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Morbidity Associated with Colostomy Reversal After Cytoreductive Surgery and HIPEC

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ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has improved the survival in selected colorectal cancer patients with peritoneal metastases. In these patients, the risk of a low anastomosis is sometimes diminished through the creation of a colostomy. Currently, the morbidity and mortality associated with the reversal of the colostomy in this population is unknown.

Methods. Our study involved two prospectively collected databases including all patients who underwent CRS–HIPEC. We identified all consecutive patients who had a colostomy and requested a reversal. The associations between four clinical and ten treatment-related factors with the outcome of the reversal procedure were determined by univariate analysis.

Results. 21 of 336 patients (6.3 %) with a stoma with a mean age of 50.8 (standard deviation 10.2) years underwent a reversal procedure. One patient was classified as American Society of Anesthesiologists (ASA) grade III, 6 as ASA grade II, and the remaining as ASA grade I. Median time elapsed between HIPEC and reversal was 394 days (range 133–1194 days). No life-threatening complications or mortality were observed after reversal. The reversal-related morbidity was 67 %. Infectious complications were observed in 7 patients (33 %). Infectious complications after HIPEC were negatively correlated with the ultimate restoration of bowel continuity ($P = 0.05$). Bowel continuity was successfully restored in 71 % of the patients.

Conclusions. Although the restoration of bowel continuity after CRS–HIPEC was successful in most patients, a relatively high complication rate was observed. Patients with infectious complications after HIPEC have a diminished chance of successful restoration of bowel continuity.

Colorectal carcinoma is the third most common cancer worldwide, accounting for approximately 1 million newly diagnosed patients per year and over 600,000 deaths due to this disease.[1] Approximately 10–25 % of colorectal cancer patients develop peritoneal metastases, of whom 25 % present with the peritoneum as the sole site of distant metastases.[2–4] The peritoneum is a thin membrane that covers the abdominal wall and internal organs.[5] Peritoneal metastases are believed to be the result of tumor cell shedding into the peritoneal cavity, either spontaneously or as a result of spill during surgical procedures, ultimately resulting in the development of tumor deposits on the peritoneal surface.[6,7] In the past, peritoneal metastases were regarded as a condition amenable only to treatment with palliative intent because of the belief that the condition inevitably leads to rapid death. However, isolated peritoneal metastases are regarded as a form of localized disease spread and thus are amenable to local control via cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[8–11]

During the CRS procedure, multiple resections are often carried out to remove all intra-abdominal tumor, among

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which are resections of the intestines. CRS–HIPEC is known as a procedure with a relatively high major morbidity (grade III/IV) rate, ranging from 12 to 52 %.[12] A large portion of tumor bulk is situated in Douglas pouch following the natural intraperitoneal flow.[13] Consequently, the rectum is transected below this point, resulting in a low or ultralow anastomosis if the surgeon opts for immediate reconstruction of bowel continuity.

These ultralow anastomoses are known to carry a high risk of complications such as leakage.[4,15] To avoid ultralow anastomoses and thus lower the risk of additional complications in an already highly morbid procedure, colostomies are created.[15,16]

Several studies have reported a reduced quality of life (QoL) in patients living with a colostomy.[17,18] This results in a proportion of patients requesting a reversal procedure to restore the bowel continuity as soon as medically prudent.[17] Nevertheless, several studies have reported that colostomy reversal is accompanied by significant morbidity and mortality, describing rates of anastomotic leakage of up to 25 % and mortality of up to 14 %.[17,19]

The morbidity and mortality accompanying such a reversal procedure in a population that has previously undergone extensive surgery in the form of CRS–HIPEC is currently unknown. Our aim is to investigate all consecutive colostomy reversal procedures in a prospective cohort of CRS–HIPEC patients.

PATIENTS AND METHODS

Patient Selection and Data Collection

We studied two prospectively collected databases evaluating all patients who underwent CRS-HIPEC in two Dutch institutes (National Cancer Institute—Antoni van Leeuwenhoek Hospital, and the Catharina Hospital in Eindhoven) between January 2000 and December 2009. We subsequently identified all patients who received a stoma as part of the CRS–HIPEC procedure who actively wished to have the procedure reversed. All consecutive patients who received a colostomy with a follow-up of more than 6 months after the reversal procedure were included for further analysis. We excluded patients with an ileostomy and reversal of the colostomy due to dysfunction of the colostomy.

Patients were followed up according to the standard of care at both institutions, which is in accordance with the Dutch HIPEC protocol.[15,20] Patient characteristics gathered included the following: age, gender, medical history, comorbidity, American Society of Anesthesiologists (ASA) grade, and tumor type. Treatment-related factors assessed included the following: HIPEC procedure details, hospital stay, time between HIPEC procedure and colostomy reversal, reversal procedure details, mortality, hospital stay after reversal procedure, number of invasive procedures for the reversal procedure, and whether the reversal procedure was ultimately successful.

The postoperative complications were assigned grades ranging from grade I to grade V (Supplementary Data).[21]

Surgical Procedure

The CRS–HIPEC procedure was carried out in a uniform fashion by the surgical teams of both institutes according to a previously published protocol.[15] The objective of CRS is to remove all macroscopically visible tumor in the abdominal cavity, with only limited disease remaining (<2.5 mm). The parietal peritoneum is routinely stripped and the omentum surgically removed according the technique pioneered by Sugarbaker.[10] All affected viscera are surgically removed. Bowel continuity is restored after the intra-abdominal lavage with the cytostatic compound to prevent the postoperative entrapment of tumor cells that may cause local recurrence in the future. In most patients in whom the Douglas pouch was affected and in whom rectal resections were therefore unavoidable, a colostomy was created in order to avoid ultralow anastomosis (Hartmann procedure).[15]

The HIPEC procedure was performed according to the coliseum technique (open) in all cases in both institutes. The duration of the HIPEC procedure was 90 min at a temperature held constantly between 39 and 41 °C. Mitomycin C was the cytostatic drug of choice in all cases.

Data Analysis

Data analysis was performed utilizing the statistical package for the socials sciences (SPSS, Chicago, IL), version 20 for OsX. Descriptive statistics were used to describe clinical and treatment-related factors in the cohort.

Clinical and treatment-related factors were analyzed for an association with the occurrence of complications after the reversal procedure, and to assess whether bowel continuity was successfully restored.

Differences were computed by the unpaired t test for numerical data that were normally distributed, the Mann–Whitney U test for numerical data that were not normally distributed, or the χ^2 test for unpaired ordinal and categorical data. A P value of ≤ 0.05 was considered statistically significant.

RESULTS

From January 2000 to December 2009, a total of 747 consecutive patients underwent CRS-HIPEC treatment. Of

these patients, 32 patients (9.5 %) underwent a reversal procedure after the recovery period. We excluded six patients on the basis of the presence of an ileostomy after CRS–HIPEC; three patients were excluded because the reversal was unavoidable because of dysfunction or leakage of the colostomy; and two patients were excluded from the analysis as a result of a clinical follow-up after the reversal procedure of less than 6 months (Fig. 1).

Patient Characteristics

All patient characteristics are listed in Table 1. This cohort consisted of 21 patients, 7 men (33 %) and 14 women (66 %). The mean age was 50.8 years with a standard deviation of 10.2 years. Before the CRS–HIPEC, a median of two abdominal procedures were performed per patient (range 1–4). On average, four resections were performed during the CRS–HIPEC procedure. Resections included the following: peritoneotomies, surgical removal of organs and viscera affected by disease spread (ovaries, uterus, sections of the small and large intestines, spleen, and stomach), and, in 6 of 21 (28.6 %), the synchronous removal of the primary tumor. In 17 of 21 eligible patients (81 %), a macroscopically complete cytoreduction was achieved. In the remaining four cases, a complete cytoreduction was not technically feasible, and a minimum of residual disease was left in situ (<2.5 mm = R2a). All these patients presented with pseudomyxoma peritonei (Table 2).

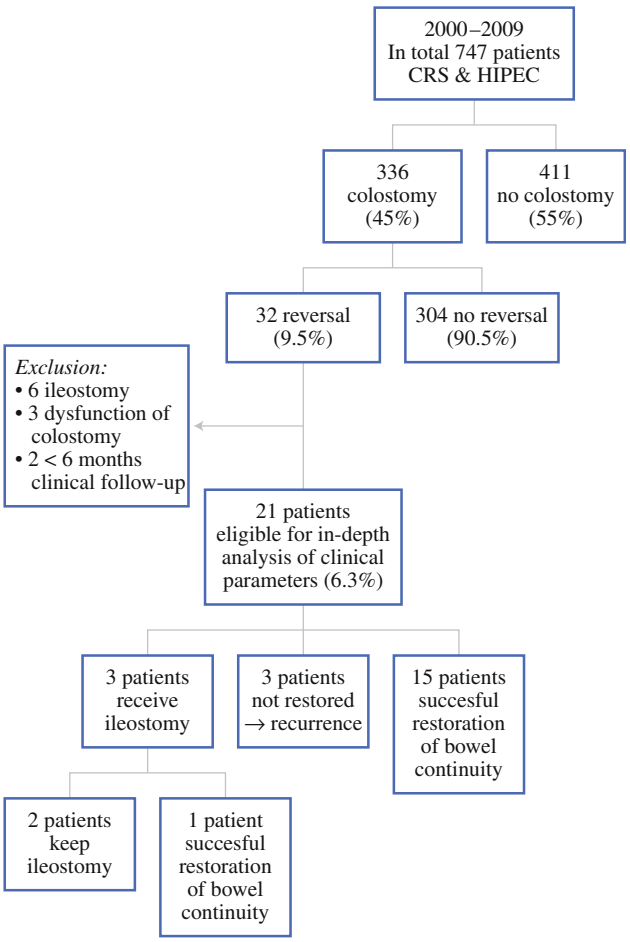

FIG. 1 Flow chart depicting patient flow after CRS–HIPEC

Outcome Reversal

The median time elapsed between colostomy reversal and the initial CRS–HIPEC procedure was 394 days (range 133–1194 days). In 7 patients, the reversal procedure was carried out within 1 year of follow-up after CRS–HIPEC. The rate of documented comorbidities remained unchanged (Table 1). The median hospital stay after reversal was 8 days (range 4–36 days).

Complications after the reversal procedure occurred in 14 of 21 patients (67 %). Grade II complications were observed in three patients and grade III complications in eleven patients. No grade IV complications or mortality were observed after the reversal procedure (Fig. 2). The median number of invasive procedures necessary to alleviate the colostomy reversal-associated complications was 1 (range 1–5). Median follow-up after the reversal procedure was 34 months (range 8–119 months).

Three of 21 patients (14 %) ended up with an ileostomy. This was due to complications after reversal (Table 1). In one patient, multiple laparotomies were performed to resolve fistulas, which resulted in an ileostomy. Another patient had an anastomotic stenosis after reversal, and the last patient presented with an acute ileus due to intra-abdominal adhesions. In an additional three patients, the colostomy was not reversed as a result of tumor recurrence found during the reversal procedure. Of these patients, two had a macroscopically incomplete resection during CRS-HIPEC for pseudomyxoma peritonei (R2a).

Ultimately, bowel continuity was successfully restored in 71 % of the patients who underwent the procedure. Additionally, one patient who received an ileostomy after the reversal subsequently underwent a successful reversal procedure of the ileostomy. Bowel continuity was successfully restored in 76 % of all patients.

Univariate Analysis of Risk Factors

No significant correlation was observed between four clinical factors and ten treatment-related factors and (1) the occurrence of complications after the reversal procedure, (2) the placement of an ileostomy after the reversal, and (3) whether or not the bowel continuity was successfully restored ($P > 0.05$) (Table 3).

TABLE 1 Detailed clinical overview of 21 patients requesting and undergoing colostomy reversal

Patient no.	Gender	Age	Comorbidity	ASA classification	Tumor type	Adjuvant chemotherapy	No. of procedures before HIPEC	Time between HIPEC and reversal	Complication HIPEC (grade)	No. of invasive interventions to treat complication of HIPEC	Complication reversal procedure (grade)	No. of invasive interventions to treat complication reversal	Result of reversal
1	F	58	–	I	PMP	No	2	9	Anemia (II)				Successful
2	M	58	–	I	PMP	No	2	31	Pneumothorax (III)		Fistula (III)	1	Successful
3	F	54	–	I	PMP	No	3	13	Invasion in ureter → resection and placement JJ stent (III)		Iatrogenic (III)	1	Successful
4	F	48	DMII, Hep A+B, hypercholesterolemia	III	PMP	No	2	19	Anastomotic leakage (III)	3	Infectious and incisional herniation (III)	1	Successful
5**	F	39	–	I	PMP	No	2	7	Fistula and iatrogenic (III)	2	Fistula (III)	5	Ileostomy
6	M	46	–	I	Adenocarcinoma	No	1	15					Successful
7	M	37	–	I	Adenocarcinoma	Yes	1	14			Iatrogenic and fistula (III)	2	Successful
8	F	62	Hypertension	II	Adenocarcinoma	No	3	12	Infectious (II)		Acute ileus due to adhesions (III)	1	Ileostomy
9	F	44	MS, anemia, DES daughter	II	PMP	Yes	3	12	Abscess formation (III)	1	Ileus (II)		Successful
10	M	31	–	I	PMP	No	2	13	Pulmonary embolism (II)				No reversal due to recurrence
11	F	50	CU, hypertension	II	Adenocarcinoma	Yes	1	12			Anemia (II)		Successful
12	M	55	–	I	PMP	No	2	38	Acute ileus caused by adhesions (III)	2	Anastomotic stenosis → short bowel (III)		Successful
13**	F	43	–	I	Adenocarcinoma	Yes	1	9					Successful
14	F	40	Hypothyroidism	I	PMP	No	1	15	Anemia (II)		Infectious (II)		Successful
15	F	62	–	I	PMP	No	2	16	Infectious (III)	1			No reversal due to recurrence
16**	F	38	–	I	Adenocarcinoma	Yes	3	4					Successful
17	F	60	MI, epilepsy	II	Adenocarcinoma	No	1	15					Successful
18	F	54	–	I	Adenocarcinoma	No	1	13			Anastomotic stenosis (III)	1	Ileostomy
19**	M	66	Depression, hypertension, hypercholesterolemia, hypothyroidism	II	PMP	No	1	6			Abscess (III)	1	No reversal due to recurrence
20**	M	65	Osteoporosis	II	Adenocarcinoma	No	4	4	Acute ileus due to adhesions (III)	1	Incisional Herniation (III)	1	Successful
21**	F	57	–	I	Adenocarcinoma	No	Unknown	8			Abscess and acute ileus due to adhesions (III)	1	Successful

HIPEC hyperthermic intraperitoneal chemotherapy, *ASA* American Society of Anesthesiologists, *PMP* pseudomyxoma peritonei

TABLE 2 Detailed overview of clinical course in 4 patients after R2a resection of PMP

Patient no.	Resection outcome HIPEC	Gender	Age	Time between HIPEC and reversal	Result of reversal	Reason
3	R2a	F	54	13	Successful	–
4	R2a	F	48	19	Successful	–
10	R2a	M	31	13	Unsuccessful	Recurrence
15	R2a	F	62	16	Unsuccessful	Recurrence

HIPEC hyperthermic intraperitoneal chemotherapy, *PMP* pseudomyxoma peritonei

Assessment of the four clinical and ten treatment-related factors in relation to (1) the occurrence of complications after the reversal procedure, (2) the placement of an ileostomy after the reversal, and (3) whether or not the bowel continuity was successfully restored showed that an infectious complication (including abscess formation) after CRS–HIPEC and the presence of a fistula led to more ileostomy placements in completely resected patients (R1) ($P = 0.05$) and was also negatively correlated with the ultimate restoration of bowel continuity ($P = 0.05$). High complication grade, the presence of an infectious complication, and the need for invasive procedures after the reversal procedure were all negatively correlated with the successful restoration of bowel continuity in completely resected patients ($P = 0.05$, 0.003, and 0.05, respectively).

DISCUSSION

An increase in median overall survival has been reported since the introduction of CRS–HIPEC, with a median overall survival in some series reported to be up to 62 months.[6,22] This might cause an increase in requests for stoma reversal procedures with the goal to improve the QoL experienced by longer-surviving HIPEC patients.[17,18] Patients with a colostomy have been reported to encounter both physical and psychological difficulties.[18]

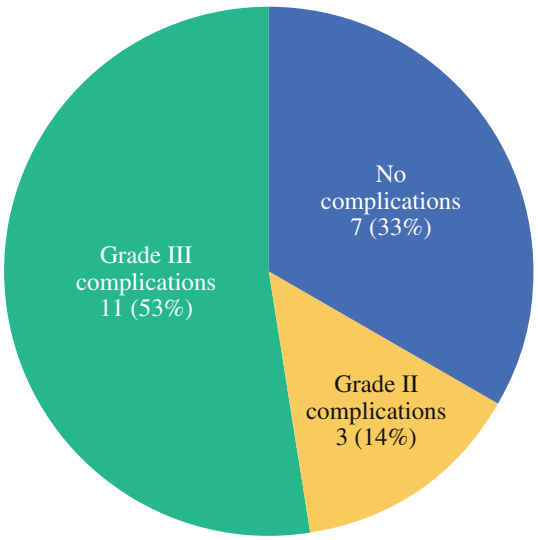

FIG. 2 Distribution of complications and complication grade after reversal

Little is currently known about the incidence of colostomy reversal requests in CRS–HIPEC patients and the possible associated complications. Available data on stoma reversal procedures are based on studies in heterogeneous patient populations with several underlying pathologies (oncologic and benign), making implementation into clinical practice in CRS–HIPEC patients challenging.[17]

For this procedure in particular, the major aspect is the patient's wishes concerning QoL.[17] As a result, we included patients who actively requested the procedure because they deemed their QoL to be lower as a result of the colostomy. The majority of the patients will not undergo a reversal procedure after initial CRS–HIPEC treatment because it is believed that the expected gain in QoL does not outweigh the associated risks. CRS–HIPEC is associated with high postoperative morbidity, resulting in technically challenging surgeries because of the large amount of adhesions. Patients are not encouraged to undergo a reversal procedure because that would entail one or more subsequent highly morbid procedures in a relatively short time. Second, even though treatment is with curative intent, disease will recur in some patients. Such cases are not amenable to reversal.[23] Last, a proportion of patients will not request a reversal because they do not experience diminished QoL with the colostomy or they are still recovering from the QoL deficit caused by treatment.[18,24]

However, if actively requested, 71 % of the patients will undergo successful restoration of bowel continuity. Infectious complications, including the formation of fistula, were detrimental to the outcome of the reversal. These patients received significantly more ileostomies and had ultimately less successful bowel continuity restorations ($P = 0.05$).

We observed that in three patients, adequate staging was not possible before undertaking the reversal procedure, translating into failure of the planned reversal procedure as a result of the intraoperative discovery of recurrent disease. This is a known clinical difficulty in the CRS–HIPEC population. This finding emphasizes the importance of the

TABLE 3 Univariate analysis of risk factors in 17 optimally resected patients

Variable	Complications after reversal		*P*	Ileostomy		*P*	Reversal		*P*
	No	Yes		No	Yes		Unsuccessful	Successful	
Clinical									
Mean age, years	49	52	NS	51	52	NS	53	51	NS
Gender									
Male	1	5	NS	6	0	NS	1	5	NS
Female	4	7		8	3		3	8	
ASA classification									
I	4	7	NS	9	2	NS	2	9	NS
II	1	5		5	1		2	4	
Tumor type									
PMP	1	6	NS	6	1	NS	2	5	NS
Adenocarcinoma	4	6		8	2		2	8	
Treatment related									
Adjuvant chemotherapy									
No	3	9	NS	9	3	NS	4	8	NS
Yes	2	3		5	0		0	5	
Complicated HIPEC									
No	3	5	NS	7	1	NS	2	6	NS
Yes	2	7		7	2		2	7	
Infectious complication of HIPEC									
No	5	8	NS	12	1	0.05	1	12	0.05
Yes	0	4		2	2		2	2	
Complication grade (HIPEC)									
Not applicable	3	5		7	1		2	6	
II	1	2	NS	2	1		1	2	NS
III	0	5		4	1		1	4	
Time elapsed between CRS-HIPEC and reversal									
<1 year	3	4	NS	6	1	NS	2	8	NS
≥1 year	2	8		8	2		2	5	
Complicated reversal	NA	NA	–						
No				5	0	NS	0	4	NS
Yes				9	3		5	8	
Infectious complication of reversal	NA	NA	–						
No				11	1	NS	0	12	0.003
Yes				3	2		3	2	
Complication grade (reversal)	NA	NA	–			NS			NS
Not applicable				5	0		0	5	
II				3	0		0	3	
III				6	3		3	6	
Invasive procedures needed to resolve complications of reversal	NA	NA	–			NS			NS
Not applicable				5	0		0	5	
No				3	0		0	3	
Yes				6	3		3	6	

ASA American Society of Anesthesiologists, *PMP* pseudomyxoma peritonei, *HIPEC* hyperthermic intraperitoneal chemotherapy, *CRS* cytoreductive surgery, *NA* not applicable, *NS* not significant ($P > 0.05$)

All data are presented as *n* except age, which is expressed in years

improvement of clinical tools used for the follow-up of CRS–HIPEC, which is currently done with suboptimal imaging and biomarkers.[25] The translational study conducted by van Dam et al.[26] illustrates the potential added value of novel techniques such as fluorescent tumor-specific antibodies in intraoperative (laparoscopic) imaging in CRS–HIPEC patients. Despite the considerable effort necessary for further development, we believe that these tools will certainly aid in further advancing overall care in the CRS–HIPEC population.[25]

All patients were treated and followed up in accordance with the Dutch HIPEC protocol.[15,20] In this cohort, patients who underwent a macroscopically incomplete (R2a) resection had a significantly higher chance of not undergoing a reversal procedure as a result of recurrence of disease. It is known from literature that the resection outcome after CRS–HIPEC is one of the most important treatment-related prognostic factors.[8,15]

We found a relatively high incidence of complications (67 %), in comparison to the literature.[27] Our cohort consisted of patients who had an extensive oncologic and surgical history, which could partially explain the complication rate we observed.[14,27,28] The number of previous procedures in our cohort was high (median 2, range 1–4). This HIPEC cohort appeared to have more favorable clinical characteristics, such as lower ASA classification and younger age compared to previously published cohorts, in which colostomy reversal outcomes were reported in both malignant and benign disease.[14,27] In one of the previously published cohorts, 37 % of the patients were classified as ASA III/IV, as opposed to our cohort, which only included one patient (5 %) who was classified as ASA III. In the oncologic cohort, 67 % of the patients were older than 60 years, in contrast to 25 % in our cohort.[14] The median age in the benign disease cohort was 63 years, as opposed to 54 years in our post-CRS–HIPEC cohort.[17]

The nature of complications observed here is comparable to that observed in a previously published cohort.[27] Likewise, these patients often require additional invasive procedures, thus lengthening the duration of hospitalization. As was also observed in our cohort, infectious complications have been previously described as a possible limiting factor for stoma reversal.[14]

The peritoneum is known to play an essential role in the containment of intra-abdominal infectious complications and wound healing.[5] It is currently unknown how the entire CRS–HIPEC treatment affects the integrity of the tissue, which is used for the continuity restoration. Moreover, to our knowledge, there are currently no publications that have investigated this particular clinical question in the HIPEC populations treated with other techniques (open vs. closed) or different HIPEC compounds, such as oxaliplatin. The effect of stripping of the affected peritoneum on the containment of intra-abdominal infectious complications and wound healing in this cohort of patients has not yet been studied. Theoretically, the natural intra-abdominal defense could be compromised as a result of the removal of potentially large parts of peritoneum during CRS, the physiologic effect of the additional intra-abdominal trauma, and the subsequent release of inflammatory cytokines.[5] Furthermore, the effect of the intra-abdominal lavage with a chemotherapeutic agent such as mitomycin C on wound healing after treatment is still largely unknown.

In conclusion, we found a relatively high complication rate after performing the Hartmann reversal procedure. The bowel restoration success rate was ultimately 71 %, but it must be kept in mind that patients with infectious complications after HIPEC have a diminished chance of successful restoration of bowel continuity.

The results of our study are informative for surgeons facing the requests of the highly selected and successfully treated CRS–HIPEC patients to reverse a colostomy. The decision to have the procedure reversed is, first and foremost, based on the wish of the patient, provided that the patient is in an acceptable condition and is free of tumor before undergoing surgery.

DISCLOSURE The authors declare no conflict of interest.

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