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# Analysis of Prognostic Factors in Seventy Patients Having a Complete Cytoreduction plus Perioperative Intraperitoneal Chemotherapy for Carcinomatosis from Colorectal Cancer

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**BACKGROUND:** Although lymph node and liver metastases are recognized as indications for resection of metastatic disease from colorectal cancer, carcinomatosis has not traditionally been regarded as having surgical treatment options. Reports have suggested that complete surgical removal of carcinomatosis combined with thorough irrigation of the peritoneal cavity with chemotherapy could result in longterm survival in selected patients. Proper selection factors are important because palliative surgery in these patients has not proved beneficial.

**STUDY DESIGN:** From a database of 156 patients with carcinomatosis from colorectal cancer, a retrospective analysis of data prospectively recorded in 70 patients with complete cytoreduction was performed. Eleven clinical and treatment factors were studied in univariate and multivariable analyses using survival as an end point.

**RESULTS:** By univariate analysis, patients with peritoneal cancer index (PCI) of  $< 20$  had a median survival of 41 months compared with 16 months for patients with  $PCI > 20$  ( $p = 0.004$ ). The difference in negative versus positive lymph nodes was also significant; differences in survival that were improved but not significant were present for age greater than 30 years, mucinous histology, location within the colon versus rectum, and absence of an adverse factor such as cancer perforation or obstruction present at the time of primary cancer resection. Only  $PCI < 20$  versus  $PCI > 20$  and lymph node status were significant in the multivariable analysis.

**CONCLUSIONS:** Favorable longterm results of complete cytoreduction in patients treated for carcinomatosis are associated with a limited volume of carcinomatosis observed at the time of cytoreduction and in patients with negative lymph nodes at the time of primary operation. (J Am Coll Surg 2006; 203:878–886. © 2006 by the American College of Surgeons)

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Peritoneal carcinomatosis affects approximately 10% of patients with colorectal cancer at diagnosis.<sup>1</sup> In addition, up to 25% of patients with recurrent disease present with carcinomatosis.<sup>2</sup> The benefits of cytoreduction plus perioperative intraperitoneal (IP) chemotherapy have been suggested in peritoneal carcinomatosis secondary to colorectal cancer.<sup>3</sup> In phase II studies performed in selected patients, the 5-year overall survival ranged from 18% to 43%.<sup>4–16</sup> A single randomized phase

III study showed benefit from the combined treatment.<sup>15</sup> These data suggest that a current treatment option for peritoneal carcinomatosis from colorectal cancer is cytoreductive surgery, including peritonectomy, combined with perioperative IP chemotherapy.<sup>17,18</sup> In all reports published to this date, complete cytoreduction is the most important prognostic factor for these patients. In these studies, which have evaluated prognostic factors, patients with suboptimal cytoreduction have always been evaluated along with patients who have a complete cytoreduction. For example, Verwaal and colleagues<sup>19</sup> evaluated 102 patients with peritoneal carcinomatosis of colorectal origin treated with hyperthermic IP chemotherapy. The authors revealed that only 50 patients were R1 (no residual tumor) after cytoreduction. But the overall prognostic analysis was performed with

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**Abbreviations and Acronyms**

CCR = completeness of cytoreduction  
IP = intraperitoneal  
PCI = peritoneal cancer index

102 patients. In another study, Glehen and coauthors<sup>9</sup> evaluated 53 patients treated with cytoreductive surgery and IP chemohyperthermia. The completeness of cytoreduction (CCR) was classified as CCR-1, CCR-2, and CCR-3 in 23, 11, and 19 patients, respectively. Again, prognostic indicators were calculated based on the overall sample. As a result of these important data about the management of peritoneal carcinomatosis from colorectal cancer, only patients who are candidates for a complete cytoreduction are electively treated using this combined treatment approach.<sup>6,7</sup>

The purpose of this study was to evaluate prognostic factors in patients with colorectal cancer and peritoneal carcinomatosis managed by complete cytoreductive surgery combined with perioperative IP chemotherapy at the Washington Cancer Institute.

**METHODS**

From June 1981 to November 2004, 156 patients with peritoneal carcinomatosis secondary to colorectal cancer underwent cytoreductive surgery combined with perioperative IP chemotherapy. All primary cancers were biopsy confirmed. Appendix tumors were excluded. Among these patients, 70 patients had complete cytoreduction operations and were the focus for this study. Data were collected prospectively at the National Cancer Institute, Bethesda, MD (1981 to 1986); Emory University, Atlanta, GA (1986 to 1989); and at the Washington Hospital Center (1989 to 2004) and entered into a database at the Washington Cancer Institute. All operations were performed by one of the authors (PHS). Cytoreductive surgery included peritonectomy procedures with a goal to remove all visible evidence of disease. Visceral resections were indicated if the tumor had infiltrated the visceral peritoneum. If heated intraoperative IP chemotherapy was used, all anastomoses were performed after chemotherapy irrigation was completed.

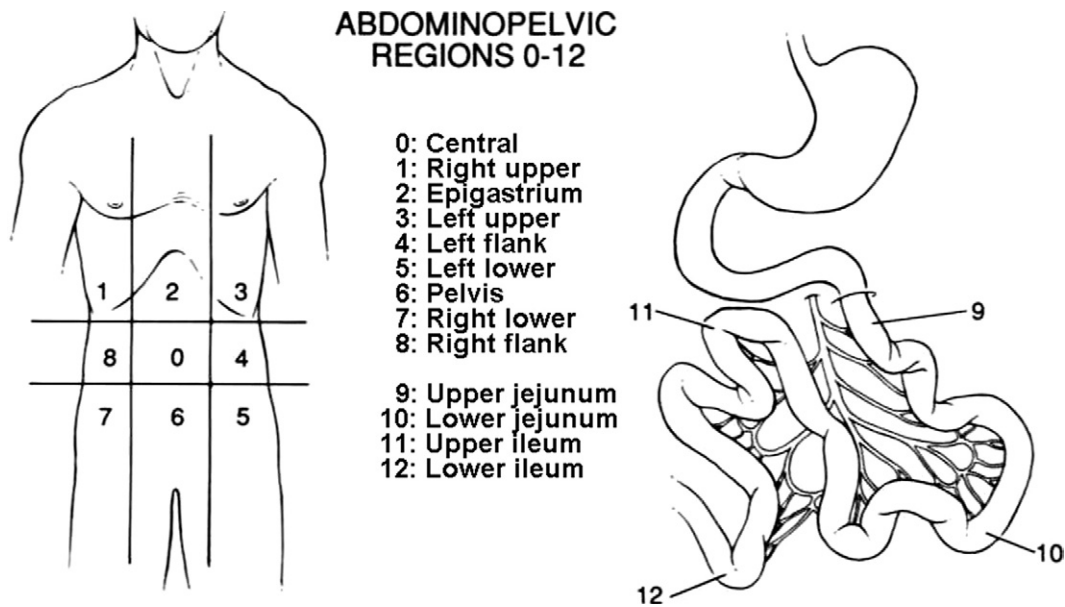
The completeness of cytoreduction score was used to assess the volume of disease remaining at the end of the operation.<sup>8</sup> The completeness of cytoreduction is indi-

cated by CCR-0 through CCR-3 scores. A CCR-0 resection indicated that no tumor was visualized in the abdomen or pelvis at the end of the surgical procedure. A CCR-1 resection indicated tumor nodules less than 2.5 mm in greatest diameter remained. In a CCR-2 resection, residual tumor nodules were between 2.5 mm and 2.5 cm in greatest diameter. In a CCR-3 resection, residual tumor nodules greater than 2.5 cm in diameter remained or there was a confluence of tumor nodules at any anatomic site. Because of the limited penetration of IP chemotherapy by diffusion into carcinomatosis nodules, only CCR-0 and CCR-1 patients were thought to have potentially curative treatment; these two groups of patients were considered to have complete cytoreduction and are included in this study.

Perioperative IP chemotherapy using mitomycin C and 5-fluorouracil was used after complete cytoreductive surgery in all patients. The dose of mitomycin C was 10 mg/m<sup>2</sup> in women and 12.5 mg/m<sup>2</sup> in men. The first 36 patients received early postoperative IP mitomycin C in 1 L of 1.5% dextrose peritoneal dialysis solution instilled on postoperative day 1. There was a 23-hour dwell before a 1-hour drainage of the chemotherapy solution. Then 5-fluorouracil at 650 mg/m<sup>2</sup> in 1 L of 1.5% dextrose peritoneal dialysis solution was instilled for 23 hours. After a 1-hour drainage, 4 additional days of IP 5-fluorouracil were given, for a total of 6 days of early postoperative IP chemotherapy.

In these 36 patients, 6 additional 1-week cycles of combined IP and systemic chemotherapy were given. The 5-fluorouracil was given IP at 650 mg/m<sup>2</sup> for 5 consecutive days. The mitomycin C was given at 10 mg/m<sup>2</sup> in women and 12.5 mg/m<sup>2</sup> in men on the middle day of the 5-day cycle. The combined intravenous and IP chemotherapy was given once per month for 6 months.

In 34 of these 70 patients treated after 1997, the same dose of mitomycin C was used as hyperthermic IP chemotherapy in the operating room.<sup>20</sup> The first 9 of these 34 patients were enrolled in a clinical trial to test the safety of hyperthermic mitomycin C combined with early postoperative IP 5-fluorouracil. To deliver the heated intraoperative chemotherapy, a Tenckhoff catheter and four closed suction drains were placed through the abdominal wall. Two temperature probes were secured to the skin edge. Using a running or interrupted monofilament suture, the skin edges were secured to a Thompson self-retaining retractor. During 90 minutes



**Figure 1.** The peritoneal cancer index provides an assessment of tumor volume and distribution throughout the abdomen and pelvis. (From: Jacquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res* 1996;15:49–58, with permission.)

of irrigation, the surgeon could manipulate all viscera. A roller pump forced the chemotherapy solution through the Tenckhoff catheter and pulled it out through the drains. A heat exchange kept the IP fluid at 41° to 42° C. These patients received the 5-fluorouracil on postoperative days 1 to 5.

The location of the primary colorectal cancer was defined as colon or rectum. Patients with cancers that required dissection below the peritoneal reflection documented by operative notes were included in the rectal cancer group. Patients with colon cancer, including sigmoid colon cancer, in whom the extraperitoneal space was not dissected, were considered as having nonrectal cancer.

Lymph nodes were determined to be positive if reported as such in a review of the pathology report from the referring institution. Copies of these reports were obtained as part of the initial evaluation of all 70 patients.

Tumor differentiation, classified as well, moderate, or poor, was determined at our own institution from the specimens obtained from cytoreductive surgery. Well-differentiated adenocarcinoma was composed predominantly of single tubular glands. The tumor cells were well polarized, similar to epithelium of an adenoma. Atypia of the tumor cell was remarkable, and an invasive component was identified. Moderately differentiated

adenocarcinoma showed characteristics between well-differentiated and poorly differentiated adenocarcinoma; it was composed of solid sheets of malignant cells admixed with glandular formations. The polarity of the tumor cells was minimal or absent. Poorly differentiated adenocarcinoma was composed of highly irregular glandular structures, or it lacked glandular differentiation. The polarity of the cancer cells had disappeared completely. In some cases, signet-ring cells were seen.

During surgical exploration of the abdomen, a peritoneal cancer index (PCI) was determined. The tumor size was evaluated in 13 abdominopelvic regions: the umbilical region, right upper quadrant, epigastrium, left upper quadrant, left flank, left lower quadrant, pelvis, right lower quadrant, right flank, upper jejunum, lower jejunum, upper ileum, and the lower ileum (Fig. 1). For the PCI data accumulation, it was assumed that the upper and lower jejunum are in the left upper and left lower quadrants, respectively, and that the upper and lower ileum are in the right upper and right lower quadrants, respectively. Tumor size was assessed specifically within each of the 13 abdominopelvic regions. Assessment of tumor size was categorized into 4 groups: 0, no detectable disease; 1, minimal disease (tumor thickness < 0.5 cm); 2, moderate disease (tumor thickness  $\geq$  0.5 cm and  $\leq$  5 cm); and 3, macroscopic disease (tumor thickness > 5 cm). In 15 patients eval-

**Table 1.** Univariate Analysis of Clinical and Treatment Characteristics with Median Survival for Subgroups of Patients

Variable	n	Median survival, mo	p Value
<b>Gender</b>			
Male	27	24	0.17
Female	43	36	
<b>Age, y</b>			
≤ 30	8	17	0.06
> 30	62	36	
<b>Mitomycin C treatment</b>			
Normothermic	36	33	0.71
Hyperthermic	34	33	
<b>Location</b>			
Colon	64	35	0.12
Rectum	6	17	
<b>Lymph node</b>			
Negative	14	186	0.039
Positive	53	29	
Unknown	3		
<b>Tumor differentiation</b>			
Well	11	41	
Moderate	50	33	0.79
Poor	9	33	
<b>Peritoneal cancer index</b>			
≤ 20	60	41	0.004
> 20	10	16	
<b>Interval primary resection to cytoreductive surgery, mo</b>			
≤ 12	35	29	0.89
> 12	27	36	
Unknown	8		
<b>Mucinous type</b>			
Yes	36	47	0.11
No	34	25	
<b>Adverse factors at primary resection</b>			
Yes	11	21	0.054
No	59	40	
<b>Signet-ring morphology</b>			
Yes	5	21	
No	64	33	0.44
Unknown	1		

p values were calculated from the log-rank test that compared the Kaplan-Meier survival curves.

uated before routine use of the PCI, this assessment was retrospectively evaluated from operative notes and pathology reports.

Mucinous tumors were those defined by mucus involvement of 60% or more of the field of view of the microscope. Mucinous versus nonmucinous cancer type

was determined at our own institution from the specimens obtained from cytoreduction surgery.

Adverse factors noted at the primary colorectal cancer resection included obstruction or perforation. Perforations included those that occurred spontaneously or were inadvertently done during the primary cancer resection. This information was obtained from operative notes and pathology reports reviewed as a part of the initial evaluation of all 70 patients.

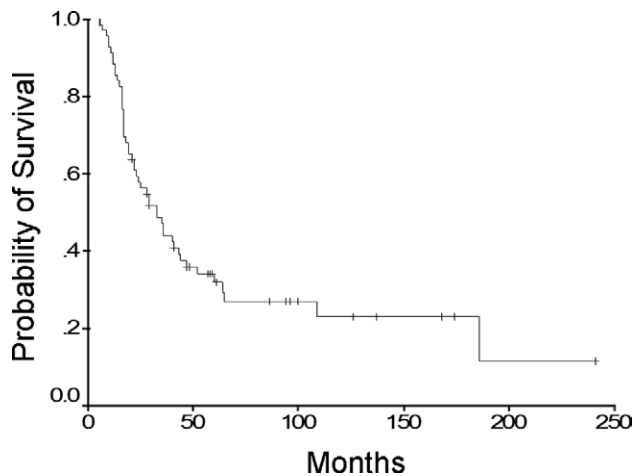
The signet-ring morphology was characterized by a profound loss of polarity of the nucleus of the cell caused by an accumulation of mucinous material within the cytoplasm. This caused the appearance of a signet-ring cell. These cells usually present within poorly differentiated mucinous carcinomas.

### Statistical analysis

The following variables were statistically evaluated: gender; age < 30 years versus > 30 years; type of mitomycin C treatment; location of primary tumor; lymph node involvement at the primary operation; tumor differentiation; PCI ≤ 20 versus PCI > 20; time between first procedure and cytoreduction (≤ 12 months versus > 12 months); mucinous versus nonmucinous type; adverse clinical features at the time of first operation, including obstruction, spontaneous perforation, or iatrogenic intraoperative perforation; and presence versus absence of signet-ring morphology.

The cut point for the continuous variable of age < 30 years versus age > 30 years was determined by a long-standing definition of young colorectal cancer patients as < 30.<sup>21</sup> The cut point of 20 for the PCI was selected for three reasons. It showed significance in earlier publications,<sup>12</sup> it showed significant data in this article, and it was the cut point that identified a group of patients who showed little or no benefit from this treatment.

The statistical analysis of all 11 prognostic factors used overall survival as the end point. Survival was determined from the time of cytoreductive surgery. All deaths, including those that occurred postoperatively or in hospital, were included in the analysis. For the univariate analysis, the chi-square test was used for most categorical variables, and Fischer's exact test was used when five or fewer items were being assessed. For continuous variables, the Student's *t*-test was used for univariate comparisons. Survival curves were constructed using the Kaplan-Meier product limit estimate and compared using the log-rank test. The multivariable



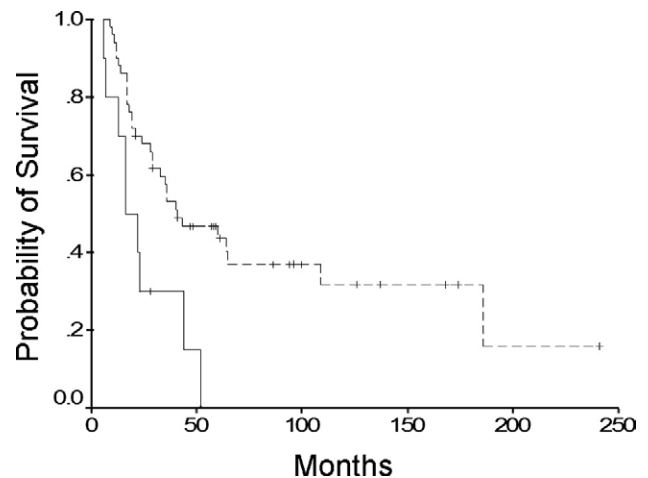
**Figure 2.** Overall survival of 70 patients with carcinomatosis from colorectal cancer treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. All patients had a complete cytoreduction. Survival was determined from the date of cytoreduction for carcinomatosis.

analysis was performed using the Cox proportional hazards regression model. Significant or near significant prognostic factors identified in the univariate analysis were used. These included the following variables: PCI < 20 versus > 20, positive versus negative lymph nodes, age < 30 years versus > 30 years, and adverse factors at primary colorectal operation. The model was developed in a backward stepwise manner. These statistical analyses were performed using SPSS for Windows, version 11 (SPSS, Inc). A p value of 0.05 was considered statistically significant.

## RESULTS

### Patient characteristics

Patient characteristics are listed in Table 1. There were 43 women (61%) and 27 men (39%). The mean age was 45.5 years (range 18 to 71 years), with 8 patients age 30 or younger. Peritoneal carcinomatosis was secondary to adenocarcinoma of the colon in 64 patients and from the rectum in 6 patients. Lymph node status in the primary operation was positive in 53 patients (76%), negative in 14 (20%), and unknown in 3 (4%). The primary tumor was well differentiated in 11 patients (15.7%), moderately differentiated in 50 patients (71.4%), and poorly differentiated in 9 patients (12.9%). The mean PCI was 13.6, and the median PCI was 13 (range 2 to 33). Adverse factors occurred in 11 patients (16%); total intestinal ob-



**Figure 3.** Kaplan-Meier survival curves for patients with peritoneal cancer index  $\leq 20$  (dashed line,  $n = 60$ ) versus peritoneal cancer index  $> 20$  (solid line,  $n = 10$ ). Log-rank  $p = 0.004$ .

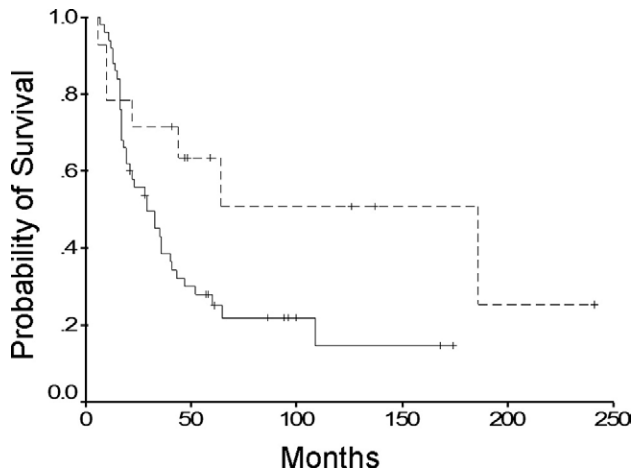
struction was observed in 6 patients, and intestinal perforation occurred in 5 patients.

### Survival

Mean followup was 46.5 months (range 6 to 241 months). The median survival of 70 patients who underwent complete cytoreductive surgery combined with perioperative IP chemotherapy was 33 months (Fig. 2). The overall 1-, 3-, and 5-year survivals were 88%, 44%, and 32%, respectively.

The univariate analysis demonstrated that PCI and lymph node involvement were significant prognostic factors (Table 1). The median survival of patients with PCI  $\leq 20$  was 41 months, compared with 16 months for patients with PCI  $> 20$  ( $p = 0.004$ ; Fig. 3). Patients with negative lymph node involvement at the time of the first operation had a better prognosis than did positive lymph node patients ( $p = 0.039$ ; Fig. 4). Age  $\leq 30$  years versus age  $> 30$  years was not significant ( $p = 0.06$ ). Also, presence versus absence of adverse factors (perforation or obstruction) at the time of the first operation was not statistically significant (Table 1,  $p = 0.054$ ).

A multivariable analysis using a Cox regression model was performed to identify independent prognostic factors for survival. Variables analyzed included PCI, lymph node involvement, presence versus absence of adverse factors at the time of the first operation, and age  $\leq 30$  years versus age  $> 30$  years. Both PCI  $> 20$  and lymph node involvement at the time of the first procedure persisted as significant (Table 2). Age  $\leq 30$



**Figure 4.** Kaplan-Meier survival curves for patients with lymph node negative (dashed line,  $n = 14$ ) or lymph node positive (solid line,  $n = 53$ ). Log-rank  $p = 0.03$ . In three patients, information about lymph node status was unavailable.

years and adverse factor at the time of first surgery did not show statistical significance.

## DISCUSSION

In colorectal cancer, prognostic indicators are evaluated in patients who have undergone potentially curative resection. These are patients in whom the surgical assessment from preoperative evaluation and visual inspection at the time of operation suggest that the disease was completely resected. In contrast, in the peritoneal carcinomatosis literature, the series that have evaluated prognostic factors included patients with both complete and incomplete cytoreduction operations.<sup>9,14,19</sup> This has occurred because the number of patients with complete cytoreduction is generally small. These studies clearly show that complete cytoreduction is the most important prognostic factor in treating colorectal carcinomatosis, and patients with incomplete resection profit little from this approach.<sup>10</sup> Most oncologists currently suggest that only patients in whom complete cytoreduction is contemplated are candidates for combined treatment. This study was performed to evaluate prognostic factors among patients with colorectal cancer and peritoneal carcinomatosis treated by complete cytoreduction.

As a result of these data and earlier carcinomatosis studies published in the oncology literature, selection factors important in this group of patients are complete cytoreduction, low tumor volume, and negative lymph nodes at the time of primary colorectal cancer resection. An estimate of 5-year survival of these optimally selected

carcinomatosis patients is approximately 50%. These results of treatment need to be critically compared with survival of carcinomatosis patients treated by systemic chemotherapy and palliative surgery. Also, in the future, these treatment results need to be compared with survival of patients who have complete cytoreduction and systemic (as compared to IP) chemotherapy. Median survival of 6 to 7 months and 0% 5-year overall survival were reported in 3 of the principal studies on peritoneal carcinomatosis secondary to colorectal cancer.<sup>1,22,23</sup> In the data on the natural history of colorectal carcinomatosis, these remain as landmark studies. But a major criticism of these three series is the absence of well-defined systemic chemotherapy treatments with modern drugs such as oxaliplatin, irinotecan, capecitabine, cetuximab, or bevacizumab.

In 2005, Venook<sup>24</sup> reviewed the results from recently completed trials with modern chemotherapeutic regimens in patients with metastatic colorectal cancer. These regimens yielded overall median survival ranging from 6.4 to 20.1 months. Unfortunately, the results of systemic chemotherapy treatments in patients with peritoneal carcinomatosis in these collected series are not separated out. Patients with isolated peritoneal carcinomatosis represent a small percentage of this large group of patients.

In a classic study using oxaliplatin and 5-fluorouracil, de Gramont and coworkers,<sup>25</sup> in 2000, reported on 420 patients with metastatic disease. They categorized the metastatic site as other than lung and liver (probably some patients with peritoneal carcinomatosis) in approximately 11% of this large sample of patients. Rothenberg and associates<sup>26</sup> studied 463 patients divided into 3 groups. They reported only 12% to 24% of metastatic disease in sites other than liver or lung. Recently, Colucci and colleagues<sup>27</sup> reported a trial with 360 patients with metastatic colorectal cancer, in which an irinotecan, leucovorin, and fluorouracil regimen was compared with an oxaliplatin, leucovorin, and fluorouracil regimen. The incidence of peritoneal carcinomatosis was only 6% and 7% in the two arms. In conclusion, recent studies with systemic chemotherapy have not provided data by which to evaluate the results of treatment of peritoneal carcinomatosis patients. This refinement of these data are needed to establish the natural history of carcinomatosis patients with the newer systemic chemotherapy agents.

**Table 2.** Multivariable Survival Analysis by Cox Proportional Hazards Model of 70 Colorectal Cancer Patients Treated with Complete Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy

Variable	Hazards ratio	95% CI	p Value
PCI $\leq$ 20 versus $>$ 20	4.69	1.73–12.65	0.002
Lymph node positive versus negative	2.96	1.08–8.13	0.03
Age $\leq$ 30 y versus $>$ 30 y	0.53	0.16–1.70	0.29
Adverse factor at primary resection	0.42	0.16–1.11	0.08

Significant or near significant prognostic factors identified in the univariate analysis were used. This included the following variables: PCI  $<$  20 versus  $>$  20, lymph node positive versus negative, age  $<$  30 y versus  $>$  30 y, and adverse factors at primary colorectal surgery. The model was developed in a backward stepwise manner.

PCI, peritoneal cancer index.

This is not the first study to suggest that the PCI is an important prognostic indicator in patients with optimal cytoreductive surgery. In a multivariable analysis, Verwaal and coauthors<sup>19</sup> observed that the number of affected regions was a significant prognostic factor. Elias and Pocard<sup>28</sup> studied 24 patients who underwent complete or almost complete cytoreductive surgery combined with IP oxaliplatin. They reported that the peritoneal extension of the disease (PCI  $>$  24) was a significant poor prognostic variable.

It is known that negative lymph nodes in primary colorectal cancer patients indicate a better prognosis than positive lymph nodes do. In our study with carcinomatosis, multivariable analysis showed that patients with negative lymph nodes at the time of first operation had improved survival. In the study from Lyons by Glehen and coworkers,<sup>10</sup> in the multivariable analysis, lymph node involvement was also associated with reduced survival. Most likely, lymph node involvement indicates a propensity for systemic disease; even if patients with peritoneal carcinomatosis and positive lymph nodes remain disease free in the abdomen and pelvis, liver and other systemic sites of disease are likely to develop. Unfortunately, patients with colon cancer and peritoneal carcinomatosis with negative lymph nodes represent a minority of the group with peritoneal dissemination. Only 20% of the patients studied here were lymph node negative. A more aggressive cancer biology in colorectal carcinomatosis patients as compared with appendiceal carcinomatosis patients may explain the marked differences in outcomes between these two groups.

Patients who present with obstruction or perforation have a poorer prognosis than those without these conditions. Inadvertent perforation of the tumor during resection for colorectal cancer is considered a very bad prognostic indicator. In 1984, Slanetz<sup>29</sup> reported 5-year survivals in patients with intraoperatively perforated co-

lon and rectal cancer of only 14% and 9.3%, respectively. If a lymph node–positive colon cancer was perforated during the resection, the local recurrence was 87%. In this series, all patients in whom a perforation was observed at the time of the first operation were also lymph node positive. Nonetheless, median survival in patients with adverse factors at the time of the first procedure was 21 months, compared with 40 months for patients without adverse factors ( $p = 0.056$ ; log-rank test). On multivariable analysis, this variable still was not statistically significant ( $p = 0.082$ ).

It has been reported that young patients with colorectal cancer have poor prognosis.<sup>30</sup> We observed a significant number of patients with age equal to or less than 30 years (8 of 70 patients). The median survival of patients 30 years or younger was 17 months, versus 36 months in patients older than 30 years ( $p = 0.06$ ). On multivariable analysis, the  $p$  value was 0.29 when adjusting for other significant or near significant variables, including PCI, lymph node status, and adverse factors discovered at primary colon or rectal cancer operation. It is possible that peritoneal carcinomatosis will be determined to be more aggressive in this group of young patients when larger numbers of patients are available for study.

The prognostic implications of histologic type of colorectal carcinoma are not fully understood. But it is well known that the mucinous-type tumor has a tendency to cause dissemination to the peritoneum.<sup>31</sup> It has been reported that the incidence of mucinous histologic type of primary colorectal cancer is 10% to 20%. It is interesting to note that in this series, 51% of patients were classified as having mucinous carcinoma. This seems to support the impression that mucinous histologic type of colorectal cancer more frequently results in peritoneal carcinomatosis. Although the prognosis of primary mucinous carcinoma is reportedly worse in some series,<sup>31–33</sup> two population-based studies did not show a reduced survival when analysis by stage was per-

formed.<sup>34,35</sup> In this study, survival was not significantly different when the histologic types were compared.

The location of the tumor (colon versus rectum) was associated with poor prognosis in the study by Verwaal and associates.<sup>19</sup> Also, data from this institution suggested that rectal cancer patients with carcinomatosis had a poor prognosis.<sup>36</sup> The median survival of 6 patients with rectal cancer was 17 months compared with 35 months for patients with colon cancer. This difference was not significant ( $p = 0.126$ ), but only small numbers of patients were available for analysis. We believe that cytoreduction after an anterior resection or abdominoperineal resection is more difficult than after a right or left colectomy. A complete cytoreduction in the pelvis after rectal resection may be impossible because of fibrin-entrapped cells remaining in the pelvic space.

An important concern about the utility of cytoreduction surgery and perioperative IP chemotherapy for colorectal carcinomatosis is about the morbidity and mortality of this procedure. In a recent review, morbidity and mortality from 9 different institutions varied from 23% to 44%, and 0% to 12%, respectively.<sup>37</sup> In a multiinstitutional review of 506 patients, the morbidity was 23% and the mortality 4%.<sup>10</sup> In the past, as these treatments were first reported, the complication rates were much higher; patients having these treatments with earlier radiation therapy or intestinal obstruction had a 26% incidence of postoperative bowel perforation.<sup>38</sup> More knowledgeable patient selection and judicious use of a diverting ostomy has decreased these serious complication rates. The current morbidity and mortality for these procedures may approach those accepted for other complex gastrointestinal procedures such as pancreaticoduodenectomy and total gastrectomy. McQuellon and colleagues<sup>39</sup> reported favorable quality-of-life consequences of the combined treatment. Yet to be addressed in this group of patients are the delayed complications that may result from an extensive cytoreductive procedure. These include both anatomic (bowel obstruction, perforation, hemorrhage) and functional (short bowel syndrome, uncontrolled diarrhea) longterm complications that have resulted. The incidence of permanent ostomy needs to be established because to date, no information is available. A difference in the longterm survival of patients with serious complications versus those without complications needs to be established. Until the direct consequences (early complications) and addi-

tional risk in the long run have been established, these treatments should be restricted to peritoneal surface oncology centers with careful and prolonged assessments of morbidity and mortality.

The full range of selection factors that should be considered in colorectal cancer patients with carcinomatosis cannot be determined from this article, because only a small fraction of patients who sought treatment finally had a complete cytoreduction. But our data showed that colorectal carcinomatosis patients who have a complete cytoreduction, a limited volume of carcinomatosis observed with cytoreduction surgery, and negative lymph nodes at the time of primary operation have an improved prognosis. These data can be interpreted to suggest that the extent of the cancer spread (measured by PCI) combined with the aggressiveness of the tumor biology (indicated by lymph node status) are the factors that control prognosis.

#### Author Contributions

Study conception and design: da Silva, Sugarbaker

Acquisition of data: da Silva

Analysis and interpretation of data: da Silva, Sugarbaker

Drafting of manuscript: da Silva

Critical revision: da Silva, Sugarbaker

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