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ORIGINAL ARTICLE

Mapping the location of peritoneal metastases using the peritoneal cancer index and the correlation with overall survival: a retrospective study

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Summary

Purpose: *Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising treatment for patients with peritoneal carcinomatosis (PC). Our objective was to identify new prognostic factors within the Peritoneal Cancer Index (PCI) score in PC patients.*

Methods: *140 patients (60 ovarian, 45 colon, 14 gastric, 10 pseudomyxoma peritonei, 5 mesothelioma, 6 sarcoma) with PC treated with CRS+HIPEC from 2007 to December 2013 were retrospectively included. Tumor extent and location were assessed by the PCI and residual disease was recorded using the Completeness of Cytoreduction (CC) score. All clinical data were computed in univariate and multivariate analysis using survival as primary endpoint.*

Results: *The PCI remains the most important factor concerning the long-term survival. Involved areas 4, 5 and 8 are more favorable in survival vs areas 9, 10 and 11, which predict a significantly worse outcome (p<0.002). Prognosis varies not only depending on how many peritoneal areas are involved but also on the location of the primary tumor.*

Conclusion: *We demonstrated that the involvement of different areas in the PCI system has a significant impact on the final prognosis and survival.*

Key words: *cytoreductive surgery, HIPEC, peritoneal cancer index, survival*

Introduction

The therapeutic approach to peritoneal metastases requires the presence of a test suitable to describe the extent of disease and to identify, accordingly, patients who will be the most appropriate surgical candidates. Moreover, the presence of a universal staging and scoring system enables the multidisciplinary team to predict more precisely the management plan, determining which patients would benefit more from an aggressive treatment, taking into account previous experience from the literature.

Several attempts have been made towards the formulation of a commonly used scoring system for peritoneal metastases, such as the Japanese Society for Gastric Cancer Carcinomatosis Staging (JRSGS) [1], the Lyon Staging System [2], or the Dutch Simplified Peritoneal Cancer Index (SPCI) [3]. However, the most widely used index is the PCI, as described by Jacquet and Sugarbaker in 1996 [4]. The PCI is a detailed clinical integration of tumor distribution and size, in which tumor volume in 13 different abdominopelvic regions is added up to form a score ranging from 0 to 39. Not only does the PCI serve as an assess-

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Table 1. Patient and disease characteristics

Patients, N	*140*	
Mean age, years	*58.3*	
Characteristics	*N*	*%*
Origin of peritoneal carcinomatosis		
Ovary	60	42.8
Colon	45	32.1
Stomach	14	10
Pseudomyxoma peritonei	10	7.1
Mesothelioma peritonei	5	3.6
Sarcoma	6	4.3
Peritoneal carcinomatosis index (PCI)		
PCI <15	75	53.6
PCI ≥15	65	46.4
Completeness of cytoreduction		
CC-0	91	65
CC-1	49	35

ment tool of peritoneal metastases, but it has also been used as a prognostic indicator for disease outcome. However, it does not take into account tumor biology. Also, it cannot be directly correlated with resectability in that a low PCI score may be associated with unresectable disease at crucial anatomic sites such as the common bile duct.

The purpose of the present study was to present and analyse the different patterns of dissemination of peritoneal metastases as assessed by the PCI for 5 different intraabdominal malignancies and to identify variations in prognosis depending on disease location.

Methods

Over a 7-year period (2007-2013), our team has treated 140 PC patients with CRS & HIPEC. Tumor extent and location were assessed with PCI (Figure 1) [5]. PCI combines size and distribution parameters to determine a numerical score. The lesion size (LS) is used to quantify the size of peritoneal nodules. LS-0 indicates no tumor seen, LS-1 indicates tumor implants up to 0.5 cm, LS-2 indicates tumor implants between 0.5 and 5 cm, and LS-3 indicates tumor implants larger than 5 cm or a layering of cancer. The distribution of tumor is determined within the 13 abdominopelvic regions. Two transverse planes and two sagittal planes are used to divide the abdomen into 9 abdominopelvic regions (AR-0 through AR-8). These lines define 9 regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1, defining the space beneath the right hemidiaphragm. The small bowel is assessed as an additional 4 abdominopelvic regions designated AR-9 through AR-12 and includes the upper jejunum, lower jejunum, upper ileum and lower ileum, respectively. The summation of the lesion size score in each of the 13 abdominopelvic regions is the PCI ranging from 0 to 39.

All patients were operated on by the same surgical team. CRS is performed via a xiphoid-pubis incision and with the use of a self-retaining retractor to achieve maximal exposure of the peritoneal cavity. At the beginning of the operation sharp adhesiolysis is performed, followed by selective peritonectomies of all the areas of the involved peritoneum. Greater and lesser omentectomy are routinely performed, as well as resection of the falciform ligament. Upper abdomen cytoreduction may often involve splenectomy, distal pancreatectomy and dissection of the perihepatic spaces and the hepatoduodenal ligament. As for the gastrointestinal tract, small lesions on the stomach, small intestine and colon are cauterized, while larger lesions require resection. Pelvic disease may require the formation of a loop ileostomy, rectal resection, as well as bilateral salpingo-oophorectomy, with hysterectomy not routinely performed. The study included patients on whom complete CC (CC-0 and CC-1) was performed.

All patients were followed on a regular basis according to a predetermined plan. Patients were seen and a physical examination performed on a 3-monthly basis. If a tumor marker had been determined as relevant in the preoperative workup, this tumor marker was obtained on a 3-monthly basis. Radiologic studies included CT scan of chest, abdomen, and pelvis on a 6-monthly basis. If the CT was difficult to interpret or there were discordant findings between tumor markers and CT, a MRI of abdomen and pelvis or positron emission tomography-CT (PET/CT) scan was obtained. All data were prospectively recorded.

Statistics

All clinical data were computed in univariate and

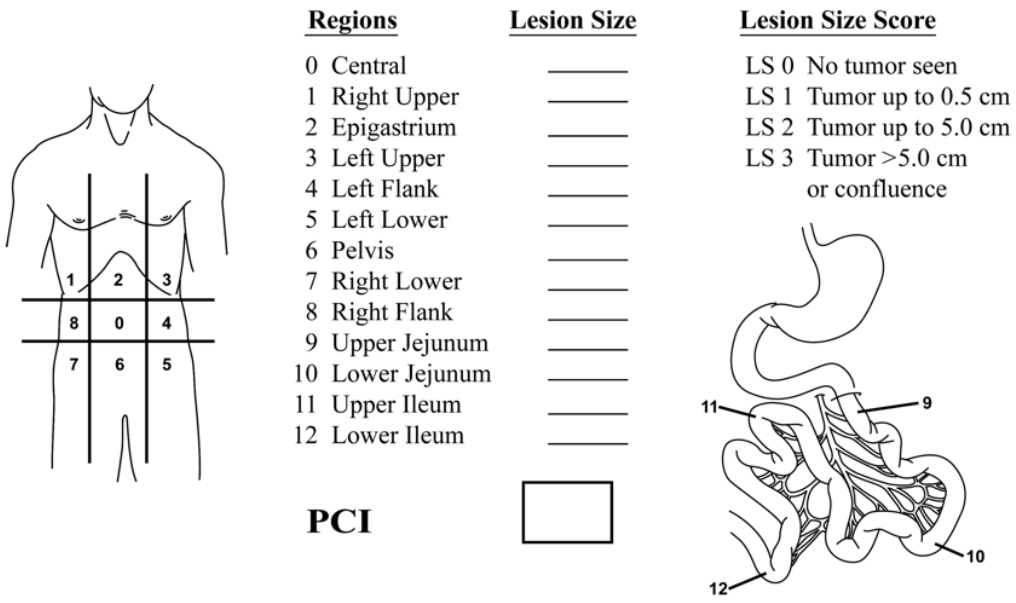

Figure 1. Ki-67 immunostaining in parathyroid carcinoma. Numerous Ki-67 positive cells are evident (H&E x20).

multivariate analysis using survival as a primary end point. Lesion size 2 and 3 were included in the analysis. Presence or absence of disease at specific regions was compared univariately in terms of survival. Patient characteristics and outcome were analysed by descriptive statistics. Normally distributed variables were compared using the Student's t-test as appropriate, and nonparametric tests were used when variables were not normally distributed. Survival was measured with the Kaplan-Meier method and log rank test. A p-value <0.05 was considered significant in all analyses. All statistical analyses were conducted using the SPSS software (version 17.0) and Microsoft Office Excel.

Results

The origins of peritoneal metastases in our patients were (Table 1): n=60 of ovarian origin, n=45 of colorectal origin, n=14 of gastric origin, n=10 with pseudomyxoma peritonei, n=5 with mesothelioma and n=6 with sarcoma.

Analysis of all anatomic sites together

Patients with a PCI lower than 15 had a significantly prolonged overall survival vs those with a PCI greater than 15 (16.9 months vs 5.8 months, p<0.05).

Involvement of areas 4, 5 and 8 was associated with a better outcome in terms of survival vs the areas 9, 10 and 11, the involvement of which predicted a worse outcome.

Analysis of all anatomic sites individually

When studied separately per tumor origin, overall survival had significant differences depending on the lesion location. Specifically (Table 2):

- for gastric cancer, favorable areas were 4, 5 and 8 (median overall survival/mOS= 11.8 months) and unfavorable areas were 3, 10 and 11 (mOS = 6.3 months) (p<0.02)
- for colon cancer, favorable areas were 2, 5 and 8 (mOS = 29.6 months) and unfavorable areas were 1, 9 and 11 (mOS = 12.4 m) (p<0.003)
- for ovarian cancer, favorable areas were 6, 5 and 12 (mOS = 32.4 months) and unfavorable areas were 9, 10 and 11 (mOS = 18.2 months) (p<0.05)
- for pseudomyxoma peritonei, favorable areas were 0, 4 and 8 (mOS = 41.3 months) and unfavorable areas were 3, 9 and 10 (mOS = 26.4 months) (p<0.03)
- for peritoneal mesothelioma, favorable areas were 2, 4 and 5 (mOS = 27.2 months) and unfavorable areas were 9, 11 and 12 (mOS = 12.8 months) (p<0.001)

A summary of the favorable PCI regions is shown in Figure 2.

Table 2. Overall survival depending on tumor location and peritoneal area involvement.

	Favorable areas	*OS (months)*	*Unfavorable areas*	*OS (months)*	*p value*
Stomach	4,5,8	11.8	3,10,11	6.3	<0.02
Colon	2,5,8	29.6	1,9,11	12.4	<0.003
Ovary	6,5,12	32.4	9,10,11	18.2	<0.05
Pseudomyxoma	0,4,8	41.3	3,9,10	26.4	<0.03
Mesothelioma	2,4,5	27.2	9,11,12	12.8	<0.001

OS: overall survival

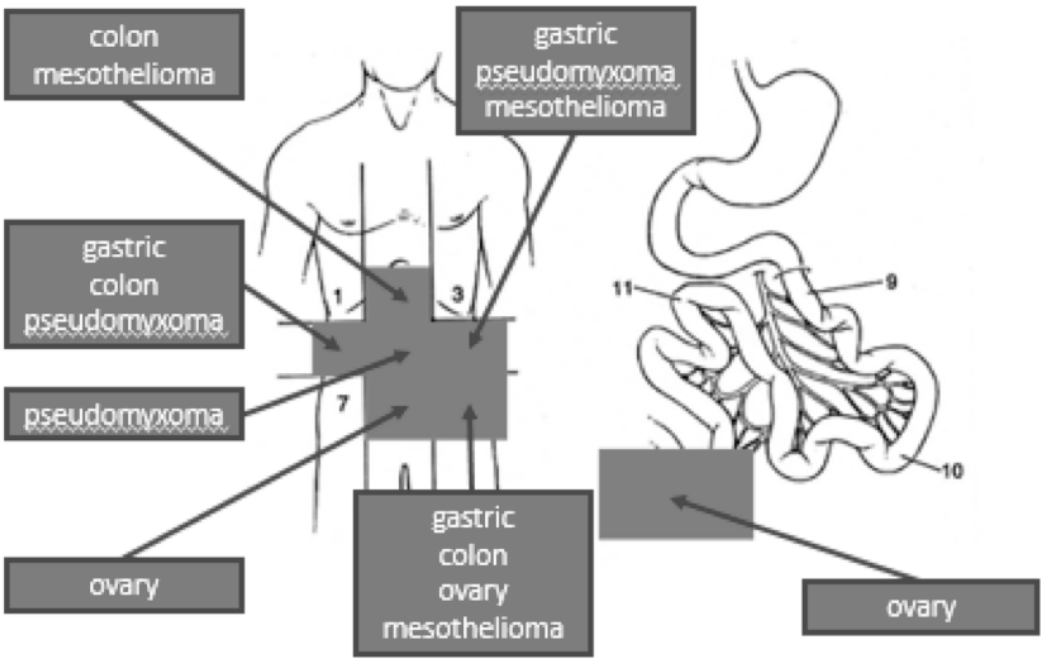

Figure 2. Favorable locations.

- Area 0 was favorable for pseudomyxoma peritonei.
- Area 2 was favorable for colon cancer and peritoneal mesothelioma.
- Area 4 was favorable for gastric cancer, pseudomyxoma peritonei, and peritoneal mesothelioma.
- Area 5 was favorable for gastric cancer, colon cancer, ovarian cancer, and peritoneal mesothelioma.
- Area 6 was favorable for ovarian cancer.
- Area 8 was favorable for gastric cancer, colon cancer, and pseudomyxoma peritonei.
- Area 12 was favorable for ovarian cancer.

A summary of unfavorable PCI regions is shown in Figure 3.

- Area 1 was unfavorable for colon cancer.
- Area 3 was unfavorable for gastric cancer and pseudomyxoma peritonei.
- Area 9 was unfavorable for colon cancer, ovarian cancer, pseudomyxoma peritonei, and peritoneal mesothelioma.
- Area 10 was unfavorable for gastric cancer, ovarian cancer, and pseudomyxoma peritonei.
- Area 11 was unfavorable for gastric cancer, colon cancer, ovarian cancer, and peritoneal mesothelioma.
- Area 12 was unfavorable for peritoneal mesothelioma.

Discussion

Revised hypothesis regarding peritoneal metastases

Peritoneal metastases result from the spread and implantation of cancer cells within the peritoneal cavity resulting in malignant tissue depos-

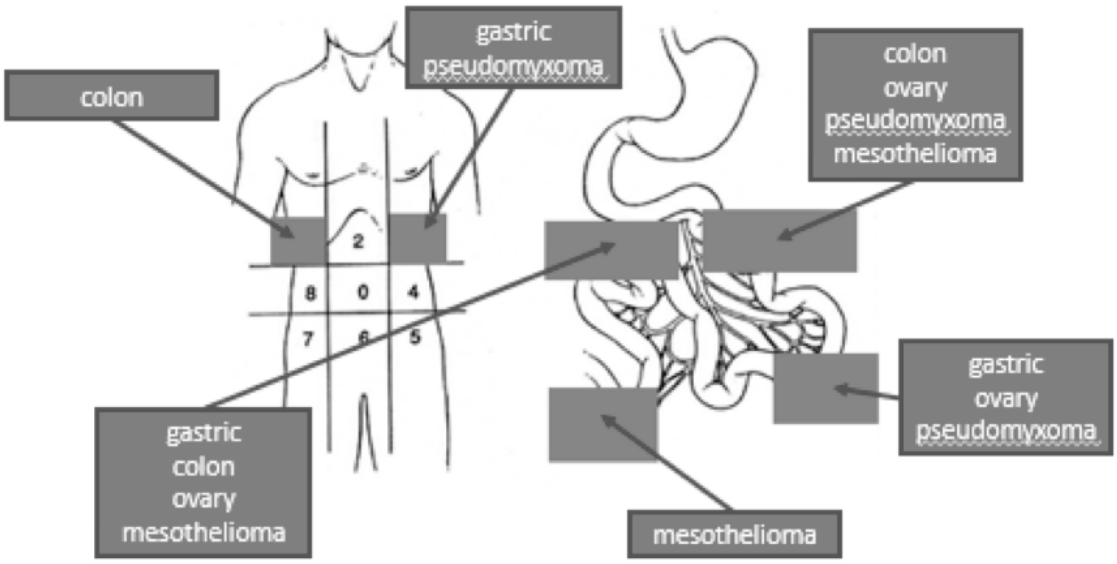

Figure 3. Unfavorable locations.

its involving both the parietal peritoneum and the visceral peritoneum lining the abdominal and pelvic organs. It is a common event that develops in the natural history of many diseases that have an origin within the abdomen and pelvis and represents a major unsolved problem encountered in cancer management. In the past, peritoneal tumor dissemination arising from colorectal cancer, appendiceal cancer, gastric cancer, gynecologic malignancies or peritoneal mesothelioma has been assumed as a sign of advanced tumor stage or disease recurrence, and was associated with the presence of systemic disease. Newer concepts of peritoneal metastases for patients with isolated peritoneal metastases of gastrointestinal cancer, ovarian cancer and primary peritoneal malignancies have emerged based on the revised hypothesis that peritoneal metastases may be a local-regional disease. Therefore, it warrants a local-regional therapeutic approach. These new treatment protocols are based on a combination of CRS and perioperative chemotherapy.

Distribution of peritoneal metastases

A study on intraperitoneal tumor dissemination was published by Carmignani et al. [6], reporting that the distribution of cancer deposits in the peritoneal cavity is not a random event but follows specific patterns determined by intraperitoneal fluid hemodynamics, intestinal peristalsis, and gravity. The presence of mucinous component was associated with a wider distribution but relatively sparing structures active in peristalsis. Organs such as the omentum and omental appendages (which have phagocytosis and peritoneal fluid resorption) had a relatively high volume and incidence of implants.

Intraperitoneal dissemination is a multistep process, implicating several molecular mechanisms, such as the detachment from serosa (E-cadherin, S100A4), adhesion to mesothelial cells (CD-44), contraction of mesothelial cells (CD44, CEA, cytokines - interleukins, EGF, HGF, VEGF-C, adhesion molecules - integrins, CD44), invasion (motility factors, matrix metalloproteinases, urokinase), vascular neoangiogenesis (VEGF, VEGF-C, bFGF), lymphangiogenesis, lymphatic dilatation (VEGF-C, VEGF-D), exposure of lymphatic stomata or lymphatic orifiifices and invasion through lymphatic orifices on the milky spots [7-12]. Peritoneal free neoplastic cells attach to the mesothelial cells, invade into the submesothelial tissue, proliferate and grow into established metastases with neoangiogenesis.

The intraperitoneal progression of ovarian cancer has been widely studied, both in vitro and in vivo. Epithelial ovarian cancer has a distinctive preference for intraperitoneal dissemination vs the hematogenous or lymphatic routes of spread. The neoplastic cells have both invasive and adhesive properties that determine the patterns of dis-

semination. Cancer cells may invade beneath the peritoneal mesothelial layer or form tumor colonies adhering to its surface depending on their molecular properties [13].

The quantitative assessments to measure for peritoneal metastases have been compared in a study by Yonemura et al. [14]. They suggested peritoneal metastases with a limited extent to include P1 and P2 per the Japanese classification [1], stage I and II per the Lyon classification [2] with a PCI less than 13. Peritoneal metastases with large extent included P3, stage III and IV, and correspond with a PCI of 13 or greater. They suggested that all three classifications correlate with prognosis.

The PCI is the most commonly used staging system for PC, and also an independent prognostic indicator for long-term outcomes. The formulation of a suitable tool to assess the extent and location of tumor dissemination in the peritoneal cavity is useful in the patient selection process, with a purpose to identify which patients will benefit more from CRS and HIPEC and to avoid aggressive therapeutic approaches in patients unlikely to benefit from CRS plus HIPEC.

Perhaps the most reliable information gathered from the use of the PCI has been its ability to predict outcome based on the total score. Early on, Sugarbaker and Jablonski showed that it had a profound influence on the outcome of patients with appendiceal and colorectal malignancy that underwent standardized CRS combined with perioperative intraperitoneal chemotherapy [15]. In the randomized trial by Verwaal and Zoetmulder in patients with colorectal peritoneal metastases and involvement of 6 or more abdominopelvic regions were associated with a significantly dismal prognosis [3]. The French multi-institutional study confirmed the importance of PCI in the prognosis of colorectal peritoneal metastases. In the global survival of 496 patients with peritoneal metastases from colorectal cancer, there was a 50% survival with a PCI of 1-6, 25% survival with a PCI of 7-12 and 13-19, and only 10% survival at 5 years with a PCI greater than 19 [16]. The same publication confirmed the importance of PCI in gastric cancer. Patients with a PCI of 1-6 had a 5-year survival of 35%. Patients with a PCI of 7-12 had a 15% 5-year survival. Patients with a PCI greater than 13 did not, in any instance, survive 5 years. Tentes et al. have shown the accuracy of PCI in assessing prognosis in ovarian cancer patients treated with CRS and HIPEC [17].

The current manuscript shows that not only the total PCI score but also the individual abdominal and pelvic regions may have very definite prognostic implications. The pattern of tumor dissemination and the involvement of specific abdominopelvic regions may be used as a prognostic indicator of survival. The area most frequently associated with poor prognosis is the abdominopelvic region 9 which indicates cancer involvement of the upper jejunum. As shown in Figure 3, the abdominopelvic regions 9, 10, and 11 were most frequently associated with decreased survival. This corresponds with the important clinical observation that the most frequent cause for incomplete cytoreduction is peritoneal metastases on the small bowel and its mesentery.

Favorable locations may correspond to areas of the abdominal and pelvic anatomy which are most amenable to complete CRS. This would be the greater omentum (abdominopelvic region 0) in patients with pseudomyxoma peritonei, ovarian cancer within abdominopelvic region 6 (pelvis), and ovarian malignancy in abdominopelvic region 12 (terminal ileum). These areas can be completely removed as part of a cytoreductive surgical procedure. The cause for other abdominopelvic regions to have a favorable survival is less clear. With colorectal cancer, area 1 (right upper quadrant) has been associated with poor prognosis because disease at this site usually involves the diaphragm (full thickness) and predicts a difficult cytoreduction elsewhere within the abdomen and pelvis.

Our data regarding the usefulness of specific PCI regions to assess prognosis supports the recent publication by Benizri and colleagues [5]. They identified as prognostic factors for survival from colorectal carcinomatosis PCI < 9 and involvement of areas 4, 5, 7, 8, 10, and 11. Moreover, involvement of area 10 was a significant prognostic factor in multivariate analysis. A recent study by Elias et al. [18] in carcinomatosis of colorectal origin identified involvement of area 12 (lower ileum) and PCI ≥15 as independent prognostic factors; PCI ≥15 may be considered as a relative contraindication for treatment of peritoneal metastases of colorectal origin with CRS & HIPEC.

These data may be of value in determining the criteria used to interpret a preoperative CT scan for its prognostic implications. Knowing that the small bowel regions 9, 10, and 11 are associated with poor prognosis, allows these regions, when involved on CT scan, to be interpreted as a "concerning radiologic feature" [19]. Also, involvement of the abdominopelvic region 1 in colorectal peritoneal metastases may indicate an unlikely complete cytoreduction and be used as a "concerning radiologic feature". It

is more likely that these specific radiologic findings, rather than the global CT-PCI, will be found to be of prognostic significance for the radiologic prediction of complete cytoreduction. It is clear that the peritoneal dissemination of metastatic disease is not a random process but controlled by physical factors and molecular structures of the cancer cell and on the peritoneal surfaces. Understanding these factors will greatly contribute to our knowledgeable management of peritoneal metastases.

Conclusion

The PCI remains the most effective staging system in peritoneal carcinomatosis. However, more research is required in order to formulate a modified, weighed PCI system, in which the origin of the peritoneal carcinomatosis and the dissemination pattern will be used to estimate prognosis, thus optimizing the selection of patients who will benefit from CRS and HIPEC.

References

1. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. Jap J Surg 1981;11:127-139.
2. Gilly FN, Carry PY, Sayag AC et al. Regional chemotherapy (with mitomycin C) and intra-operative hyperthermia for digestive cancers with peritoneal carcinomatosis. Hepatogastroenterology 1994;41:124-129.
3. Verwaal VJ, van Ruth S, de Bree E et al. 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.
4. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH (Ed): Peritoneal Carcinomatosis: Principles of Management. Springer Science & Business Media, 1996.
5. Benizri EI, Bernard JL, Rahili A, Benchimol D, Bereder JM. Small bowel involvement is a prognostic factor in colorectal carcinomatosis treated with complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. World J Surg Oncol 2012 Apr 11;10:56.
6. Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. Cancer Metast Rev 2003;22:465-472.
7. Yonemura Y. Gene families associated with formation of peritoneal dissemination. In: Yonemura Y, Shoten M (Eds): Peritoneal dissemination. Kanazawa, 1998, pp 47-95.
8. Vleminckx K, Vakaet I Jr, Mareel M et al. Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell 1991;66:107-119.
9. Takeichi M. Cadherins: a molecular family important in selective cell-cell adhesion. Annu Rev Biochem 1990;59:237-252.
10. Yonemura Y, Nojima M, Kaji M et al. E-cadherin and urokinase-type plasminogen activator tissue status in gastric carcinoma. Cancer 1995;76:941-953.
11. Davies BR, Davies MP, Gibbs FE et al. Induction of the metastatic phenotype by transfection of a benign rat mammary epithelial cell line with the gene for p9Ka, a rat calcium-binding protein, but not with the oncogene EJ-ras-1. Oncogene 1993;8:999-1008.
12. Yonemura Y, Endou Y, Kimura K et al. Inverse expression of S100A4 and E-cadherin is associated with metastatic potential in gastric cancer. Clin Cancer Res 2000;6:4234-4242.
13. Kishikawa T, Sakamoto M, Ino Y, Kubushiro K, Nozawa S, Hirohashi S. Two distinct patterns of peritoneal involvement shown by in vitro and in vivo ovarian cancer dissemination models. Invas Metast 1995;15:11-21.
14. Yonemura Y, Bandou E, Kawamura T, Endou Y, Sasaki T. Quantitative prognostic indicators of peritoneal dissemination of gastric cancer. Eur J Surg Oncol 2006;32:602-606.
15. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg 1995;221:124-132.
16. Glehen O, Elias D, Gilly F-N. Présentation du rapport de l'AFC. In: Elias D, Gilly F-N, Glehen O (Eds): Carcinoses Péritonéales D'Origine Digestive et Primitive: Rapport du 110ème Congrès de L'Association Française de Chirurgie—Monographie de L'Association française de Chirurgie (in French). Arnette: Rueil-Malmaison, France, 2008, pp 101–151.
17. Tentes AA, Tripsiannis G, Markakidis SK et al. Peritoneal cancer index: a prognostic indicator of survival in advanced ovarian cancer. Eur J Surg Oncol 2003;29:69-73.
18. Elias D, Mariani A, Cloutier AS et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. Eur J Surg Oncol 2014;40:1467-1473.
19. Rivard JD, Temple WJ, McConnell YJ, Sultan H, Mack LA. Preoperative computed tomography does not predict resectability in peritoneal carcinomatosis. Am J Surg 2014;207:760-765.