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Surgical Debulking and Intraperitoneal Chemotherapy for Established Peritoneal Metastases From Colon and Appendix Cancer

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Background: Aggressive treatment of peritoneal metastases from colon cancer by surgical cytoreduction and infusional intraperitoneal (IP) chemotherapy may benefit selected patients. We reviewed our institutional experience to assess patient selection, complications, and outcome.

Methods: Patients having surgical debulking and IP 5-fluoro-2′-deoxyuridine (FUDR) plus leucovorin (LV) for peritoneal metastases from 1987 to 1999 were evaluated retrospectively.

Results: There were 64 patients with a mean age of 50 years. Primary tumor sites were 47 in the colon and 17 in the appendix. Peritoneal metastases were synchronous in 48 patients and metachronous in 16 patients. Patients received IP FUDR (1000 mg/m^2 daily for 3 days) and IP leucovorin (240 mg/m^2) with a median cycle number of 4 (range, 1–28). The median number of complications was 1 (range, 0–5), with no treatment related mortality. Only six patients (9%) required termination of IP chemotherapy because of complications. The median follow-up was 17 months (range, 0–132 months). The median survival was 34 months (range, 2–132); 5-year survival was 28%. Lymph node status, tumor grade, and interval to peritoneal metastasis were not statistically significant prognostic factors for survival. Complete tumor resection was significant on multivariate analysis ($P = .04$), with a 5-year survival of 54% for complete (n = 19) and 16% for incomplete (n = 45) resection.

Conclusions: Surgical debulking and IP FUDR for peritoneal metastases from colon cancer can be accomplished safely and has yielded an overall 5-year survival of 28%. Complete resection is associated with improved survival (54% at 5 years) and is the most important prognostic indicator.

Key Words: Colon cancer—Appendix cancer—Intraperitoneal chemotherapy—Cytoreduction.

Metastatic spread of colorectal cancer to the peritoneal cavity is common and is clinically important because of the high proportion of cases that progress to malignant bowel obstruction. Peritoneal metastases are found in 5% to 10% of patients at the time of initial colon resection (synchronous metastases) and in 20% to 50% of patients presenting with recurrence (metachronous metastases).[1] The risk of peritoneal metastases is highest for primary colorectal cancers that penetrate the colonic serosa or that present with bowel obstruction or colonic perforation. The risk is also high in appendix cancers, which frequently perforate and seed the peritoneal cavity early in their course. Once established, peritoneal metastases are difficult to treat effectively. Standard management is systemic chemotherapy, which may delay onset of symptoms but is not curative.[2] Consequently, other therapeutic approaches have been undertaken in an attempt to improve outcome. Aggressive surgical debulking alone can sometimes provide good palliation but is generally not

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undertaken on an elective basis because of the risk of complications and short duration of disease control.

Intraperitoneal (IP) delivery of chemotherapy offers a potential therapeutic advantage over systemic chemotherapy by producing high regional concentrations of drug while simultaneously minimizing systemic toxicities.[3–6] Hyperthermic perfusion of the peritoneal cavity with a heated (42°C) solution containing either cisplatin or mitomycin has been performed in colorectal cancer patients. The perfusion is typically performed in the operating room under general anesthesia for 60 to 90 minutes. Pharmacological studies indicate that a 5- to10-fold higher drug concentration can be achieved in peritoneal fluid compared with systemic drug levels.[7] However, penetration of drug into established tumors is limited, and use of peritoneal perfusion is generally restricted to patients for whom complete or near-complete surgical debulking can be accomplished.[8,9] Sugarbaker and Sugarbaker et al.[7,8,10–16] have reported a large experience with aggressive cytoreductive surgery combined with heated IP perfusion with mitomycin for metastatic colon and appendix cancers. The published data indicate a mortality risk of 1.5% to 5% and a perioperative morbidity of 27% to 35%. Major causes of mortality and morbidity are enteric fistula, pancreatitis, postoperative bleeding, hematological toxicity, and anastomotic leak.

An alternative approach is infusional IP chemotherapy in which the drug is infused after surgery via an indwelling IP catheter. The principal advantages of this method are a longer duration of drug exposure and the ability to give multiple cycles of treatment. The safety and efficacy of IP cisplatin have been well studied in ovarian cancer patients. In colon cancer patients, safety and pharmacokinetic data are available for IP 5-fluorouracil (5-FU) and IP 5-fluoro-2'-deoxyuridine (FUDR). After IP administration of FUDR, peak drug levels are 100- to 10,000-fold higher in peritoneal fluid compared with plasma.[17] Moreover, peritoneal drug levels remain higher than plasma for >6 hours. Area under the curve calculations of regional drug exposure indicate a profound pharmacological advantage for IP delivery.[17] Several centers have reported giving IP FUDR or 5-FU as a component of postoperative adjuvant therapy for patients with stage II and III colon cancer.[18–21] However, there are few published data that describe the use of surgical debulking and infusional IP therapy for patients presenting with established peritoneal metastases.

For more than a decade at our institution, selected patients with established peritoneal metastases from colorectal cancer have been treated with surgical debulking and postoperative infusional IP FUDR and leucovorin (LV). We have retrospectively reviewed this experience and present the patient characteristics, results, and implications of our data.

SUBJECTS AND METHODS

Patient Identification and Data Collection

Patients with primary cancers of the colon or appendix who underwent surgery with placement of an IP port were identified from prospective clinical databases. The complete hospital medical record was reviewed for each patient, including operative and pathology reports, progress notes, and discharge summaries. Sixty-four patients were identified for analysis. All patients were treated at Memorial Sloan-Kettering Cancer Center (MSKCC) from April 1987 to September 1999 with surgical exploration and placement of an IP port for chemotherapy. Twenty-five patients were treated for initial cancer diagnosis at MSKCC, and the remaining 39 patients were referrals from other institutions. Only patients with surgically resected carcinomas of the colon or appendix were included in the analysis. All patients were treated with IP FUDR for established peritoneal metastases from their primary tumor.

Patients were evaluated before surgery by both a medical oncologist and a surgeon and judged to be potential candidates for IP chemotherapy. Consent for surgical debulking and placement of the IP port was obtained before surgery by the attending surgeon. Final patient selection for port placement was made in the operating room on the basis of the operative findings. The IP port consisted of an implanted device with a subcutaneous titanium reservoir and an IP single-lumen 14.3F silastic catheter (Bard Port®, product No. 0603006, Bard Access Systems, Salt Lake City, UT). The port was accessed transcutaneously with noncoring needles and was flushed with heparinized saline after each use. The timing, dose, and schedule of IP chemotherapy were selected by the medical oncologist.

Eight patients who had an IP port placed for metastatic colon cancer were not included in this review. Two patients had received IP etoposide rather than FUDR. Also excluded were six patients who had an IP port placed at the time of surgical debulking but who did not subsequently receive IP chemotherapy.

Complications

Complications were identified by chart review and recorded as reported in the medical record by the treating physicians. All complications related to surgical debulking and port placement were recorded. Complications

that occurred after removal of the IP port were not included in this analysis.

Survival Analysis

Outcome data were obtained from medical records, clinical databases, and, when appropriate, patient interviews. Because date and sites of recurrence could not be reliably determined, no attempt was made to evaluate disease-free survival or patterns of recurrence. Survival interval was calculated from the date of initial IP port placement. Linear regression was used to evaluate association of patient and treatment variables with survival. Both univariate and multivariate analyses were performed. Survival curves were plotted with the Kaplan-Meier method,[22] and differences were assessed by the log-rank test. The Cox proportional hazards model was used to determine the relative influence of covariates. Statistical analyses were performed by using SPSS software (SPSS Inc., Chicago, IL). A P value of $\leq .05$ was considered significant.

RESULTS

Patient Characteristics

Clinical characteristics of the 64 patients included in this analysis are listed in Table 1. Table 2 lists the pathologic features and American Joint Committee on Cancer Staging criteria of the primary tumors at initial colon resection. Twenty-two patients had an unknown T, and 16 patients had an unknown N stage because of incomplete records. The median age was 49 years, and there was a female preponderance (67%). Primary tumors were located in the colon in 73% and in the appendix in 27% of cases. Of the 17 appendiceal cancers, 2 were adenocarcinoid tumors, and 6 presented with typical pseudomyxoma peritonei. Most of the cancers were locally advanced at initial presentation, with T4 disease in 67% and regional lymph node involvement in 60% of cases.

TABLE 1. *Clinical characteristics of patients at the time of IP port placement (n = 64)*

Variable	Data
Patient	
Age	median, 49 y (range, 17–76)
Sex	43:21 (female:male)
Primary colon cancer (n)	
Appendix	17
Right colon	18
Transverse colon	6
Left colon	7
Sigmoid	16
Previous exposure to systemic chemotherapy	
None	51
Preoperative 5-FU/LV	9
Adjuvant 5-FU/LV	2
Adjuvant 5-FU/LV and Preoperative 5-FU/LV	1
Preoperative 5-FU/LV/irinotecan	1

IP, intraperitoneal; 5-FU, 5-fluorouracil; LV, leucovorin.

TABLE 2. *Pathologic features from initial colon resection*

Variable	Appendix (n = 17)	Colon (n = 47)
AJCC stage		
I	0	0
II	0	1
III	0	4
IV[a]	17	42
Peritoneal metastases		
Metachronous	7	9
Synchronous	10	38
T stage		
3	0	14
4	7	21
Unknown	10	12
N stage		
0	4	14
1	2	9
2	2	17
Unknown	9	7
M stage		
0	0	5
1	17	42
Tumor histology		
Adenocarcinoma	4	35
Mucinous adenocarcinoma	11[b]	12
Adenocarcinoid	2	—
Tumor grade		
Well	8	2
Moderate	3	31
Poor	4	14
Not specified (adenocarcinoid)	2	—

AJCC, American Joint Committee on Cancer.
[a] Metastatic sites at presentation in 59 patients: peritoneum (n = 49), ovary (n = 20), liver (n = 4), spine (n = 1), pleura (n = 1).
[b] Six cases were pseudomyxoma peritonei.

The majority of patients (75%) had peritoneal metastases identified at the time of initial colon resection (synchronous metastases). The remaining patients were treated for metachronous peritoneal metastases. Ten patients had resection of ovarian metastases, and four patients had resection of liver metastases in addition to debulking of peritoneal metastases and IP port placement. One patient with an isolated spinal metastasis received radiotherapy to that area before IP port placement. Most patients (80%) received IP chemotherapy as front-line treatment. Only 20% of patients had prior exposure to systemic chemotherapy. All patients previously treated with chemotherapy received 5-FU either in an adjuvant or preoperative manner. One patient had additional exposure to irinotecan therapy.

Surgery

Before IP chemotherapy was started, all patients underwent surgical resection of primary large-bowel cancer and placement of an IP port. In 21 cases (33%) the IP port was placed at the initial surgery for removal of the primary colon or appendix cancer. In 43 cases (67%), the primary cancer had been resected at a previous operation. Table 3 lists the spectrum of procedures performed concurrently with IP port placement. The most common additional procedure was colon resection to remove either primary, locally recurrent, or metastatic disease involving the colon. A variety of procedures were performed to achieve tumor debulking, the most frequent being excision of peritoneal mass, omentectomy, hysterectomy, and small-bowel resection. Fulguration of peritoneal nodules was used as an adjunct surgical technique in nine patients.

Only patients who could be debulked to minimal residual disease were selected for IP port placement. In this series, 63 of 64 patients had debulking such that all residual lesions were <2 cm in diameter, and 19 (30%) patients had all gross residual disease resected.

Chemotherapy

After tumor debulking, all patients received IP FUDR and LV. Treatment was generally initiated during the same hospitalization as port placement, most often on the second postoperative day (range, 1–10 days). Criteria for initiating treatment included a stable surgical closure of the abdominal fascia with adequate initial wound healing and an uneventful postoperative recovery.

The standard doses of FUDR and LV most often used were 1000 mg/m^2 and 240 mg/m^2, respectively. The drugs were mixed together in 1000 or 2000 ml of sterile saline, depending on body surface area, and given by gravity infusion through the IP port over approximately 1 hour. To promote drug distribution, patients were encouraged to remain supine for one or two additional hours and to shift position intermittently. The drugs were administered daily by IP infusion for three consecutive days, and each 3-day treatment constituted one cycle. Subsequent cycles were given every 2 weeks. The median number of administered cycles of IP chemotherapy was 4 (range, 1–28). Treatment was well tolerated; no patient had early termination of chemotherapy because of toxicity. Nausea and abdominal discomfort were the most common patient complaints. Fifty percent of patients received systemic intravenous (IV) chemotherapy either concurrently or after IP chemotherapy.

TABLE 3. *Operative procedures and residual disease at IP port placement*

Variable	n
Operative Procedures	
Intraperitoneal port placement	64
Colon resection	35
Excision of peritoneal mass	15
Omentectomy	11
TAH/BSO	7
Small-bowel resection	6
Liver resection	4
Abdominal wall resection	3
Cholecystectomy	3
Splenectomy	3
Appendectomy	2
Diaphragm resection	2
Partial cystectomy	1
Partial pancreatectomy	1
Partial vaginectomy	1
Ureteral resection	1
Ureteral stent placement	1
Residual disease	
None	19
Gross <2 cm	44
Gross >2 cm	1

TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy; IP, intraperitoneal.

Complications

There were no deaths attributable to surgery or IP chemotherapy. Thirty-five patients (54%) had no documented complications. Overall, there were a total of 44 complications in the remaining 29 patients. Seventeen patients (27%) had one complication, nine patients (14%) had two complications, and three patients (5%) had three complications. Documented complications are listed in Table 4.

There were 18 perioperative complications occurring in 16 patients (25%). Most of these were infections that required antibiotic therapy only. The perioperative infection rate of the IP port site was low (1 of 64; 1%). Three patients (5%) required reoperation. The most significant complication was seen in a 50-year-old patient who developed an enterocutaneous fistula and an infected IP port after surgical debulking and one cycle of IP chemotherapy. The patient was re-explored on postoperative day 14 for fistula closure, creation of ileostomy, and removal of the infected port. Further IP therapy was discontinued.

Twenty-six complications occurred in 13 patients (20%) during subsequent IP chemotherapy. There were eight bowel obstructions requiring hospitalization, but only five required surgical intervention (lysis of adhesions). Six operations for IP port revisions were performed for various indications (inability to access catheter, angulation with poor flow, or occlusion). These were subcutaneous operations under local anesthesia, and in four cases the problems were successfully cor-

TABLE 4. *Complications of treatment*

Complication	Occurrences	Treatment	IP chemotherapy terminated
Perioperative (during hospitalization for IP port placement, n = 18)			
Wound infection	7	Antibiotics	No
Pneumonia	2	Antibiotics	No
Clostridial difficile colitis	1	Antibiotics	No
Bacteremia	1	Antibiotics	No
Urinary tract infection	1	Antibiotics	No
Gastrointestinal bleeding	1	Transfusion	No
Pneumothorax in OR	1	Tube thoracostomy	No
IP port malfunction	1	Revision in operating room	No
Bowel obstruction	1	Exploratory laparotomy/LOA	No
Anastomotic leak, IP port infection	1, 1	Exploratory laparotomy, fistula closure/end ileostomy, IP port removal	Yes
Late postoperative (during hospitalizations subsequent to IP port placement, n = 26)			
Bowel obstruction	3	Conservative	No
Fever	3	Antibiotics	No
Urinary tract infection	3	Antibiotics	No
IP port malfunction	2	IP infusion temporarily held	No
Deep venous thrombosis	2	Anticoagulation	No
Pulmonary embolus	1	Anticoagulation	No
Bowel obstruction	5	Exploratory laparotomy/LOA	No
IP port malfunction	4	Revision in operating room	No
IP port infection	1	IP port removal	Yes
IP port malfunction	2	IP port removal	Yes

IP, intraperitoneal; LOA, lysis of adhesions.

rected. Three ports were removed because of occlusion (two cases) or infection (one case). Thus, overall four patients (6%) had premature termination of IP therapy as a result of a technical complication. The percentage of patients requiring reoperation for any reason was 23% (15 of 64), but the rate of repeat laparotomy was only 11% (7 of 64).

Survival Analysis

Median follow-up for the entire study group was 17 months. Sixteen patients (25%) were disease free, 21 patients (33%) were alive with disease, and 27 patients (42%) were dead at time of the analysis. All deaths were related to progressive disease. The survival curve for all patients is shown in Fig. 1. Median survival after placement of the IP port was 34 months, with an actuarial 5-year survival of 28%. On univariate analysis, complete resection was the only statistically significant variable ($P = .04$). Lymph node status, interval to peritoneal metastasis (synchronous vs. metachronous), location (appendix vs. colon), presence of liver or ovarian metastases, diagnosis of pseudomyxoma peritonei, duration of IP therapy, and concurrent or subsequent IV systemic chemotherapy were not significant factors for survival on univariate analysis (Table 5). On multivariate analysis, complete tumor resection was associated with significantly improved survival ($P = .04$). Patients who had an incomplete resection had a 2.5-fold higher hazard rate of dying from disease progression as compared with patients who had complete resection.

Survival curves for patients having complete and incomplete resections are shown in Fig. 2. The 5-year survival after complete resection was 54%, compared with 16% for incomplete resection. Seven patients lived

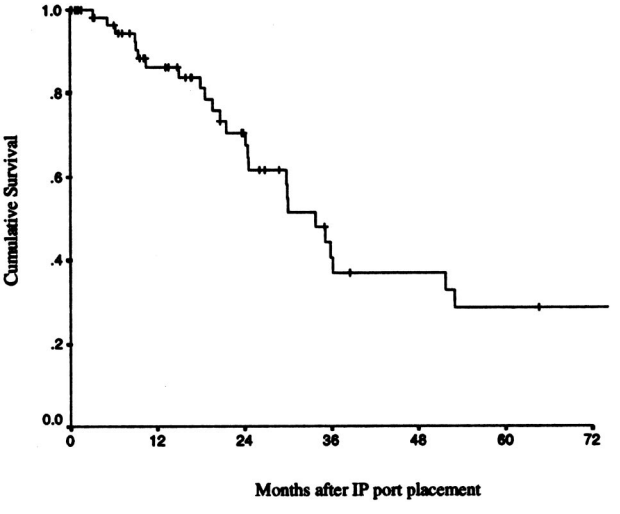

FIG. 1. Overall survival for the entire patient group (n = 64). IP, intraperitoneal.

TABLE 5. *Analysis of factors affecting survival*

Variable	Univariate analysis *P* value	Multivariate analysis *P* value	Relative risk
Complete resection	.04	.04	2.5 (1–6.1)
Location (colon vs. appendix)	.06	NS	–
Other metastasis (liver, ovary)	.08	NS	–
Duration of IP chemotherapy (≤3 cycles vs. >3 cycles)	.08	NS	–
Interval to peritoneal disease (synchronous vs. metachronous)	.1	NS	–
Concurrent/subsequent intravenous chemotherapy	.1	NS	–
Grade			
Well vs. moderate/poor	.3	Not done	–
Poor vs. moderate/well	.4	Not done	–
Lymph node status	.6	Not done	–

IP, intraperitoneal; NS, not significant.

beyond 5 years, and their resection status and other descriptive data are listed in Table 6.

To assess the importance of complete resection as a prognostic variable, survival curves for complete and incomplete resection were compared for several subsets of patients. When patients with pseudomyxoma peritonei (n = 6) were excluded from the analysis, a strong survival advantage was again associated with complete resection ($P = .007$). Median survival was unchanged. With the exclusion of patients who had prior exposure to systemic therapy at the time of IP port placement (n = 13) and of pseudomyxoma peritonei patients (n = 6), a survival advantage continued to be associated with complete resection ($P = .024$). Median survival in the complete resection group remained unchanged at 108 months, whereas it slightly increased in the incomplete resection group from 30 to 34 months.

DISCUSSION

Standard therapy for patients with metastatic colorectal cancer is systemic chemotherapy. Historically, 5-FU-based regimens have been the mainstay of therapy and have yielded median survival in the range of 8 to 10 months.[23] It has recently been reported in a randomized trial that the combination of irinotecan/5-FU/LV is superior to a widely used regimen of 5-FU/LV (response rate of 39% vs. 21%; median survival of 15 vs. 13 months).[24] The three-drug regimen has become standard of care for previously untreated patients with metastatic colorectal cancer.

The rationale for IP chemotherapy is to expose the peritoneal cavity to higher concentrations of cytotoxic drugs for longer durations than are possible with IV delivery.[7] For tumors that will remain largely confined to the peritoneal cavity for most of their natural history, IP treatment could increase efficacy and reduce toxicity. These theoretical advantages have been well studied for cisplatin in the treatment of epithelial ovarian cancer. IP cisplatin has been studied as primary treatment in stage III disease, as consolidation therapy after primary treatment with IV cisplatin regimens, and as salvage therapy in both cisplatin-sensitive and cisplatin-resistant relapse. A survival advantage and reduced toxicity have been demonstrated in front-line treatment of stage III ovarian cancer in two randomized trials.[25] For patients who have responded to front-line IV cisplatin but have small-volume residual disease, consolidation therapy with IP cisplatin has shown significant response rates (40% to 50%), and comparisons with historical controls suggest a survival benefit.[26,27] As salvage therapy for IP recurrence of ovarian cancer treated initially with IV cisplatin, small studies have suggested a benefit for IP cisplatin only when the disease was sensitive to initial cisplatin therapy and when the disease could be surgically debulked to 1 cm or less residual disease.[28]

In this article, we have retrospectively evaluated our institutional experience with surgical debulking and infusional IP chemotherapy with FUDR and LV for patients with established metastatic spread of colon or appendix cancer to the peritoneal cavity. Although a survival advantage for this approach has never been documented in a prospective trial, our favorable experience with IP FUDR/LV used as a component of adjuvant therapy for resected primary colon cancer[18] and the frequent failure of systemic treatment for peritoneal metastases prompted us to offer IP treatment to selected patients. It should be emphasized that the patients analyzed in this review were only those with established peritoneal metastases who were treated by surgical debulking and IP FUDR/LV for stage IV disease. Patients who received IP FUDR/LV in the adjuvant setting were not included in this review.

In this study, 80% of patients received IP FUDR/LV as a component of their initial cancer therapy. Our survival results, therefore, largely reflect the outcomes for

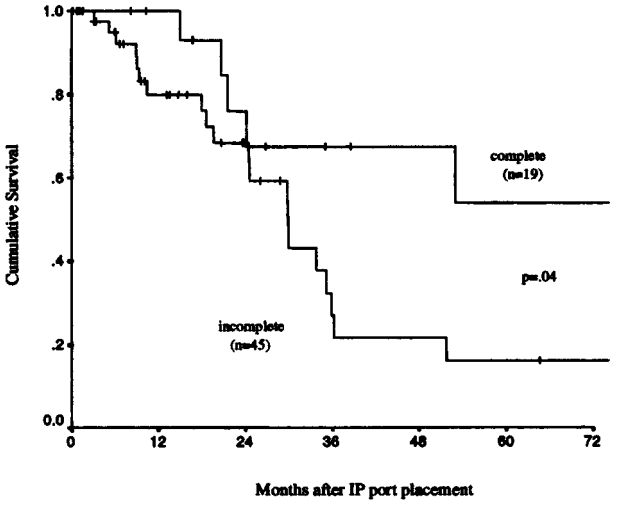

FIG. 2. Overall survival based on completeness of surgical debulking at the time of intraperitoneal (IP) port placement.

colon cancers that are previously untreated and chemotherapy naive. Most peritoneal metastases were encountered synchronously with locally advanced primary large-bowel cancers, and spontaneous shedding of cancer cells into the peritoneal cavity from the primary tumor seemed to be the dominant route of spread. Ovarian metastases were extremely common (26 of 43 women; 60%), and this suggests that transperitoneal spread to the ovary contributed to development of ovarian metastases. Six patients with pseudomyxoma peritonei were included in the study group. Although these tumors represent a group with more indolent biology and favorable survival, because of their small number and relatively short follow-up they did not significantly influence the outcome of the entire study population. Median survival was unchanged when such patients were excluded from analysis. Finally, it is important to emphasize that patients included in this series seem to have a limited peritoneal tumor burden that was amenable to aggressive debulking. Although it was not possible in retrospect to quantify the extent of peritoneal disease, we did observe that 19 of 64 patients were completely debulked of all gross disease, and 63 of 64 patients had residual disease of <2 cm maximal diameter. In summary, our survival figures reflect a highly selected patient population with metastatic adenocarcinoma of the appendix or colon treated with up-front IP FUDR as a component of therapy.

Treatment was remarkably well tolerated. No patient died as a result of treatment, and the 18 perioperative complications consisted largely of minor infections. There was one anastomotic leak with a secondary IP port infection. The only complications leading to termination of IP therapy were one perioperative port infection, two late port malfunctions, and one late port infection. Therefore, only four patients (6%) were unable to continue IP therapy as a result of complications. Side effects from IP chemotherapy infusion were mild and self-limited. Our complication rates compare favorably with data reported for heated IP perfusion. Jacquet et al.[29] have reported a 5% perioperative mortality, a 35% morbidity, and a 10% anastomotic leak rate.

The median survival of 34 months seen for all patients in this series is superior to that reported for stage IV colon cancer treated by systemic chemotherapy; this ranges from 8 to 15 months.[23,24] In our patient population with metastatic disease largely confined to the peritoneal cavity, patient selection undoubtedly contributed to the prolonged median survival observed in this study. The younger age of patients included in the study may also have contributed to prolongation of survival. It is therefore not possible to determine accurately the extent to which treatment influenced the increased median survival. Because three 5-year survivors were seen in the incompletely resected group, it can be speculated that IP chemotherapy contributed to tumor control and survival in a subset of patients. Complete surgical removal of all gross disease was, however, the only factor identified on multivariate analysis that predicted an improved median

TABLE 6. *Characteristics of 5-year survivors (n = 7)*

Age/Sex	Location	Resection	Pathology	Grade	IP chemotherapy (No. cycles)	Follow-up	Status
44F	Sigmoid	Incomplete	Adeno	Poor	6	65 mo	NED
20F	Left colon	Complete	Mucinous	Mod	6	75 mo	NED
56M	Sigmoid	Complete	Adeno	Poor	3	82 mo	NED
63F	Right colon	Incomplete	Mucinous	Well	4	83 mo	DOD
57M	Transverse	Complete	Adeno	Mod	6	85 mo	AWD
57F	Left colon	Complete	Adeno	Mod	6	108 mo	DOD
28M	Appendix	Incomplete	Mucinous	Well	4	132 mo	AWD

Adeno, adenocarcinoma; mucinous, mucinous adenocarcinoma; Mod, moderate; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

and 5-year survival. We believe that the benefit of complete tumor removal may have at least three components: less extensive and less biologically aggressive metastatic disease at presentation, maximal cytoreduction of cancer cells, and increased efficacy of IP chemotherapy. Tumor location, lymph node status, duration of IP chemotherapy, and addition of systemic chemotherapy did not significantly influence overall survival. We believe that patients who appear on imaging studies or at operation to have peritoneal disease that is amenable to complete resection are the best candidates for this treatment approach.

Our survival results are similar to those presented for surgical debulking and heated IP chemotherapy with mitomycin reported by Sugarbaker.[8] Although the rate of complete resection in that study was not reported, the overall treatment results (5-year survival, 40% for complete and 3% for incomplete resection) seem similar to our results. Although the median survival rates in these retrospective analyses are encouraging, long-term cure rates are low. In our study, there were seven 5-year survivors, but only three have no evidence of cancer (Table 6).

In considering the appropriate use of IP therapy for colon and appendiceal cancer, it is important to emphasize that our analysis indicates that such an approach will probably benefit only patients with minimal residual disease. It is clearly this population in which randomized trials evaluating IP and systemic chemotherapy are warranted. However, until data from such trials are available, it is not possible to define the role of IP chemotherapy for patients with large-bowel cancer. Our recommendation would be that patients with IP disease amenable to aggressive surgical debulking should be placed in appropriately designed clinical trials to further study the role of complete resection of peritoneal disease in combination with IP chemotherapies.

In the absence of a clinical trial, our current practice is to use combined systemic and IP chemotherapy. The sequencing of chemotherapy depends on the clinical presentation. For patients who are referred with peritoneal metastases that have been identified by imaging studies or at a previous operation, we recommend initial treatment with systemic chemotherapy. Surgical debulking and IP therapy are reserved for patients whose disease is stable or responsive to systemic chemotherapy. For those patients whose peritoneal disease is discovered at their initial operation and who have had both optimal tumor debulking and placement of an IP port, we favor a course of IP chemotherapy in the immediate postoperative period. After completion of three to six cycles of IP chemotherapy, patients then receive systemic chemotherapy.

In conclusion, the safety profile and survival data observed in this study are encouraging. We recommend further evaluation of the role of surgical debulking and IP therapy in appropriately designed clinical trials. Availability of other novel agents for IP use may also be a promising arena for development of this approach.

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