ORIGINAL CONTRIBUTION

Treatments and Outcomes of Peritoneal Surface Tumors Through a Centralized National Service (United Kingdom)

S. Rout, M.B., Ch.B.[1] • A. G. Renehan, F.R.C.S., Ph.D.[1,2] • M. F. Parkinson[1]
M. P. Saunders, M.R.C.P., Ph.D.[3] • P. E. Fulford, F.R.C.S.[1]
M. S. Wilson, F.R.C.S., M.D.[1] • S. T. O'Dwyer, F.R.C.S., M.D.[1]

1 Peritoneal Tumour Service, Department of Surgery, the Christie NHS Foundation Trust, Manchester, United Kingdom
2 School of Cancer, Enabling Sciences and Technology, University of Manchester, Manchester, United Kingdom
3 Department of Clinical Oncology, the Christie NHS Foundation Trust, Manchester, United Kingdom

PURPOSE: Treatment of peritoneal surface malignancies with combined cytoreductive surgery and heated intraperitoneal chemotherapy may improve oncologic outcome. To better define treatment pathways, five-year results in patients referred to one of two centralized national treatment centers in the United Kingdom were analyzed.

METHODS: A prospective database of patients referred to the Manchester Peritoneal Tumor Service, established in 2002, was analyzed. Outcomes were evaluated using Kaplan-Meier life tables and Cox models.

RESULTS: Two hundred seventy-eight patients (median age, 56.9 (range, 16–86) years) were considered by a dedicated multidisciplinary team and tracked on seven clinical pathways. Among the 118 surgically treated, the most common diagnosis was pseudomyxoma peritonei (101 patients, 86%). Major complications occurred in 11 patients (9%); there was no 30-day mortality. Where complete cytoreduction was achieved, three-year and five-year tumor-related survival rates were 94% and 86%, respectively. In the Cox model, incompleteness of cytoreduction ($P = 0.001$) and high-grade tumor ($P < 0.0001$) were independent prognosticators of poor outcome.

CONCLUSION: The establishment of a national treatment center has allowed refinement of techniques to achieve internationally recognized results. Having achieved low levels of morbidity and mortality in the treatment of mainly pseudomyxoma peritonei of appendiceal origin, the technique of cytoreductive surgery and heated intraperitoneal chemotherapy may be considered for peritoneal carcinomatosis of colorectal origin.

KEY WORDS: Peritoneal surface tumor; Pseudomyxoma peritonei; Heated intraperitoneal chemotherapy; Sugarbaker procedure.

Peritoneal surface tumors comprise a clinically heterogeneous group of intra-abdominal malignancies including those arising as 1) secondary spread from gastrointestinal (including appendiceal) and gynecologic carcinomas; 2) primary peritoneal neoplastic processes, such as primary peritoneal carcinoma and peritoneal malignant mesothelioma; and 3) pseudomyxoma peritonei (PMP). Historically, these tumors have generally presented as advanced disease (*e.g.*, bowel obstruction, ascites, or pain) associated with short survival and poor quality of life. Surgery and chemotherapy were offered with palliative intent.

Since the mid-1990s, there have been significant advances in both the understanding of the pathologies of peritoneal surface tumors and of their treatments.[1] Specifically, it has become clear that a proportion of patients have peritoneal surface malignancy that lends itself to locoregional treatment involving the combination of macro-

Supported by the National Health Service National Commissioning Group for Highly Specialised Services.

Read at the meeting of The American Society of Colon and Rectal Surgeons and Tripartite, Boston, Massachusetts, June 7 to 11, 2008.

Address of correspondence: Dr. Andrew Renehan, Department of Surgery, University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX United Kingdom. E-mail: arenehan@picr.man.ac.uk

Dis Colon Rectum 2009; 52: 1705–1715
DOI: 10.1007/DCR.0b013e3181b5504e

scopic tumor excision, *i.e.,* cytoreductive surgery (CS), and hyperthermic intraperitoneal chemotherapy (HIPEC). Such a radical approach (also referred to as the "Sugarbaker procedure") is particularly suitable for PMP, a rare neoplasm (one to two cases per 1,000,000 population) of mainly appendiceal origin, characterized by disseminated peritoneal mucinous tumor deposition and progressive accumulation of mucinous ascites.[2]

Recognizing the rarity of some peritoneal tumors and the complex level of subspecialization required to deliver best standard of care for these patients, the Department of Health in the United Kingdom commissioned services for the treatment of these tumors through two national centers, Basingstoke, established in 2000, and Manchester, established in 2002. Results from the former have been published.[3,4] The purpose of this paper is to report the treatments and outcomes from the Manchester center.

MATERIALS AND METHODS

Patients

This analysis is based on data from a prospective database of all patients with a potential diagnosis of a peritoneal surface tumor referred to the Peritoneal Tumor Service at the Christie Hospital National Health Service Foundation Trust, Manchester (UK), since its establishment in 2002 to December 2007. Each case was assessed through dedicated multidisciplinary team meetings comprising colorectal and hepatobiliary surgeons, a clinical oncologist, radiologists, and pathologists. For each case, clinical records, pathology review, radiologic examinations (mainly CT of the thorax, abdomen, and pelvis), and in most cases, tumor marker measurements (carcinoembryonic antigen, cancer antigen 125 (CA-125), and CA19–9) were assessed.

The commissioning agreements with the Department of Health excluded the treatment of peritoneal carcinomatosis of gastric, pancreatic, and ovarian origin, and such cases were not reviewed by this multidisciplinary team. The national commissioning agreements also excluded the management of peritoneal carcinomatosis of appendiceal and colorectal origins, and other surface diseases, such as malignant mesothelioma and primary peritoneal carcinoma. However, the disease profile in this series reflects reclassifications (to some of the above) after major surgery despite careful preoperative assessment.

After initial assessment, the clinical pathways were as follows: patients with disease considered amenable to complete resection were offered CS and HIPEC; patients with disease considered unlikely to be amenable to complete removal were offered debulking surgery, systemic chemotherapy, or symptom-directed palliation depending on their performance status and symptoms. Patients not fulfilling diagnostic criteria for a peritoneal surface malignancy were referred back to their referring hospital. A further group of patients, typically with a histologic diagnosis of a low-grade appendiceal mucinous neoplasm (LAMN) limited to the appendiceal lumen,[5,6] a putative early stage in PMP, were offered active monitoring with annual CT imaging.

Cytoreductive Surgery and HIPEC

CS involved a series of peritonectomy procedures (greater and lesser omentectomies, right and left upper quadrant peritonectomies, and anterior parietal and pelvic peritonectomies) with visceral resection of involved nonessential organs as required and described by Sugarbaker.[1,7,8] Disease involving the surface of the liver was treated by ablation using high-power electrocoagulation; surface disease on the spleen was an indication for splenectomy. Small-volume disease on the serosal surfaces of the small bowel was treated by "spot" diathermy or serosal dissection.[1] CS was generally undertaken as one operative episode; however, in four patients with extensive intra-abdominal dissemination, where it was judged that surgical time would exceed 12 hours (and increase morbidity), CS was scheduled as a two-stage procedure, separating the procedures with a three-month to four-month interval.

Completeness of disease removal was determined intraoperatively using the completeness of cytoreduction (CC) scoring system.[9] A score of CC-0 indicated no visible evidence of peritoneal disease; CC-1 indicated residual tumor <2.5 mm in diameter; CC-2 indicated residual tumor between 2.5 mm and 2.5 cm in diameter; and CC-3 indicated residual tumor >2.5 cm in diameter or confluence of tumor nodules remaining at any site. Where scores CC-0 and CC-1 were achieved, patients were classified as complete cytoreduction; CC-2 and CC-3 were classified as debulking surgery.[1] The principle factor limiting completeness of cytoreduction was extensive small-bowel involvement. Gastric encasement was not in itself a contraindication to gastrectomy, but in this series, the former was invariably associated with extensive small-bowel involvement, and accordingly, gastric resection was infrequent. However, to achieve CC-0 or CC-1, techniques to excise and/or ablate disease surrounding the stomach, leaving intact the gastric substance, were used.

Peritoneal disease burden was assessed intraoperatively using the Peritoneal Cancer Index (PCI),[10] which scores 13 intra-abdominal sites from 0 (no disease) to 3 (lesion size >5.0 cm or confluence), yielding possible total scores ranging from 0 to 39.[11]

After complete cytoreduction, HIPEC was routinely administered. Two chemotherapy regimens were used: 1) high-dose mitomycin C (35 mg/m^2 in three pulses)[12] for tumors of colorectal and appendiceal origin and 2) doxorubicin (15 mg/m^2) and cisplatinum (50 mg/m^2) for peritoneal malignant mesothelioma.[13] Chemotherapy was delivered using a modification of the Coliseum technique.[14] The abdominal cavity was filled with 1.5% dextrose (Dianeal, Baxter Healthcare Corporation, Deerfield, IL) perito-

neal dialysis solution (1.5 to 3.0 liter), then perfused and temperature controlled at 41.0°C to 42.5°C for 90 minutes using the Performer® LRT system (RanD, Medolla, Italy).

Other Treatments

Where complete CS was not possible, debulking surgery was performed. In a further group of patients, it was necessary to ameliorate symptoms of abdominal discomfort and respiratory distress by drainage of mucinous ascites *via* a minilaparotomy incision without debulking surgery. Patients with advanced unresectable PMP were offered a combined regimen of mitomycin C and capecitabine in a single-arm trial.[15] Patients with histologic diagnoses other than PMP were treated with systemic chemotherapy appropriate for that cancer type per standard protocols.[16]

Postoperative Management and Follow-Up

After surgery, patients were initially managed on the critical care unit. Nasogastric suction, thoracostomy drainage of the pleural spaces, nutritional support (initial total parenteral nutrition converting to nasojejunal enteral nutrition after two to three days), and prophylaxis for deep venous thrombosis[17] (enoxaparin sodium 20 to 40 mg *s.c.* daily, intraoperative intermittent pneumatic compression, and TED graded compression antiembolism stockings) were used. Complications were recorded prospectively and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Effects, version 3.0,[10,18] and grouped into three categories as follows: Grades 1 and 2, mild to moderate complications; Grades 3 and 4, severe and life-threatening complications; and Grade 5, in-hospital mortality. Hematologic toxicity was reported using equivalent National Cancer Institute Common Terminology Criteria.[18]

Follow-up after CS for PMP included pathology review, clinical assessment, tumor marker measurements (serum carcinoembryonic antigen, CA-125, and CA19–9) every six months, and CT imaging biannually during the first two years and annually thereafter. Patients with tumors of colorectal origin were followed according to standard colorectal cancer surveillance protocols.[19]

Pathologic Classification

Histologic classification for PMP was as follows: for disseminated disease, the three categories of the Ronnett classification[20] were used—disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and PMCA with intermediate or discordant features (PMCA-I/D); appendiceal lesions confined to the appendix and periappendiceal tissues without dissemination to peritoneal surfaces were classified as LAMN.[6] We further subdivided LAMNs into Type I, where disease was restricted to the appendiceal lumen, and Type II, where there was either perforation or disease in the periappendiceal tissues.[5] For other pathologies, World Health Organization[21] classifications were used.

Statistical Analysis

Baseline proportions were compared using chi-squared and Fisher's exact probability tests as appropriate. Continuous variables of interest were skewed (Kolmogorov-Smirnov tests); accordingly, distributions of these variables were expressed as medians and ranges and compared using the Mann-Whitney *U* test. The exceptions were serum tumor markers, which were log-transformed and expressed as geometric means and 95% confidence intervals to allow them to be simultaneously included in the Cox models (see below).

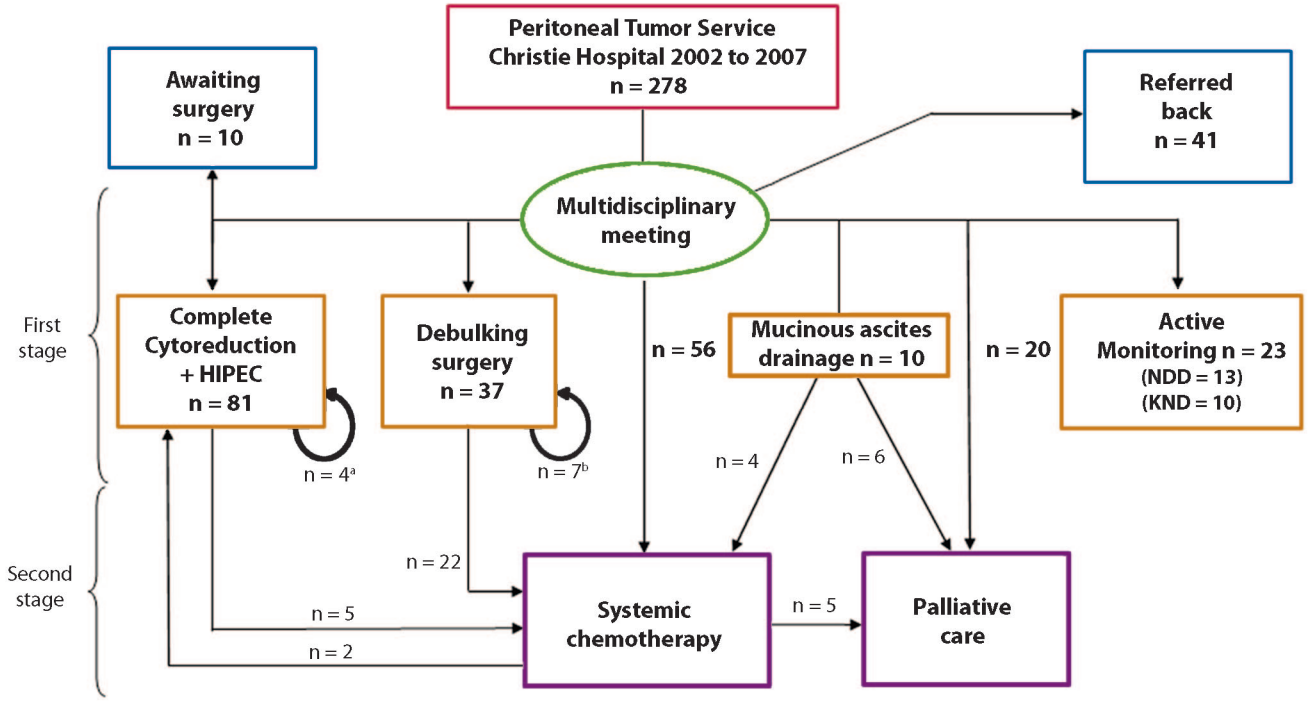
We calculated oncologic outcomes from time of operation in patients undergoing surgery using Kaplan-Meier life tables.[22] Comparisons were performed using log-rank tests. For analysis purposes, because there were several different histologic types, we explored tumor categorization using two broad groups defined by grade: low-grade histologies included LAMN, DPAM, PMCA-I/D (as an extension of the Bradley classification),[23] and rare mucinous tumors of ovarian origin; all other histologies were categorized as high-grade. For survival analyses, PCI (an ordinal variable) was categorized into four groups: 0 to 9; 10 to 19; 20 to 29, and 30 to 39. Cox proportional hazard models were developed using tumor-related survival as the dependent output, and independence of variables was assessed using additive approaches.[22] All computations were performed using Stata® 9.2 software (College Station, TX).

RESULTS

Clinical Pathways

Over the six-year period, 278 patients (median age, 56.9 (range, 16–86) years) were referred and managed along seven clinical pathways (Fig. 1). One hundred eighteen patients underwent major laparotomies: 81 (29%) underwent complete CS with HIPEC, and 37 (13%) underwent debulking surgery. Several patients were managed along multiple pathways, and their initial management was often staged into more than one treatment phase. For example, a substantial proportion of patients undergoing debulking surgery received postsurgery systemic chemotherapy, the latter often refined by the reassessment of new histologic material. Notably, two patients, originally considered inoperable but who were treated with systemic chemotherapy and subsequently restaged and reassessed, underwent potentially curative CS and HIPEC.[15]

The number of referrals increased linearly in the first half of the study period, thereafter reaching a plateau. The proportion of patients undergoing CS and HIPEC was just under one-third for each year (Fig. 1). By contrast, the proportion of patients undergoing debulking surgery declined with time ($P_{trend} = 0.005$).



	2002	2003	2004	2005	2006	2007	P_{trends}
Total referrals per year	17	34	51	55	62	59	
Complete cytoreduction	7 (41)	9 (26)	14 (27)	17 (31)	17 (27)	17 (29)	0.91
Debulking surgery	7 (41)	7 (21)	8 (16)	4 (7)	5 (8)	6 (10)	0.005

FIGURE 1. Clinical pathways of initial management. Stages refer to scenarios where intended initial management involves more than one treatment. [a]Four patients with pseudomyxoma peritonei had complete cytoreductive surgery as planned two-stage procedures due to extensive intra-abdominal dissemination. [b]Seven patients underwent repeated debulking procedures. Values in parentheses refer to percentage of cases per year undergoing major laparotomy. HIPEC = hyperthermic intraperitoneal chemotherapy; KND = known residual disease after surgery elsewhere but decision to watch and wait; NDD = no discernible disease after appendicectomy prereferral.

Baseline Characteristics

The baseline characteristics for all patients and for the 118 patients undergoing surgery are listed in Table 1. The median ages for the two surgical groups did not differ statistically. By contrast, the preoperative geometric means for the three routinely measured serum tumor markers were significantly elevated in the debulking surgery group as compared with the CS group ($P < 0.0001$ for all three markers). The most common histologic group undergoing major surgery was pseudomyxoma peritonei (101 patients, 86%); the second most common was peritoneal carcinomatosis of colorectal origin (6 patients, 5%).

Types of Procedures

Of the 81 patients who underwent complete CS, all but 3 received HIPEC. By contrast, only 4 of the 37 patients undergoing debulking surgery received intraoperative chemotherapy (see footnote in Table 2). Among the total surgical cases, more than one-half had undergone oophorectomies and/or hysterectomy before referral, reflecting the pattern of presentation of peritoneal surface tumors in the United Kingdom. Among those undergoing complete CS, approximately half had upper abdominal disease requiring peritonectomy of either one or both hemidiaphragms and liver surface ablation. Splenectomy was performed in 25 (31%) patients as part of complete cytoreduction and in 7 (18%) as part of a debulking operation. In female patients, the requirement for upper abdominal surgery was matched with the need to undertake removal of the ovaries and/or hysterectomy at the time of the same operation or at a previous operation (prereferral). Right and left colonic resections were required in approximately one-fifth of complete CS cases. Equally, approximately one-fifth to one-quarter of all surgical cases required stoma formation, with no differences between those undergoing CS or debulking surgery. However, permanent stoma rates were significantly higher after debulking surgery (21% *vs.* 4%, $P = 0.004$).

TABLE 1. Baseline characteristics of all patients and surgically treated patients

	All patients[a]	*Complete cytoreduction*[a]	*Debulking surgery*[a]
No.	278	81	37
Age (yr), median (range)	56.9 (16–86)	53.0 (16–76)	56.3[b] (33–83)
Males:females	99:179	21:60	16:22
Preoperative serum tumor markers (ng/ml), geometric mean (95% CI)			
CEA		4.5 (3.8–5.4)	21.2[c] (13.7–32.9)
CA-125		14.8 (12.2–18.0)	60.7[c] (40.3–91.3)
CA19-9		14.3 (10.4–19.6)	126.3[c] (61.3–260.3)
Peritoneal Cancer Index, median (range)	24 (0–39)	21 (0–39)	29.5 (14–39)
Histological type			
Pseudomyxoma peritonei spectrum			
LAMN Type I	12 (4)	3	0
LAMN Type II	13 (5)	10 (12)	0
DPAM	111 (40)	38 (47)	17 (46)
PCMA-I/D	39 (14)	10 (12)	9 (24)
PMCA	28 (10)	8 (10)	6 (16)
Appendiceal adenocarcinoma	11 (4)	2	1
Peritoneal carcinomatosis, colorectal origin	8 (3)	5 (6)	1
Peritoneal malignant mesothelioma	4	2	0
Primary peritoneal carcinoma	3	1	0
Other histologies	5 (2)	2[d]	3[e]
No or incomplete histology			
Pseudomyxoma peritonei clinical pattern	44 (16)	0	0

CA = cancer antigen; CEA = carcinoembryonic antigen; CI = confidence interval; DPAM = disseminated peritoneal adenomucinosis; LAMN = low-grade appendiceal mucinous neoplasm (without dissemination beyond the periappendiceal tissue); PMCA = peritoneal mucinous carcinomatosis; PMCA-I/D = PMCA with intermediate or discordant features; PMP = pseudomyxoma peritonei.

[a]Values in parentheses are percentages unless otherwise stated.

[b]Comparison of medians using Mann-Whitney *U* test: $P = 0.11$.

[c]Student's *t*-test of log-transformed values: $P < 0.0001$ for group comparisons across CEA, CA-125, and CA-19-9.

[d]One PMP from a mucinous ovarian cystic tumor; one PMP arising from an ovarian teratoma.

[e]One peritoneal carcinomatosis of small intestinal origin; one PMP arising from a goblet cell carcinoid of the appendix; one PMP of mixed origin, ovarian mucinous tumor and bilateral ovarian teratomas.

The durations of surgery varied by procedure type: the median operating time for complete CS was significantly longer than that for debulking surgery, even after adjustment for time to administer the HIPEC ($P = 0.007$; (Table 3). The median durations for patients in critical care and total hospital stay did not differ between surgical groups.

Complications of Treatment

Among the 118 surgical cases, there was no 30-day mortality. A complication of any type occurred in one-third of all surgical cases (Table 4). Mild or moderate complications were marginally higher after complete cytoreduction than after debulking surgery, reflecting higher rates of postsplenectomy thrombocytosis in the former group. Severe or life-threatening complications occurred in 11 (9%) patients with no differences between surgical groups. Overall, rates for anastomotic leakage (n = 1), reoperation for hemorrhage (n = 1), and thromboembolic events (n = 2) were low. There were no Grade 3 or 4 hematologic toxicities (neutrophil cell count $<1.0 \times 10^9$/dl) associated with the administration of HIPEC. Any type complication rates were higher in patients with elevated PCI scores, but the difference was not statistically significant (PCI $\geq$24 *vs.* $<$24: 35% *vs.* 28%, $P = 0.40$).

Oncologic Outcomes

Among the 118 surgically treated patients, only 3 were lost to follow-up. With a median follow-up of 18 (range, 1–82) months, there were 11 locoregional recurrences, or a three-year recurrence rate of 22%, after complete CS. Of the 13 cases with disease confined to the appendix and managed by active monitoring, there were no cases of disease progression after a median follow-up of 20 (range, 5–37) months.

There were 27 deaths during follow-up of the surgically treated cases: 3 from unrelated causes (1 murder, 2 cardiovascular deaths), and the remainder in the presence of tumor. The three-year and five-year tumor-related survival rates for all surgical cases were 78% and 56%, respectively. Incomplete cytoreduction was a significant predictor of poor tumor-related-survival ($P < 0.0001$; Fig. 2). Subdivision into four CC scoring categories also predicted for tumor-related survival ($P < 0.0001$), but discrimination between CC-0 and CC-1 was poor. The five-year tumor-related survival rates by PCI categories were as fol-

TABLE 2. Surgical procedures by complete cytoreduction *vs.* debulking surgery

	Complete cytoreduction[a] *(n = 81)*		*Debulking surgery*[a] *(n = 37)*	
	Prereferral	*Postreferral*	*Prereferral*	*Postreferral*
HIPEC				
Yes		78 (96)		4[c]
No		3[b]		33 (89)
Operative procedures				
Biopsy	11 (14)		14 (38)	
Appendicectomy	41 (51)	14 (18)	9 (24)	10 (27)
Partial greater omentectomy	32 (40)		12 (32)	17 (46)
Total greater omentectomy		77 (95)		16 (43)
Lesser omentectomy		72 (89)		7 (19)
Cholecystectomy		63 (78)		2
Right hemidiaphragm peritonectomy or ablation		35 (43)		3
Liver surface ablation		25 (31)		2
Left hemidiaphragm peritonectomy or ablation		18 (23)		4 (11)
Splenectomy		25 (31)		7 (19)
Right colonic resection	16 (20)	16 (20)	1	8 (29)
Left colonic resection		15 (19)		4 (11)
Small-bowel resection		3 (4)		5 (13)
Anterior parietal and/or pelvic peritonectomies		59 (72)		31 (82)
Stripping and/or ablation serosal deposits		8 (10)		3 (8)
Other	11 (14)	6[d] (7)	4 (11)	12[d] (32)
Women only (60 complete cytoreduction, 21 debulking surgery)				
Hysterectomy	38 (63)	6 (10)	9 (43)	4 (19)
Bilateral oophorectomy	38 (63)	9 (15)	11 (52)	4 (19)
Unilateral oophorectomy	4 (7)	7 (12)	1	1
Stoma formation				
Any stoma	0	16 (20)	0	10 (27)[e]
Permanent stoma	0	3 (4)	0	8 (22)[f]

CC = completeness of cytoreduction (scoring system); CS = cytoreductive surgery; HIPEC = hyperthermic intraoperative chemotherapy.
[a]Values in parentheses are percentages.
[b]One previously treated with debulking surgery and postsurgery systemic mitomycin C; one initially classified as a caecal adenocarcinoma was later reclassified as a LAMN; and one had no mucinous disease at exploratory laparotomy.
[c]One received HIPEC as part of a first-stage CS, but at the second stage, complete cytoreduction was not feasible because of extensive disease progression; three underwent nearly complete cytoreduction but had isolated residual disease >2.5 mm in a few areas and thus were classified as CC-2.
[d]Other operative procedures included one partial distal gastrectomy; one excision of gastrointestinal stromal tumor from greater curvature of stomach; one extensive adhesiolysis; one total pelvic clearance for excision of vesicovaginal fistula; one cystoprostatectomy; one gastrojejunostomy bypass; two ileotransverse bypasses; one excision of vaginal vault; two abdominal wall excisions; and one incisional hernia nonmesh repair.
[e]Chi-squared test, $P = 0.38$.
[f]Fisher's exact probability test, $P = 0.004$.

lows: 93% for PCI scores 0 to 9; 85% for 10 to 19; 66% for 20 to 29; and 45% for 30 to 39. However, this was not statistically significant ($P = 0.56$).

For the two main histologic groups that were surgically treated, PMP and peritoneal carcinomatosis of colorectal origin, the three-year tumor-related survival rates were 82% and 67%, respectively, but these differences were not statistically significant. Among the PMP cases, histologic subclassification according to the Ronnett classification significantly predicted tumor-related survival ($P = 0.0005$), but discrimination between DPAM and PMCA-I/D was not evident. Tumor grade was a significant predictor of tumor-related survival ($P = 0.0001$; Fig. 3).

We developed Cox models including gender, age at

TABLE 3. Perioperation-related durations

	Complete cytoreduction[a]	*Debulking surgery*[a]	*P*[b]
Total operative time (hr)	8.3 (2.7–12.8)	4 (1.5–11.0)	0.0001
Surgical operative time (hr)	6.3 (1.8–10.8)	4 (1.5–10.8)	0.007
Duration on critical care (days)	4 (1–9)	4 (1–48)	0.80
Total hospital stay (days)	15 (10–66)	16 (9–141)	0.45

[a]Values are median (range).
[b]Mann-Whitney *U* test.

TABLE 4. Complications for complete cytoreduction *vs.* debulking surgery

	Complete cytoreduction[a] *(n = 81)*	*Debulking surgery*[a] *(n = 37)*	*P*[b]
30-day mortality	0	0	
Any complications	29 (36)	9 (24)	0.22
Grade 1 and 2 complications	25 (31)	6 (16)	0.09
Wound infection	2	0	
Thrombocytosis[c]	11	3	
Feeding line sepsis	2[d]	0	
Thromboembolic	1[e]	1	
Cardiac dysrhythmia	3	0	
Urinary tract infection	3	0	
Lower respiratory tract infection	4	1	
Electrolyte disturbance	1	1	
Grade 3 and 4 complications	4 (5)	3 (8)	0.50
Reoperation for any cause	0	2	
Anastomotic leak	0	1[f]	
Hemorrhage	0	1[g]	
Pancreatitis	0	0	
Chest infection/pleural effusion	2	1	
Renal failure	1	0	
Idiosyncratic anesthetic reaction	1	0	
Hematologic toxicity	0	0	
Late complications			
Incisional hernia	1[h]	0	

[a]Values in parentheses are percentages.
[b]Chi-squared and Fisher's exact probability tests as appropriate.
[c]Thrombocytosis related to splenectomy in all but two cases.
[d]Parenteral feeding routinely used in complete cytoreduction cases, but not routine in debulking surgery cases.
[e]Portal vein thrombosis.
[f]Anastomotic leakage, subsequent reoperation and formation of laparostomy.
[g]Hepatic bleeding requiring packing.
[h]Repaired as a subsequent operation.

surgery, completeness of cytoreduction, tumor grade, PCI, and serum tumor marker measurements (log-transformed; Table 5). These models demonstrated that male

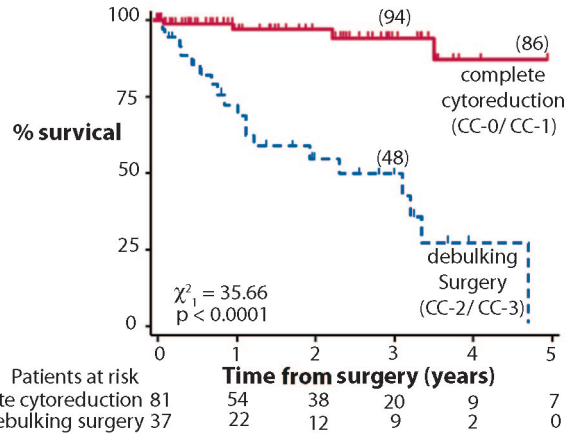


FIGURE 2. Tumor-related survival rates by completeness of cytoreduction (CC). Values in parentheses refer to rates for three-year and five-year tumor-related survival. *P* value derived from log-rank test.

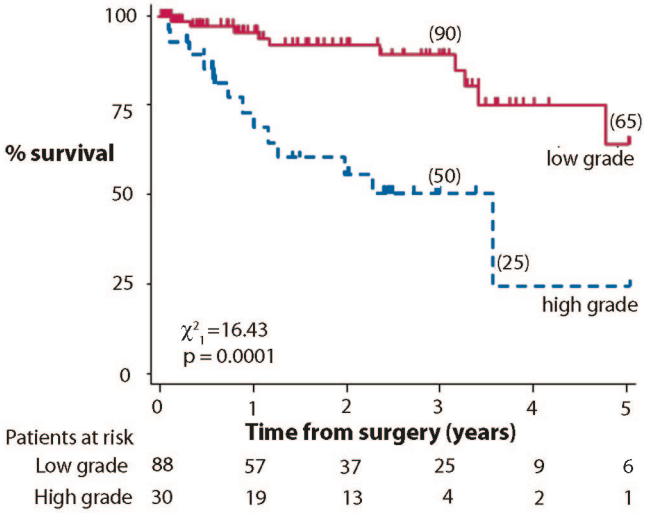


FIGURE 3. Tumor-related survival rates by tumor grade. Values in parentheses refer to rates for three-year and five-year tumor-related survival. *P* value derived from log-rank test.

gender ($P = 0.02$), incomplete cytoreduction ($P = 0.001$), and high-grade tumor ($P < 0.0001$) were independent predictors of poorer tumor-related survival. Models including serum tumor markers and PCI did not confound results and failed to show independence of these variables.

DISCUSSION

This paper has described the first six years of experience of a centralized national service for the management of peritoneal surface tumors and demonstrated the following main findings. First, just under one-third of all referrals were treated by complete cytoreduction. Of those undergoing laparotomy, 65% had a complete cytoreduction and HIPEC, a proportion almost identical to that reported for the series from Basingstoke (UK),[4] Washington,[9] and Amsterdam,[24] but less than of the 91% reported from the Milan unit.[25] We noted a reduction in the proportion of cases undergoing debulking surgery over the study period, in part reflecting the better selection of patients with unresectable disease who may benefit from systemic chemotherapy[15] and in part, as noted by others,[24] reflecting the learning curve in the selection of cases for surgery. Second, for patients not undergoing surgery, this study illustrates the requirement for a number of alternative treatment strategies through integrated multistage pathways. Thus, for example, the majority of patients with LAMN Type I were managed by a watch–and-wait policy without adverse oncologic outcome (based on current follow-up) and are the subject of an ongoing analysis. Third, despite aggressive locoregional treatments, there were no perioperative mortalities and major complication rates were low, the latter comparing favorably with the literature; for studies of similar case mix with more than 100 patients undergoing

TABLE 5. Cox proportional hazard models for tumor-related survival

	Factor conveying worse survival	*Hazard ratio*	*(95% CI)*	*P*
Age (per 10-yr increment)	Increasing age	1.39	0.85–2.30	0.19
Gender (male *vs.* female)	Male	4.10	1.34–12.53	0.01
Completeness of cytoreduction (CC-2/CC-3 *vs.* CC-0/CC-1)	Incomplete cytoreduction	11.31	2.60–49.24	0.001
Tumor grade (high *vs.* low)	High grade	12.40	3.69–41.70	<0.0001

CI = confidence interval.

CS and HIPEC, perioperative mortality rates were 2%,[26] 3%,[27] and 5%.[4] Several series report high rates of major complications, such a reoperation rates of 11%[26] and 21%,[28] but this problem was uncommon (<2%) in our series. Reflecting these advantageous patterns of complications, the median hospital stay of 15 days compares favorably with the 16 to 29 days from other series.[9,28–31] Equally, despite the use of a high-dose mitomycin C intraoperative chemotherapy regimen, we had no serious hematologic toxicities, whereas rates from 4% to 9% are quoted in the literature.[32] Fourth, our oncologic outcomes compared equally with those of other series. For example, for PMP, a recent systematic review[32] reported five-year survival rates ranging from 52% to 96% (from six series), whereas the five-year tumor-related survival rate in the present series was 53%. We believe that the internationally comparable oncologic outcomes, matched by the low morbidity rates, reflect the case selection and performance status optimization brought about through the centralized multidisciplinary team. Finally, similar to other large series,[4,9,33] the distinction between complete and incomplete cytoreduction was a major predictor of outcome in univariate analysis and independent of confounding factors using the Cox model. Ronnett and colleagues[20,34] reported that the categorization of PMP into three histologic types is discriminatory in terms of prognosis, but this was not replicated in the present series. Instead, the classification of peritoneal surface tumors into low-grade and high-grade, as an extension of the Bradley classification for PMP,[23] was a significant prognosticator in the current analysis and was independent of incompleteness of cytoreduction in the Cox model. The PCI has been shown to be a useful prognosticator in some types of peritoneal surface tumor,[11] but it was not significant in the present, mainly PMP, series. Nonetheless, PCI should be determined and reported in the patients with peritoneal malignancies to assess its potential value as a predictor of outcome and as a benchmark with which to compare treatment-related morbidities.

The present study has a number of advantages. First, data on treatments, complications, and oncologic outcomes were collected prospectively. Second, the management of the nonsurgically treated patients has been summarized, whereas other published series focused on surgical outcome dependent on histologically distinct groups. Third, a Cox model was used to determine independence of prognosticators to reinforce the development of predictors that refine management decisions. Fourth, and most important, this study has illustrated how a dedicated multidisciplinary meeting directs patients along appropriate clinical pathways to achieve the best standard of care and outcomes. This achievement was brought about through the establishment of a centralized national treatment service commissioned by the UK National Health Service National Commissioning Group for Highly Specialized Services. This is a model of healthcare delivery for rare diseases requiring highly specialized services and is unique to the United Kingdom.[1] In setting up the national center, the team optimized treatment selection criteria, preoperative and intraoperative decision-making processes, and learning from the experience of others[12] with the aim of shortening the learning curve.[24] For example, the median operating time in this series of 8.3 hours compares with 6.0 to 12.6 for other series.[25,28,29,31,33,35] Centralization additionally delivered uniformity of radiologic assessment, intraoperative chemotherapy protocols, and pathology reporting, and high compliance rates for follow-up.

The following were potential study limitations. First, peritoneal carcinomatosis of upper gastrointestinal and/or ovarian origin was not treated in this series, because these malignancies are not reimbursed under the current Department of Health commissioning agreements. For gastric cancer, a meta-analysis of 13 randomized trials supported a beneficial effect with CS and HIPEC but simultaneously warned of the potential associated high morbidity.[36] For ovarian cancer, trials suggest a benefit with intraoperative chemotherapy in patients with advanced disease,[37] but unlike other tumor groups, cytoreduction to 1 cm of disease seems to achieve adequate locoregional control. Second, the use of HIPEC was restricted (with a few exceptions) to cases where optimal cytoreduction (CC-0 and CC-1) was achieved. This contrasts to the large experience of the Washington Cancer Institute, where intraoperative chemotherapy is routinely used after incomplete CS with apparent survival benefits, but at a cost of increased levels of major complications (33%).[30] Third, the median follow-up in the present series is short. Longer term follow-up is required to further refine

optimal treatment pathways, which will inform future management decisions and continue to improve the standard of care for these patients.

The achievement of low morbidity and mortality in this early experience, of mainly PMP of appendiceal origin, supports the consideration of the wider application of CS and intraoperative chemotherapy to other peritoneal surface malignancies. Notably, there has been evidence for some time of the potential benefit of CS and HIPEC for peritoneal carcinomatosis of colorectal origin,[12,38] backed by a consensus statement from the Society of Surgical Oncology[39] and a systematic review performed by the National Institute for Clinical Excellence (London, UK).[40] Our experience with a limited number of selected patients of this type supports these proponents. The number of cases suitable for treatment will demand a need for a parallel development in training surgeons, oncologists, radiologists, and other allied specialists to assist in appropriate selection and successful treatment.

There are several unresolved questions in the field of peritoneal surface malignancies. These include refinements of histologic classifications, enhanced case selection, role of systemic chemotherapy compared with surgery, and new treatment options through a better understanding of tumor biology. For example, we have shown that PMP tumors are characterized by molecular attributes of tumor invasion potential similar to that of colorectal adenocarcinomas[41] and have speculated that these changes, termed epithelial-mesenchymal transition, may be defective in PMP such that neoplastic cells disseminate widely throughout the abdominal cavity but rarely metastasize to distant sites.[2] Centralization of cases has afforded the opportunity to establish clinical and laboratory research programs, including tissue banking, in parallel with the development of the clinical services. Through these initiatives, we envisage an enhanced understanding of the natural history of peritoneal surface malignancies, which will benefit patients in the future.

ACKNOWLEDGMENTS

The Peritoneal Tumor Service multidisciplinary team comprises the following members: S. T. O'Dwyer, M. S. Wilson, P. E. Fulford, and A. G. Renehan (colorectal surgeons); D. J. Sherlock (hepatobiliary surgeon); M. P. Saunders (clinical oncologist); B. Carrington and B. Taylor (oncology radiologists); S. Beards, S. McGuire, D. Tansey, P. Haji-Michael, C. Van Oldenbeek, and A. Bhaska (anesthetists); B. Chakrabarty, K. Sikand, and J. Shanks (oncology pathologists); M. F. Parkinson (service manager); S. Rout (research fellow); N. Warburton (data manager); and P. Crichton (senior perfusionist). The authors thank the following for their assistance in the analysis of this study: Nicola Warburton for updating the database and Gary Witham, nurse specialist.

REFERENCES

1. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol 2006;7:69–76.
2. Renehan AG, O' Dwyer ST, Stern PL. Pseudomyxoma peritonei. In: Schwab M, ed. Encyclopedia of cancer. London: Springer, 2009:2134–8.
3. Moran BJ. Establishment of a peritoneal malignancy treatment centre in the United Kingdom. Eur J Surg Oncol 2006;32:614–8.
4. Murphy EM, Sexton R, Moran BJ. Early results of surgery in 123 patients with pseudomyxoma peritonei from a perforated appendiceal neoplasm. Dis Colon Rectum 2007;50:37–42.
5. Bradley RF, Cortina G, Geisinger KR. Pseudomyxoma peritonei: review of the controversy. Curr Diagn Pathol 2007;13:410–6.
6. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 2003;27:1089–103.
7. Sugarbaker PH. Evolving strategies for surgical management of carcinomatosis. ANZ J Surg 2006;76:162–9.
8. Sugarbaker PH. Peritonectomy procedures. Cancer Treat Res 2007;134:247–64.
9. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999;6:727–31.
10. 5th International Workshop on Peritoneal Surface Malignancy, Milan, Italy, December 4 to 6, 2006. Available at: http://www.peritonealworkshop2006.com. Accessed August 9, 2008.
11. Harmon RL, Sugarbaker PH. Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. Int Semin Surg Oncol 2005;2:3–10.
12. de Bree E, Witkamp AJ, Zoetmulder FA. Intraperitoneal chemotherapy for colorectal cancer. J Surg Oncol 2002;79:46–61.
13. Yan TD, Brun EA, Cerruto CA, Haveric N, Chang D, Sugarbaker PH. Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma. Ann Surg Oncol 2007;14:41–9.
14. Stephens AD, Alderman R, Chang D, *et al.* Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol 1999;6:790–6.
15. Farquharson AL, Pranesh N, Witham G, *et al.* A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. Br J Cancer 2008;99:591–6.
16. Saunders M, Iveson T. Management of advanced colorectal cancer: state of the art. Br J Cancer 2006;95:131–8.
17. Geerts W, Ray JG, Colwell CW, *et al.* Prevention of venous thromboembolism. Chest 2005;128:3775–6.
18. Common terminology criteria for adverse events, version 3.0. Bethesda, MD: National Cancer Institute, 2006. Available at: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx. Accessed April 27, 2008.
19. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ 2002;324:813–7.
20. Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Wu L, Sugarbaker PH. Patients with pseudomyxoma peritonei associated

with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer 2001;92:85–91.
21. World Health Organization Classification of Tumours. Pathology and genetics: tumours of the digestive system. Lyon: IARC Press, 2000.
22. Hosmer DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time to event data. New York: Wiley, 2008.
23. Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 2006;30: 551–9.
24. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. Br J Surg 2007;94:1408–14.
25. Deraco M, Baratti D, Inglese MG, *et al.* Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. Ann Surg Oncol 2004;11:393–8.
26. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, Chang D. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006;13: 635–44.
27. Smeenk RM, Verwaal VJ, Zoetmulder FA. Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei—a report of 103 procedures. Eur J Surg Oncol 2006;32:186–90.
28. Piso P, Bektas H, Werner U, *et al.* Improved prognosis following peritonectomy procedures and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from appendiceal carcinoma. Eur J Surg Oncol 2001;27:286–90.
29. Zoetmulder FA, van der Vange N, Witkamp AJ, Kaag MM, Boot H, Beijnen JH. Hyperthermic intra-peritoneal chemotherapy (HIPEC) in patients with peritoneal pseudomyxoma or peritoneal metastases of colorectal carcinoma; good preliminary results from the Netherlands Cancer Institute [in Dutch]. Ned Tijdschr Geneeskd 1999;143:1863–8.
30. Glehen O, Mohamed F, Sugarbaker PH. Incomplete cytoreduction in 174 patients with peritoneal carcinomatosis from appendiceal malignancy. Ann Surg 2004;240:278–85.
31. Yan TD, Links M, Xu ZY, Kam PC, Glenn D, Morris DL. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei from appendiceal mucinous neoplasms. Br J Surg 2006;93:1270–6.
32. Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol 2007;14:484–92.
33. Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. Am Surg 2000;66:561–8.
34. Ronnett BM, Shmookler BM, Sugarbaker PH, Kurman RJ. Pseudomyxoma peritonei: new concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. Anat Pathol 1997;2: 197–226.
35. Butterworth SA, Panton ON, Klaassen DJ, Shah AM, McGregor GI. Morbidity and mortality associated with intraperitoneal chemotherapy for pseudomyxoma peritonei. Am J Surg 2002; 183:529–32.
36. Yan TD, Black D, Sugarbaker PH, *et al.* A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol 2007;14:2702–13.
37. Senior K. Intraperitoneal treatment lengthens survival in ovarian cancer. Lancet Oncol 2006;7:107.
38. Gilly FN. Phase II studies: international registry of colorectal carcinomatosis. Eur J Surg Oncol 2006;32:648–54.
39. 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.
40. National Institute for Health and Clinical Excellence (NICE). Complete cytoreduction and heated intraperitoneal intraoperative chemotherapy (Sugarbaker technique) for peritoneal carcinomatosis. London: National Institute for Health and Clinical Excellence, 2005. Available at: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11152. Accessed April 27, 2008.
41. Bibi R, Pranesh N, Saunders MP, *et al.* A specific cadherin phenotype may characterise the disseminating yet non-metastatic behaviour of pseudomyxoma peritonei. Br J Cancer 2006;95: 1258–64.

INVITED COMMENTARY

To the Editor—The treatment of peritoneal surface malignancies with cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly gaining interest in the surgical oncology world. Because of its complexity, this treatment can only be performed in specialized centers. In this issue of Diseases of the Colon & Rectum, Rout *et al.* report the institutional experience of the peritoneal tumor service of the Christie Hospital National Health Service (NHS) Foundation Trust, one of the two centralized centers commissioned by the United Kingdom Department of Health for the treatment of peritoneal surface malignancies. In the first five years of the center, 278 patients were evaluated by a multidisciplinary team; 118 of these patients had surgery, but only 78 (26 percent) underwent the full treatment of cytoreduction followed by HIPEC. In Figure 1 of their article, Rout and colleagues provide a diagram of the clinical pathways followed by their patients, but they do not report the criteria used by the multidisciplinary team to decide among the different treatment options. Without knowledge of the selection criteria, it is difficult to compare with other series, but the percentage of patients who had surgery seems low. It is possible that the difference may reflect referral patterns specific to the United Kingdom, however.

In the Material and Methods section, the authors state that patients were offered complete cytoreduction or debulking based on clinical information collected during the initial evaluation. However, they do not give the proportion of patients in whom they were unable to perform a complete cytoreduction. The improvement in the selection of patients with unresectable disease in recent years implies that the type of surgery performed was determined by the extent of the disease encountered at surgery rather than the initial decision made by the multidisciplinary team. The conclusion that patients who had a complete cytoreduction fared better than those who had debulking surgery is hardly surprising.

In Table 1, the authors present data on the histologic types of all patients, including those who never had surgery. According to these data, almost two thirds of the patients who had complete cytoreduction had lowgrade tumors— either low-grade appendiceal mucinous neoplasm or disseminated peritoneal adenomucinosis. Because these types of tumor have a relatively good prognosis, it is unclear how many of these patients truly required such aggressive treatment. In this series, 23 patients received no treatment and were actively monitored. It would be interesting to compare treatment outcomes—in regard to morbidity and health care costs, as well as survival—for patients with low-grade tumors who received surgery *vs.* those who did not.

The combination of surgical cytoreduction and intraperitoneal chemotherapy for peritoneal surface malignancies is a complex treatment method that should be provided only at specialized institutions. Therefore, the efforts of the NHS to regionalize the care of these patients in the United Kingdom should be viewed as a step in the right direction. Unfortunately, the data generated from this effort do not yet answer the main question regarding this issue—whether cytoreduction plus intraperitoneal chemotherapy helps patients with peritoneal surface neoplasm. This question can only be answered with a properly designed study in which patients are selected according to welldefined criteria, treated according to uniform protocols, and evaluated on an intentionto–treat basis. The heterogeneity of these neoplasms and their relative infrequency should not be an excuse not to conduct rigorous research. Countries with a national health care system, such as the United Kingdom, are in an advantageous position to perform such a study.

Vic J. Verwaal, M.D., Ph.D.
Amsterdam, The Netherlands