Annals of Surgical Oncology **15**(9):2426–2432
DOI: 10.1245/s10434-008-9966-2

8-Year Follow-up of Randomized Trial: Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy in Patients with Peritoneal Carcinomatosis of Colorectal Cancer

Vic J. Verwaal, MD, PhD,[1] Sjoerd Bruin, MD,[1] Henk Boot, MD, PhD,[2] Gooike van Slooten, MD,[1] and Harm van Tinteren, ScM[3]

[1]Department of Surgery, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[2]Department of Gastroenterology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[3]Statistical Department, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Introduction: The treatment of peritoneal carcinomatosis is based on cytoreduction followed by hyperthermic intraperitoneal chemotherapy and combined with adjuvant chemotherapy. In 2003, a randomized trial was finished comparing systemic chemotherapy alone with cytoreduction followed by hyperthermic intraperitoneal chemotherapy and systemic chemotherapy. This trial showed a positive result favoring the studied treatment. This trial has now been updated to a minimal follow-up of 6 years to show long-term results.

Patients and Methods: For all patients still alive, the follow-up was updated until 2007. In the original study, four patients were excluded—two because of no eligible histology/pathology and two because of major protocol violations. After randomization, four patients in the HIPEC arm and six in the control arm were not treated using the intended therapy, one patient because of withdrawal, one because of a life-threatening other malignant disease and the others because of progressive disease before initiation of the treatment. During the follow-up, one patient was crossed over from the control arm and underwent cytoreduction and HIPEC for recurrent disease, after the assigned treatment was completed. The data from these patients were censored at the moment of the cross-over. Progression-free and disease-specific survival were analyzed using the Kaplan Meyer test and compared using the log rank method. The long-term results were studied in more detail to evaluate efficacy and toxicity.

Results: At the time of this update, the median follow-up was almost 8 years (range 72–115 months). In the standard arm, 4 patients were still alive, 2 with and 2 without disease; in the ''HIPEC' arm, 5 patients were still alive, 2 with and 3 without disease. The median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm ($P = 0.020$). The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm ($P = 0.028$). The 5-year survival was 45% for those patients in whom a R1 resection was achieved.

Conclusion: With 90% of all events having taken place up to this time, this randomized trial shows that cytoreduction followed by HIPEC does significantly add survival time to patients affected by peritoneal carcinomatosis of colorectal origin. For a selected group, there is a possibility of long-term survival.

Published online June 3, 2008.
Address correspondence and reprint requests to: Vic J. Verwaal, MD, PhD; E-mail: v.verwaal@nki.nl

Key Words: HIPEC—Peritoneal carcinomatosis—Colorectal cancer—Cytoreduction—Randomized trial.

Peritoneal carcinomatosis is a specific subgroup of stage-IV colorectal cancer, characterized by intraperitoneal spread of tumor nodules.[1] This subgroup is different from systemic metastasized disease. Peritoneal carcinomatosis is present in 10% of all colorectal cancer patients.[2] It can be seen as a step between local disease and systemic spread of a malignant disease.[3,4]

With more treatment options available to patients with limited metastasized disease in liver and lung, more effective chemotherapeutic regimens may be combined with surgery or other ablative treatment to increase the life expectancy of patients affected by colorectal cancer.[5] With this longer live span after treatment of the primary colorectal cancer, the incidence of peritoneal carcinomatosis will increase both relatively and absolutely.

The treatment of peritoneal carcinomatosis of colorectal origin has changed considerably in the last decennia from just palliative care to a curative approach.[6,7] The cornerstone of this change is the introduction of cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC).[8] The fundamentals of treatment with cytoreduction followed by HIPEC were laid in the 1980s. This treatment is based on the principle that a high concentration of chemotherapy within the abdominal cavity can kill tumor cells on the surfaces of the abdominal cavity with limited diffusion into the tissue and therefore with less toxicity. As a consequence, this can only be effective in tumors with limited thickness; the best situation is when only microscopic tumors are present on the abdominal surfaces.[9]

Despite major skepticism in oncology, this treatment modality of surgical cytoreduction with HIPEC was clearly established in multiple phase-II and one phase-III studies as being superior to conventional palliative surgery and systemic chemotherapy. Glehen et al.[10] analyzed, in 2004, all major phase studies. They found a median survival time of around 2 years, after which peritoneal carcinomatosis was treated by cytoreduction followed by HIPEC. This was a major improvement relative to the only 6 months survival time known from the literature.[2,11,12]

The first complete randomized trial was published in 2003.[13] Although it was based on a relatively small number of patients, it was sufficient to reliably detect and find a difference in median survival. However, long-term results could not yet be reported.

In the present analysis, an update of the randomized trial is presented with a specific analysis of the long-term results.

PATIENTS AND METHODS

Patients and Randomization

In the randomized trial, patients with histologically proven peritoneal metastases of colorectal adenocarcinoma or positive cytology of ascites, who were diagnosed either at first presentation or at recurrence of colorectal cancer and who were younger than 71 years and fit for major surgery, were eligible for the trial.

Patients with evidence of distant metastases (liver, lung)—observed on a CT scan of the abdomen or chest X-ray—were excluded from the study. Also excluded were patients who had received fluorouracil-based chemotherapy within 12 months before randomization. An amendment to the protocol was made to allow inclusion of the latter patients, after the first year of the study. The protocol of the randomized trial was approved by the ethics committee of the Netherlands Cancer Institute.

Patients were randomized to receive standard systemic chemotherapy (5FU leucovorin) in the standard arm or cytoreduction followed by HIPEC in the experimental arm. The randomization was stratified for presentation (primary or recurrence) and site (appendix, colon, or rectum).

The medical ethics committee of the Netherlands Cancer Institute approved the study, and written informed consent was obtained from all patients. In this update of the original trial, the follow-up was completed for recurrence, death and toxicity until 2007.

The trial protocol stated that patients who progressed after the treatment should be given the best available treatment. As such, patients randomized to the conventional treatment with an intra-abdominal recurrence, once the data were fully analyzed, were offered cytoreduction and HIPEC.

The trial analysis was based on the intention-to-treat principle, in this update. To overcome this "cross-over" problem, the data of these patients were censored at time over cross-over.

Treatment

Standard Treatment

The standard treatment was based of systemic chemotherapy, and surgery was only performed if there were symptoms of intestinal obstruction and consisted of either bypass, stoma surgery or limited resections.

Patients started chemotherapy immediately after random assignment or after recovery from surgery. Chemotherapy consisted of FU (IV push-dose of 400 mg/m^2) and leucovorin (IV 80 mg/m^2). Treatment was given weekly for 26 weeks, or until progression or unacceptable toxicity. Patients who had already been treated with FU within the 12 months before random assignment were treated with irinotecan (350 mg/m2) at 3-weekly intervals for 6 months, or until progression or intolerable toxicity.

Experimental Treatment

The experimental treatment was based on a three-step treatment. The first was cytoreductive surgery, the second intra-operative hyperthermic intraperitoneal chemotherapy and the last was adjuvant systemic chemotherapy after recovery from the operative procedure.

The cytoreductive surgery consisted of a laparotomy from xyphoid to pubis. The presence of macroscopic tumor deposits was recorded in seven abdominal regions: pelvis and sigmoid; right lower abdomen; small bowel and mesentery; omentum and transverse colon; subhepatic space and stomach; right subphrenic space; and left subphrenic space.

The objective of cytoreduction was to leave no macroscopic tumor behind; but, if that could not be achieved, attempts were made to leave no residual tumor exceeding 2.5 mm in thickness. To achieve this, stripping of the parietal peritoneum was carried out as described by Sugarbaker et al.[8] Infiltrated viscera of the GI tract were resected if compatible with maintaining adequate function.

At completion of cytoreduction, the abdominal cavity was inspected for residual tumor. If there was no remaining macroscopic tumor, this was stated as R-1. If the largest residual tumor was smaller than 2.5 mm, it was regarded as an R-2a resection. In cases of residual tumors thicker than 2.5 mm, cytoreductive surgery was scored as R-2b.

The hyperthermic intraperitoneal chemotherapy was carried out according the open colliseum technique.[14] Perfusion was started with a minimum of 3 l isotonic dialysis fluid, at 1–2 l/min and an inflow temperature of 41–42°C. As soon as the temperature in the abdomen was stable above 40°C, MMC was added to the perfusate at a dose of 17.5 mg/m^2, followed by 8.8 mg/m^2 every 30 min. The total dose was limited to 70 mg maximum. If the core temperature exceeded 39°C, the inflow temperature was reduced. After 90 min, the perfusion fluid was drained from the abdomen.

After hyperthermic intraperitoneal chemotherapy, the bowel continuity was restored. A temporary colostomy was made in most cases if the rectum had been resected. A draining gastrostomy and transgastric jejunal feeding tube were inserted.

Patients stayed in the intensive care unit for 3 days after the operation. Jejunal tube feeding was begun on day 1. Parenteral nutrition was given until jejunal feeding could cover all nutritional needs.

After recovery from the operative procedure, systemic chemotherapy was intended to be started 6 weeks after the operation. However, if patients did not recover within 3 months of the operation, it was not begun. The chemotherapy consisted of the same regimens as described in the standard therapy arm.

Toxicity/Complications

All postoperative events, whether surgery or chemotherapy related, were recorded using the NCI CT scale.

Follow-up

All patients were seen at the outpatient clinic once every 3 months for 2 years, every 6 months until 5 years after the randomization and once a year thereafter. The follow-up consisted of physical examination and measurement of serum CEA and CA19.9 on every visit; on every other visit, an abdominal CT scan of the abdomen was made. With a report of any clinical symptom or rise of CEA or CA19.9 levels, prompt further investigation was made, as appropriate.

Statistical Analysis

The primary end point of the original randomized trial was disease-specific survival, measured as time from randomization to death from any cause. Patients alive at the time of analysis were censored at the time of the last follow-up examination. Patients in the standard arm who progressed and crossed over to the experimental arm were censored at the moment of cross-over. The survival was estimated using the Kaplan-Meier method and tested with the log-rank test following the intention-to treat principle.

The analysis was planned at a median follow-up of 2 years to have 80% power to detect a 20% absolute difference in survival. At least 100 patients had to be entered to detect this difference with a P value less than 0.05 (two-tailed test). The secondary end point was time to progression. Additional exploratory analyses were performed for factors predicting toxicity—the main end point was 5-year survival.

RESULTS

A total of 105 patients were assigned to the trial between January 1998 and August 2001, 51 to the standard arm and 54 to the experimental arm. The entire patient population consisted of 58 men and 47 women, with a median age of 54 years (range 28–70 years).

Two patients were considered non-eligible after the randomization: one patient in the standard arm had a histopathology of pseudomyxoma peritonei after pathological revision by experts, and one patient in the experimental arm had a histopathology of peritoneal mesothelioma. Two major protocol violations occurred: one patient withdrew consent within 24 h after the randomization (experimental arm) and one did not accept the randomization result of the standard arm and went abroad to receive the HIPEC treatment.

At the primary presentation of the colorectal tumor, 58 patients had synchronic and 47 had metachronic peritoneal carcinomatosis. The colorectal tumor was in the appendix in 18, in the colon in 75 and in the rectum in 12 patients. The patient and tumor characteristics were well balanced within both arms, except for a non-significant over-representation of males in the "HIPEC" arm (63% vs 47%; $P = 0.11$). Tumor size and differentiation grade were equally distributed in both arms. The majority of the patients had large colorectal tumors. All patients with small tumors were those who had peritoneal carcinomatosis after recurrence of colorectal cancer.

At the update of this trial, the minimum follow-up of all patients was 6 years (median follow-up 94 months; range 72 to 115 months). During the follow-up, one patient was crossed over from the control arm to the HIPEC arm due to recurrence of the disease. This was at 30 months after randomization. For survival, this patient was censored at the moment of the "cross-over".

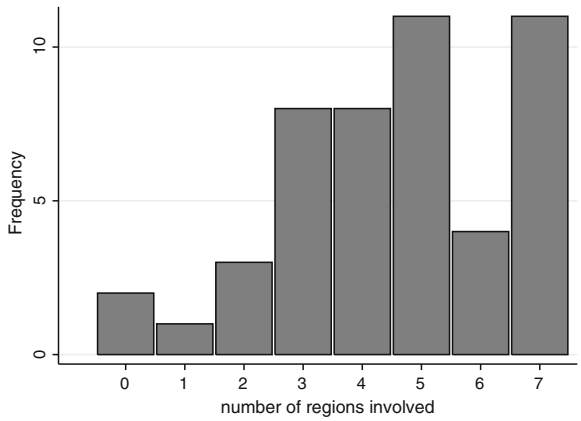

FIG. 1. Distribution of the number of regions involved.

Standard Arm

In the control arm, six patients did not start chemotherapy. This was either because of rapid progression or withdrawal of consent. Of those who started chemotherapy, only 43 completed the planned 6 months of treatment; reasons for stopping early were progression while receiving the chemotherapy in 12 patients and toxicity in two others.

Experimental Arm

In the experimental arm, four patients did not undergo cytoreduction followed by HIPEC treatment. While waiting for surgery, one died of rapid tumor progression. Two patients developed systemic metastases and were treated with systemic chemotherapy. In another, a primary lung cancer was detected shortly after randomization. This patient died of lung cancer 3 months later.

The median number of involved regions was five of the total of seven. Figure 1 shows a histogram of the number of involved regions and shows that there was a relatively high number of patients who had massive involvement of the abdomen. In Table 1, the frequency of involvement for each region is shown. This table shows that the lower part of the abdomen was the most frequently involved.

In all patients, a serious attempt for an optimal debulking was made. The cytoreduction was complete (R1 resection) in 41% of the operated patients. In a similar percentage, the debulking was near complete, leaving only residual tumor nodules of up to 2.5 mm (R2-a). In 18% of patients, no optimal debulking could be achieved (R2-b). Regardless of the completion of cytoreduction, all patients received hyperthermic

TABLE 1. *Distribution over regions*

	Frequency involved
Pelvis	46
Ileocecal	37
Omentum and colon transverse	44
Small bowel	43
Subhepatic	24
Subphrenic left	18
Subphrenic right	25

TABLE 2. *Distribution of residual tumor after cytoreduction*

	Frequency involved
Pelvis	1
Ileocecal	5
Omentum and colon transverse	11
Small bowel	27
Subhepatic	16
Subphrenic left	9
Subphrenic right	15

intraperitoneal chemotherapy. Table 2 shows the distribution of the residual tumor. This table shows clearly that small bowel involvement resulted in an incomplete cytoreduction in many patients.

Toxicity was relatively high. Two patients died in the ICU due to an uncontrollable abdominal sepsis, one 11 days and the other 40 days after the operation. Two other patients died as a result of the treatment. They died more than 3 months after the operation—one was still in the ICU suffering from an abdominal sepsis and the other died at home as a result of a massive lung embolus.

Survival

Disease-specific survival was 12.6 months in the standard arm and 22.2 months in the experimental arm ($P = 0.028$). The Kaplan Meyer curve is shown in Fig. 2.

The progression-free survival was 7.7 months in the standard arm and 12.6 months in the experimental arm ($P = 0.020$).

Detailed analysis of the long-term results in the experimental arm showed that the main impact factor on survival was the completeness of the cytoreduction. Figure 3 is a survival curve of the patients in the experimental arm, grouped by the completeness of the cytoreduction. It shows a median survival of 48 months and a 5-year survival of 45% for those patients for whom a complete cytoreduction (R-1) could be achieved. No treatment-related death occurred in these patients. The highest proportion of such deaths

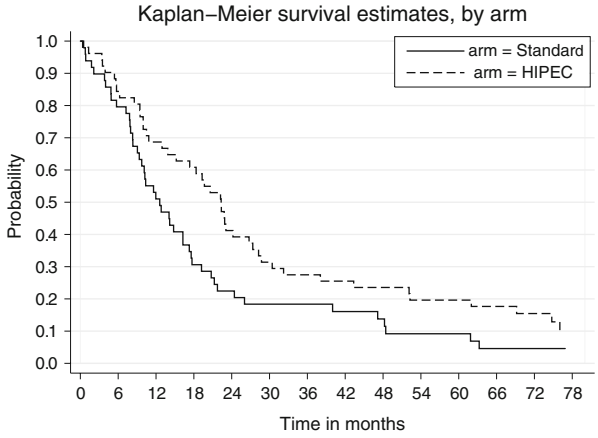

FIG. 2. Disease-specific survival of patients treated for peritoneal carcinomatosis, divided by treatment.

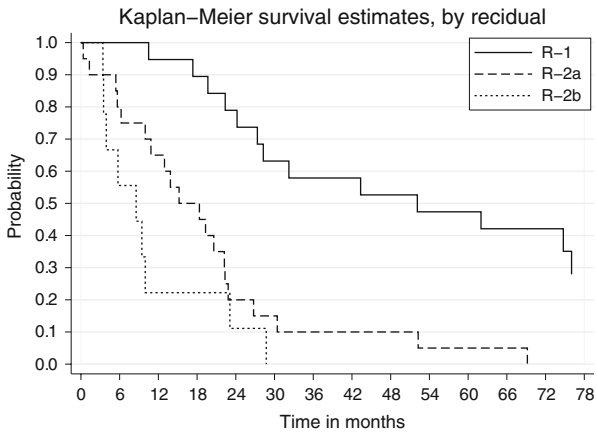

FIG. 3. Long-term results of cytoreduction followed by HIPEC in peritoneal carcinomatosis, divided to completeness of cytoreduction.

was found in those who had a gross incomplete resection (R-2b), but all treatment-related deaths occurred in those who had seven regions involved.

DISCUSSION

After the first publication of the original randomized trial in 2003,[13] an increasing number of phase-II studies have been published. Glehen summarized a large number of these studies in his so-called "world series"[10]—his multi-center over view had an overall median follow-up of 53 months and showed a consistent median survival of 19.2 months. For patients that underwent a complete cytoreduction, the median survival was 35.4 months. For those in whom the cytoreduction was gross incomplete, the median

survival was only 8.4 months. This meta analysis is by far the largest ever published on peritoneal carcinomatosis treatment but is likely to host a large heterogeneity in patients and treatment. Some institutes used the open colliseum techniques, others the closed method. There are also differences in chemotherapy doses and even in the type of chemotherapy used intra-abdominally. Perhaps an even more important drawback of the study is the un-described difference in selection criteria used at different centers. In our presented update of the randomized trial, a median survival of 22.2 months was found. Because this study was based on a randomized trial, all patients who met the inclusion criteria were included without further selection in this long-term follow-up study.

Apart from the good results of the experimental treatment, the relatively good result of the standard therapy arm is striking with very modest systemic chemotherapy of 5FU leucovorin. In every-day practice, patients with a per-operative documented peritoneal carcinomatosis have difficulties in getting chemotherapy treatment. Nodules seen of the peritoneum are seldom seen on CT imaging. Therefore, these patients are often not treated, because the response to chemotherapy cannot be determined. Only in the adjuvant setting is chemotherapy given without measurable disease.

The recent improvement in treatment of stage-IV colorectal cancer has been tremendous.[15] A major step forward was the introduction of oxaliplatin- and irinotecan-based systemic chemotherapy. The improved response rates and extension of disease-free period and overall survival has been documented in many studies.[16] With the introduction of VEGF inhibitors, the response rates even further improved and a median survival of stage-IV colorectal cancer of 22 months may be achieved.[17,18] Because all study protocols require bi-dimensional measurement of the metastasis for response evaluation, these results were achieved mainly in patients with liver and lung metastases. For the above-mentioned reason, patients affected by peritoneal carcinomatosis were often seen as ineligible for these studies because of the lack of measurable disease.[19] The selection of only patients with measurable disease and the ''de-selection'' of patients affected by peritoneal carcinomatosis hampers the translation of the results of systemic chemotherapy trials to peritoneal carcinomatosis patients. Folbrecht et al. compared the effectiveness of systemic chemotherapy in patients with systemic metastasis and peritoneal carcinomatosis. They found a poorer survival in those with the latter.[20]

Imaging of peritoneal carcinomatosis remains a major problem. CT scans, and even FDG-PET scan, depend on the amount of tumor per centimeter square. Peritoneal carcinomatosis forms a layer of tumor over the peritoneum and internal organs. It is obvious that the layer the peritoneal carcinomatosis forms fills only a small part of a square centimeter box. Therefore, peritoneal carcinomatosis does often not fulfill the RESIST criteria of 1 cm in diameter for measurable disease. Furthermore, current techniques of imaging underestimate the amount of peritoneal carcinomatosis significantly.[21]

Although the original trial was entitled ''Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer'', this was often misread as HIPEC versus systemic chemotherapy. Within the randomized trial, both treatments contained systemic chemotherapy, one arm as main treatment and one as adjuvant treatment. Therefore, what is answered in the trial is the question whether surgical cytoreduction and HIPEC add survival time to systemic treatment of peritoneal carcinomatosis. Rephrasing the trial gave the insight that probably both intraperitoneal and systemic treatments are important in treating peritoneal carcinomatosis of colorectal origin.

Long-term results have previously been described by our group.[22] In that report, the 5-year was 20% for the entire group and 43% for the patients in whom a complete resection was performed. This study contained a combination of patients treated in the randomized trial before and after and led to an inconsistent selection process. The currently presented study was characterized by the fixed eligibility criteria protocol of the randomized trial. Thus, it was not possible to select only favorable patients. Despite this strict patient selection, we still found a 20% 5-year survival.

As a result of the original randomized trial and studies of prognostic factors as well as complications, the selecting criteria are sharpened.[23,24] Patients with a tumor load exceeding five of the seven regions are now excluded from this treatment because they have less chance of a favorable survival outcome and a largely increased complication rate.

Smeenk et al. showed in their publication a significant improvement in the number of patients in whom a completeness of cytoreduction can be achieved. They also found an increase in median survival of 20% for those patients who were treated after the randomized trial.[25] Realizing that the data

presented in this paper are the results of patients operated between 1998 and 2001, it can be expected that patients treated have a median survival of 25%. Those in whom a complete cytoreduction can be achieved probably have a more than 50% chance of being alive 5 years after the operation.

In December 2006, a consensus meeting on the HIPEC treatment was held in Milan (Italy), at which a consensus document was made in order to achieve some uniformity regarding the procedures.[26] Although this consensus document was mainly built on expert opinion, it showed a strong desire for a uniform treatment. This document also provides a better starting point for any new HIPEC team and, together with the many workshops available for HIPEC training, the learning curves of new-coming institutes will be much faster than in the last decade of the 20th and in the early start of the current century.

REFERENCES

1. Glehen O, Osinsky D, Beaujard AC, et al. Natural history of peritoneal carcinomatosis from nongynecologic malignancies. *Surg Oncol Clin N Am* 2003; 12:729–39, xiii.
2. Jayne DG, Fook S, Loi C, et al. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89:1545–50.
3. Sugarbaker PH. Intraperitoneal chemotherapy for treatment and prevention of peritoneal carcinomatosis and sarcomatosis. *Dis Colon Rectum* 1994; 37:S115–22.
4. Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. *Langenbecks Arch Surg* 1999; 384:576–87.
5. Troisi RJ, Freedman AN, Devesa SS. Incidence of colorectal carcinoma in the U.S.: an update of trends by gender, race, age, subsite, and stage, 1975–1994. *Cancer* 1999; 85:1670–6.
6. Yan TD, Chu F, Links M, et al. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma: non-mucinous tumour associated with an improved survival. *Eur J Surg Oncol* 2006; 32:1119–24.
7. Sugarbaker PH. A curative approach to peritoneal carcinomatosis from colorectal cancer. *Semin Oncol* 2005; 32:S68–73.
8. Sugarbaker PH. Peritonectomy procedures. *Cancer Treat Res* 2007; 134:247–64.
9. Spratt JS, Adcock RA, Sherrill W, et al. Hyperthermic peritoneal perfusion system in canines. *Cancer Res* 1980; 40:253–5.
10. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; 22:3284–92.
11. Bloemendaal AL, Verwaal VJ, van Ruth S, et al. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol* 2005; 31:1145–51.
12. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88: 358–63.
13. 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; 21:3737–43.
14. Witkamp AJ, de Bree E, Van Goethem R, et al. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev* 2001; 27:365–74.
15. Gill S, Thomas RR, Goldberg RM. Review article: colorectal cancer chemotherapy. *Aliment Pharmacol Ther* 2003; 18:83–692.
16. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938–47.
17. Tabernero J, Van Cutsem E, Diaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2007; 25:5225–32.
18. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335–42.
19. de Bree E, Koops W, Kroger R, et al. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004; 86:64–73.
20. Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat Res* 2007; 134:425–40.
21. Baulieu F, Bourlier P, Scotto B, et al. The value of immunoscintigraphy in the detection of recurrent colorectal cancer. *Nucl Med Commun* 2001; 22:1295–304.
22. Verwaal VJ, van Ruth S, Witkamp A, et al. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12:65–71.
23. Verwaal VJ, van Tinteren H, van Ruth S, et al. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004; 91:739–46.
24. Verwaal VJ, van Tinteren H, van Ruth , et al. Toxicity of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2004; 85:61–7.
25. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg* 2007; 94:1408–14.
26. Esquivel J, Sticca R, Sugarbaker P, et al. 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; 14:128–33.