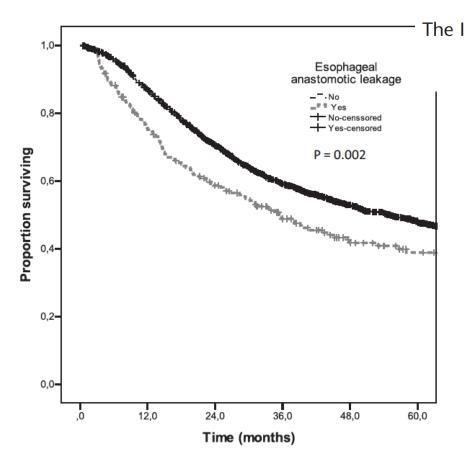
- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- But for peritoneal disease there is no margin So you can not perform a RO resection

Use intra peritoneal chemotherapy to perform a CC0 resection

- Select patient with limited metastatic disease : PCI
- Control the aggression of your surgery



Impact of anastomotic leakage on the long-term survival of patients undergoing curative resection for oesophagal cancer.



The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence After Surgical Resection for Esophageal Malignancy

(Ann Surg 2015;262:972–980)

Severe esophageal anastomotic leak (seal) was associated with a significant reduction in median overall (35,8 versus 54,8 months; p=0,002) and disease-free (34 vs 47,9 months; p=0,005) survivals. After adjustment of confounding factors, seal was associated with a 28% greater likelihood of death (HR = 1,28, 95% CI)

Sheraz Markar, MRCS,* Caroline Gronnier, PhD,†‡\$ Alain Duhamel, PhD,¶|| Jean-Yves Mabrut, PhD,**

Jean-Pierre Bail, MD,†† Nicolas Carrere, PhD,‡‡ Jérémie H. Lefevre, PhD,\$\$ Cécile Brigand, PhD,¶¶

Jean-Christophe Vaillant, MD,|||| Mustapha Adham, PhD,*** Simon Msika, PhD,†††

Nicolas Demartines, MD,‡‡‡ Issam El Nakadi, MD,\$\$\$ Bernard Meumier, MD,¶¶¶



Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vivo.

Matched groups of patients operated for colon cancer with and without anastomotic fistula or intra abdominal abscess: disease free survival is different and experiment with fluid from drainage ...

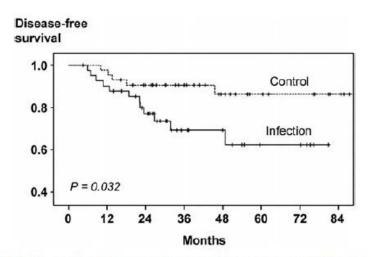


FIGURE. Kaplan-Meier analysis of disease-free survival in patients with or without peritoneal infection after surgery for colorectal cancer.

Postoperative peritoneal fluid from infected patients operated for colon cancer enhanced both

•cell migration and cell invasion capacities of human cancer cell lines (colon and breast cell lines)

With serum samples, these effects were only observed in

cell migration assays

Salvan S et al. Ann Surg 2014; 260:939–944



Intraoperative hypothermia increase complications

- Intraoperative hypothermia was reported as a factor affecting postoperative complication
 - Increase rate of surgical wound infection
 - Increase perioperative blood loss + blood transfusion rate
 - Prolonged hospitalization
 - Increase incidence of postoperative adverse myocardial events

Kurz A, et al. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. **1996** May 9;334(19):1209-15.

Frank SM, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial.

JAMA. **1997** Apr 9;277(14):1127-34.



Intraoperative hypothermia increase complications, during cytoreductive surgery for ovarian cancer

Table 3. Association Between Hypothermia and Individual Early Postoperative Complications

Outcome	Total (n=146)	Hypothermic (n=81)	Normothermic (n=65)	OR	Univariable 95% Cl	P
Death with 30 d	5 (3.6)	5 (6.2)	0 (0.0)	9.42	0.51-173.55	*
Infectious complication	18 (12.3)	14 (17.3)	4 (6.2)	3.19	1.08-11.71	.05
VTE event	17 (11.6)	14 (17.3)	3 (4.6)	4.32	1.33-19.37	.027
Cardiac event	7 (4.8)	6 (7.4)	1 (1.5)	5.12	0.84-97.90	.14
Bowel leak	5 (3.4)	4 (4.9)	1 (1.5)	3.32	0.48-65.87	.29
Readmission	6 (4.1)	5 (6.1)	1 (1.5)	4.21	0.66-81.73	.19
Reoperation	8 (5.5)	7 (8.6)	1 (1.5)	6.05	1.04-114.72	.10
Transfusion more than 2 units†	79 (54.1)	56 (69.1)	23 (35.4)	4.09	2.07-8.31	<.001

OR, odds ratio; CI, confidence interval; VTE, venous thromboembolic.

Data are n (%) unless otherwise specified.

VOL. 119, NO. 3, MARCH 2012

(Obstet Gynecol 2012;119:590-6)

Moslemi-Kebria et al Hypothermia and Perioperative Morbidity 593

Intraoperative Hypothermia During Cytoreductive Surgery for Ovarian Cancer and Perioperative Morbidity

^{*} Unable to estimate a P value as a result of the lack of deaths in the normothermic group.

^{*} Blood transfusion was not considered one of the early complications included in the combined primary end point.



Violent liver regeneration increase tumor progression

Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases ### Bys 2016; 103: 1521–1529

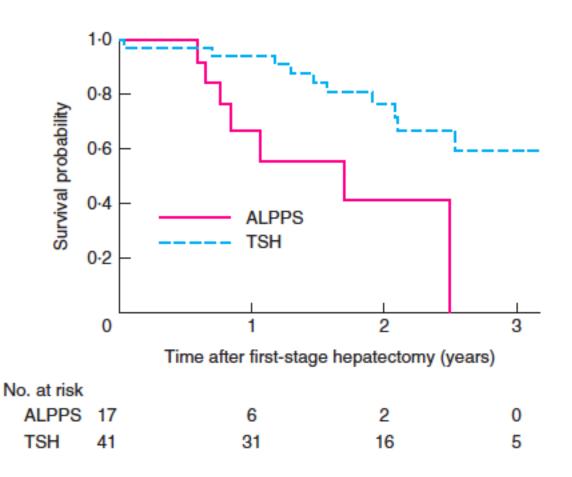
R. Adam^{1,2,4}, K. Imai^{1,2,5}, C. Castro Benitez^{1,2,4}, M.-A. Allard^{1,2,4}, E. Vibert^{1,3,4}, A. Sa Cunha^{1,2,4}, D. Cherqui^{1,3,4}, H. Baba⁵ and D. Castaing^{1,3,4}

Associating liver partition and portal vein ligation for staged hepatectomy is proposed in case of bi lobular colorectal liver metastases and compared with a two-stage hepatectomy / Liver regeneration is quick and violent that second surgical procedure is proposed after 7 days/ in a two stage hepatectomy the liver regeneration take 2 months and is associated with a post operative chemotherapy

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Violent liver regeneration increase tumor progression



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Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv



Controversy

Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases

Systematic review of all literature and meta-analysis of observational studies

E.M.V. de Cuba ^{a,1}, R. Kwakman ^{a,1,5}, D.L. Knol ^{b,2}, H.J. Bonjer ^{a,3}, G.A. Meijer ^{c,4}, E.A. te Velde ^{a,*}

Results: After screening and full-text assessment of 39 papers, six articles were included containing data on combined PM and CRLM in patients treated with curative resection of both sites and HIPEC or early postoperative intraperitoneal chemotherapy (EPIC). Three articles provided enough statistical information for meta-analysis. Pooled hazard ratio (HR) was extracted from survival curves and was 1.24 (CI 0.96–1.60). A comparison was made with patients presenting with isolated PM undergoing CRS and HIPEC and with patients with disseminated disease undergoing (modern) systemic chemotherapy.

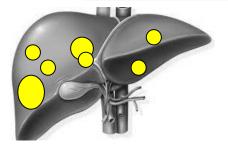
^a Dept. of Surgical Oncology, VU University Medical Center Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

b Dept. of Epidemiology and Biostatistics, VU University Medical Center Amsterdam, De Boelelaan 1118, 1081 HZ Amsterdam, The Netherlands

^c Dept. of Pathology, VU University Medical Center Amsterdam, De Boelelaan 1118, 1081 HZ Amsterdam, The Netherlands



Strategy with a curative intent

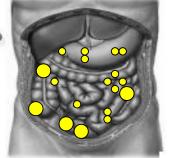




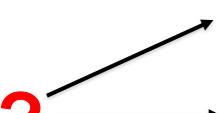
Surgery + perioperative chemotehrapy

Nordlinger, Lancet 2008





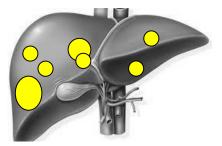
Cytoreduction + HIPEC + perioerative chemotherapy

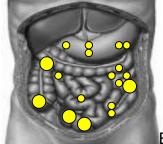


Elias, Cancer 2001

Liver and peritoneum

Liver first





Peritoneum first

Elias BJS 2003, Kianmanesh Ann Surg 2007, Izzo JSurg Oncol 2009



CHEMO

1 option





HIPEC

LIVER

CHEMO



Positive aspect:

No problem with secondary adhesion

Only one surgery

Carcinomatosis is treated upfront

Negative aspect:

High Morbidity rates in our practice

Post operative chemo is not performed because of patient general status or complication



2 options





CHEMO

HIPEC

CHEMO

LIVER

CHEMO

Positive aspect:

Carcinological impact first on the location affected by the worst prognosis: peritoneum

Strategy start with the treatment having the highest morbidity afterwards liver surgery must be secure

Negative aspect:

Adhesions around the liver induce bleeding

If tumour progression no liver surgery would be performed



- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- Use intra peritoneal chemotherapy
- Select patient with limited metastatic disease : PCI
- Control the aggression of your surgery
 - Temperature
 - Anastomotic fistula risk (stomia)
 - Use radiofrequency more than extended liver resection



The big rules

- HIPEC is standardized as other surgical cancer treatment
- organized and learning curve have been evaluated and equivalent in France or in Italy or UK
 - 30 cases to be safe
 - 140 cases to control results and mortality



Learning curve ...





Cytoreductive surgery with a hyperthermic intraperment chemotherapy program: Safe after 40 cases, but only controlled after 140 cases

T. Voron a,b, C. Eveno a,b,*, I. Jouvin a,b, A. Beaugerie a,b, R. Lo Dico a,b, S. Dagois b,c, P. Soyer b,d, M. Pocard a,b



Figure 1. Risk-adjusted sequential probability ratio test (RA-SPRT) chart for incomplete cytoreduction (A) and for grade III—IV morbidity (B). The x axis represents operation number. The y axis represents a cumulative log-likelihood ratio value (blue line). The h0 line represents the lower boundary of control limit and the h1 line represents the upper boundary of control limit.



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- R0 resection >>> R1 or R2 resection
- Perform Complete cytoreductive surgery
- Use intra peritoneal chemotherapy
- Select patient with limited metastatic disease : PCI
- Control the aggression of your surgery
- Create a team and control all actors involved in the process to decrease the learning curve
- Prepare the future ?



Surgical trauma can increase the metastatic process?

No touch technique is a surgical oncologic rule, but whatever the effort tissues have to be cut or sectioned resulting probably in a cells liberation because of lymphatic section. This situation was tested in a paper describing cell detection on peritoneum fluid during gastrectomy for gastric cancer.

More than half of the cases were no cell could be identified at the beginning of the surgery, cells are detected at the end of the gastrectomy. Therese cells have been studied and are able to growth on culture and to create a tumor if injected on nude mice.

Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Takebayashi K, et al. Ann Surg Oncol. 2014;21:1991-7.



Surgical trauma can increase the metastatic process?

Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Takebayashi K, et al. Ann Surg Oncol. 2014;21:1991-7.

However, cells detection on peritoneal fluid did not implicated that all patient presented a carcinomatosis during the follow up.

To create a carcinomatosis, peritoneum barrier had to be altered and local condition to be favourable.

But on the study, the 24 patients with viable cancer cells in the peritoneal cavity after gastrectomy showed higher peritoneal recurrence rate than those without them (p=0.033), 45% (n=11/24) versus 9% (n=1/33).



Decrease risk of implantation of cells

- Clinical situations with an increase risk
 - After a gastrectomy
 - After ovarian cancer surgery
 - After surgery for a colon T4 lesion

Ann Surg Oncol (2013) 20:183–192 DOI 10.1245/s10434-012-2473-5



ORIGINAL ARTICLE - COLORECTAL CANCER

Definition of Patients Presenting a High Risk of Developing Peritoneal Carcinomatosis After Curative Surgery for Colorectal Cancer: A Systematic Review

Charles Honoré, MD, Diane Goéré, MD, Amine Souadka, MD, Frédéric Dumont, MD, and Dominique Elias, MD, PhD





Prophylaxis for peritoneum

Publication of the results



Available online at www.sciencedirect.com

ScienceDirect

EJSO 43 (2017) 1088-1094



www.ejso.com

Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy



^a Department of Oncologic & Digestive Surgery, Hospital Lariboisière — AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France

b Université Paris Diderot, Sorbonne Paris Cité, CART, Carcinomatosis Angiogenesis Translational Research, INSERM U965, F-74575 Paris, France

^c Department of Anatomopathology, Hôpital Lariboisière — AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France





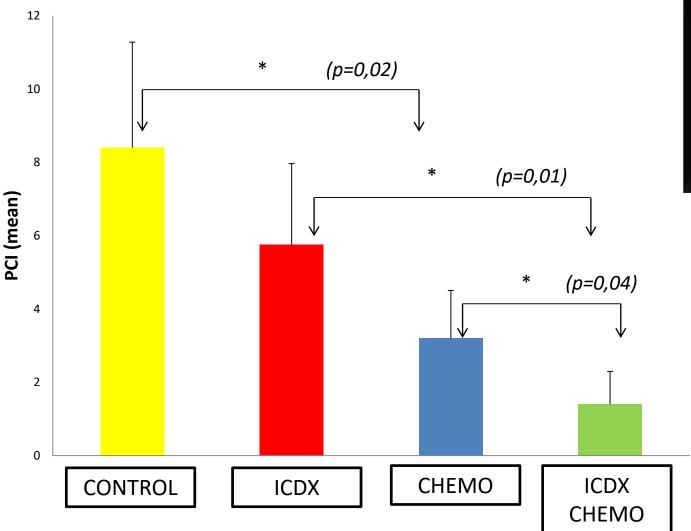
Is it possible to use a solution to prevent or decrease carcinomatosis risk?

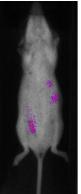
- Solution at disposition for the surgeon at the operative room
 - > Antiadhesive solution currently used used to reduce postoperative adhesions
 - ICODEXTRIN :
- Solution remains in the peritoneum 3 or 5 days not more
- Solution active for different cancer wathever the primary: colon ovarian, gastric, etc: Oxalipaltin or 5FU used as a contact chemotherapy
- > Solution able to diffuse in the all cavity and able to located finaly were carcinomatossi risk is high (subphrenic, pelvis, etc)

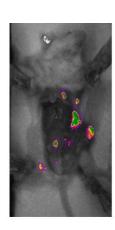




Prophylaxis for peritoneum









We need to progress

Small bowell analysis: the black box



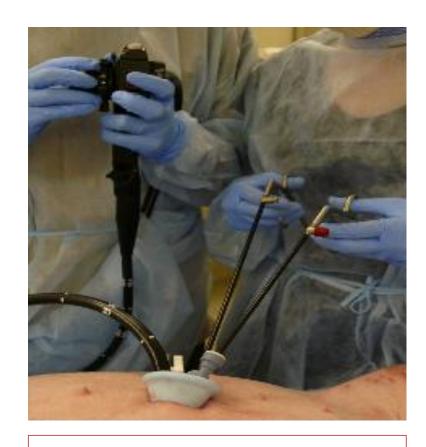
Nothing wrong on the CT on teh small bowel



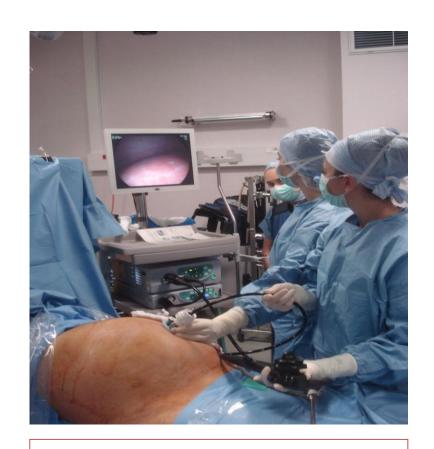
To many lesion to be resected at laparotomy



A new concept Peritoneal endoscopy



Using animal models



At the operative room





Endoscope Flexible

Advantages:

No adhesion disssection – turn around

Only one trocar ...

No tumor deposit on trocar



Single Port





Single-incision flexible endoscopy (SIFE) for detection and staging of peritoneal carcinomatosis

Haythem Najah^{1,2} · Réa Lo Dico^{1,2} · Marion Grienay³ · Anthony Dohan^{2,4} · Xavier Dray⁵ · Marc Pocard^{1,2}

Surg Endosc (2016) 30:3808–3815

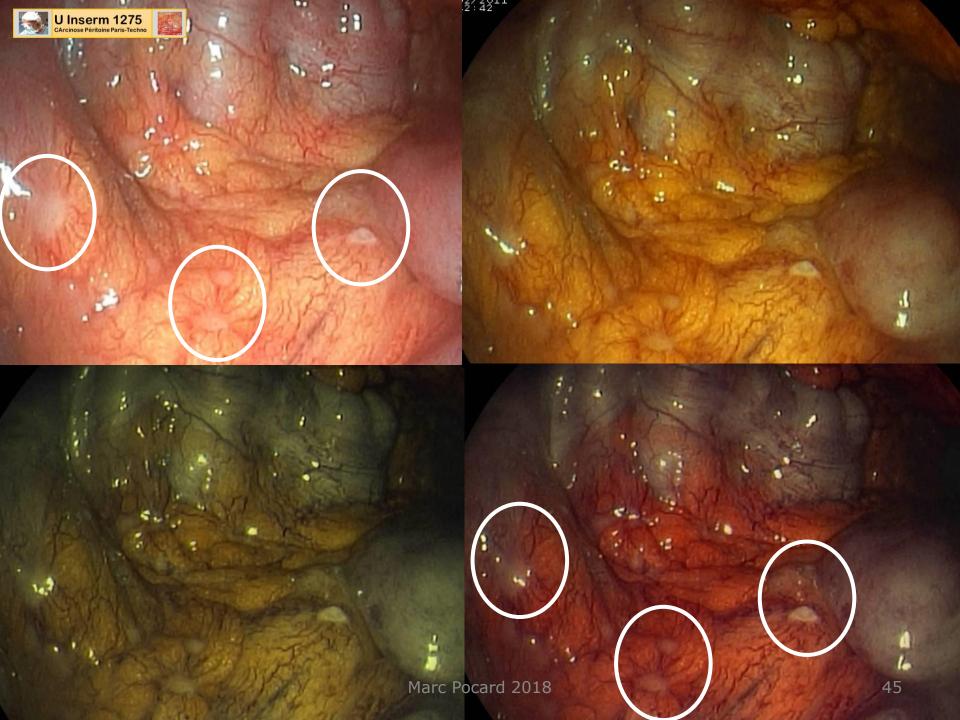
Table 2 Access rates to the different regions of peritoneal carcinomatosis by single-incision rigid endoscopy (SIRE) and single-incision flexible

endoscopy (SIFE)

	R0	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	Total
SIRE			31/47											507/611
	97.9 %	61.7 %	66 %	59.6 %	91.5 %	87.2 %	61.7 %	89.4 %	93.6 %	87.2 %	100 %	91.5 %	91.5 %	83 %
SIFE	46/47	41/47	41/47	40/47	45/47	42/47	38/47	43/47	45/47	43/47	47/47	43/47	43/47	557/611
	97.9 %	87.2 %	87.2 %	85.1 %	95.7 %	89.4 %	80.9 %	91.5 %	95.7 %	91.5 %	100 %	91.5 %	91.5 %	91.2 %
P^{a}	NA ^b	0.001	0.004	0.001	0.48	1	0.008	1	1	0.48	NA^b	NA^b	NA^b	<10 ⁻¹¹

a McNemar's Chi-squared test

b Not available—perfect concordance between the two variables

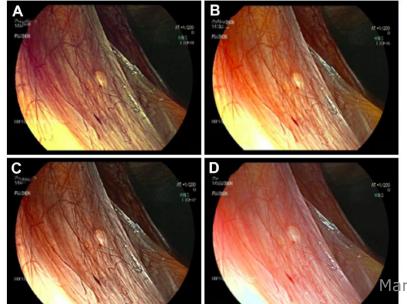




A feasibility study of the use of computed virtual chromoendoscopy for laparoscopic evaluation of peritoneal metastases

Haythem Najah^{1,2} · Réa Lo Dico^{1,2} · Anthony Dohan^{2,3} · Lucy Marry⁴ · Clarisse Eveno^{1,2} · Marc Pocard^{1,2}

Surg Endosc (2017) 31:743-751



	1st Position (%)	2nd Position (%)	3rd Position (%)	4th Position (%)
(A)				
WLE	12.8	14.4	21.3	51.5
Channel 2	46.9	28.3	16.8	8.0
Channel 6	22.1	23.7	35.7	18.4
Channel 9	18.1	33.9	26.1	21.9
(B)				
WLE	9.6	14.4	21.6	54.4
Channel 2	46.4	24.8	19.2	9.6
Channel 6	24.0	21.6	33.6	20.8
Channel 9	20.0	39.2	25.6	15.2

Overall results are shown in Table 2A. Table 2B shows the results of the senior surgeons assessment. Mc Nemar test p < 0.0001



Photodynamic Diagnosis With 5-Aminolevulinic Acid for Intraoperative Detection of Peritoneal Metastases of Ovarian Cancer: A Feasibility and Dose Finding Study

Peter Hillemanns, мр,^{1,2*} Pauline Wimberger, мр,^{1,3} Jessica Reif, мр,^{1,4} Herbert Stepp, рьр,⁵ and Rüdiger Klapdor, мр²

Lasers in Surgery and Medicine

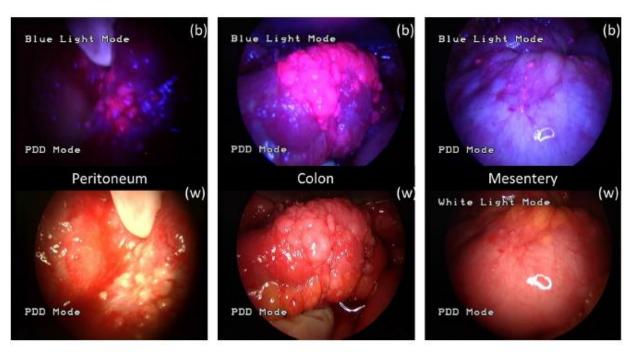


Fig. 1. Specific fluorescence of metastatic tissue. Intraoperative images of peritoneal metastases under blue (b) and white light (w). Marc Pocard 2018



Fluorescence Imaging After Indocyanine Green Injection for Detection of Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis From Colorectal Cancer

A Pilot Study

Gabriel Liberale, MD,* Sophie Vankerckhove, BSc,† Maria Gomez Caldon, MD,‡ Bissan Ahmed, PhD,† Michel Moreau, MD,§ Issam El Nakadi, MD,* Denis Larsimont, PhD,‡ Vincent Donckier, PhD,* and Pierre Bourgeois, PhD†, Group R&D for the Clinical Application of Fluorescence Imaging of the Jules Bordet's Institute

(Ann Surg 2016;264:1110-1115)

(P=0.0099). In 4 of 14 patients (29%), the surgery was modified by intraoperative ICG-FI, which detected additional PM not found using visualization and palpation.



Fluorescence Ima Detection of Peri Cytoreductive

Gabriel Liberale, MD,* Sophi Michel Moreau, MD,§ Issa and Pierre Bourgeois, Ph

(P=0.0099). In 4 of 1 operative ICG-FI, which and palpation.

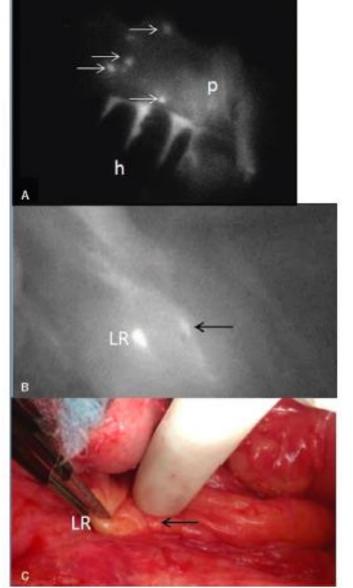


FIGURE 3. Fluorescence imaging of nodules that were undetected under white light or by palpation A. Identification of a nodule by indocyanine green fluorescence imaging in another patient B followed by attentive surgical exploration, orientated by FI findings, that allowed detection of a small palpable nodule, visible under white light C.

Green Injection for ients Undergoing Carcinomatosis

on, MD,‡ Bissan Ahmed, PhD,†
),‡ Vincent Donckier, PhD,*
on of Fluorescence Imaging

16;264:1110-1115)

ng visualization



Tomorrow for peritoneal metastasis?

- Early diagnosis using light and biology
 - FICE flexible endoscope
- Another treatment than HIPEC if CC0 is not possible (Mitomycin)
 - Prolonged intraperitoneal chemotherapy
 - PIPAC and after come back to the surgery
- A multimodality treatment strategy as for liver colon cancer metastasis:
 - FOLFIRINOX Beva or Anti-EGFR preoperatively
 - REdo HIPEC if recur
- Control the metastatic process early
 - After a gastrectomy
 - After ovarian cancer surgery
 - After colonic resection for a T4 lesion



12ème Journée Francophone des maladies péritonéales primitives et métastatiques – BIG RENAPE







National University Hospital, Singapore

HIGHLIGHTS

- · Pathophysiology of Pleural & Peritoneal Diseases
- Latest Treatment: HIPEC, PIPAC, Intraperitoneal Chemotherapy, Systemic Chemotherapy and Immunotherapy
- · Organ-specific Interactive Sessions
- · Quality of Life Studies
- · Basic and Translational Science
- Free Paper Presentations
- Pre-congress Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) Workshop

ISSPP President

Professor Marc Pocard, France

Congress Presidents

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