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Outcome differences between debulking surgery and cytoreductive surgery in patients with pseudomyxoma peritonei

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Abstract

Background: The aim of this study was to compare debulking surgery and cytoreductive surgery (CRS) in patients with Pseudomyxoma peritonei (PMP) regarding efficacy and safety.
Patients and methods: Data were extracted from medical records and treatment outcomes were analyzed for all 152 patients with PMP who were scheduled for debulking surgery and intraperitoneal chemotherapy (IPC) or CRS and IPC at Uppsala University Hospital, Uppsala, Sweden, between September 1993 and December 2008.
Results: One hundred and ten patients (73%) were treated with CRS and IPC and 40 (27%) with debulking surgery and IPC. In two patients (1%), surgery was defined as open and close. Patients with CRS and IPC had a 74% 5-year overall survival (OS) rate compared with 40% for those treated with debulking surgery ($P < 0.001$). Patients with no residual macroscopic tumour (R1 resection) had a better 5-year OS rate of 94% compared with 28% for patients with macroscopic residual tumour (R2) ($P < 0.001$). Grades II–IV adverse events were seen in 29% of debulked patients and in 47% of CRS/IPC patients ($P = 0.053$).
Conclusions: CRS and IPC seems more efficient than debulking surgery and IPC but with numerically higher morbidity. Therefore, if surgically possible, CRS should be the treatment of choice for PMP patients. However, debulking surgery may still be of benefit to selected patients for palliative purposes.

Keywords: Pseudomyxoma peritonei; Cytoreductive surgery; Intraperitoneal chemotherapy; Debulking surgery

Introduction

Pseudomyxoma peritonei (PMP) is a rare disease, with an incidence of one to two per million per year,[1] and characterized by disseminated intraperitoneal mucous and mucinous implants on the peritoneal surfaces, the omentum and in the sub-diaphragmatic space.[2] Recent studies strongly support the hypothesis that almost all cases of PMP originate from primary appendiceal neoplasms.[3,4] Different treatment strategies have been applied, including a "wait and see" approach[5] or systemic chemotherapy,[6] but neither of these options provides prolonged survival. Debulking surgery is used in some centres with a 5- to 10-year overall survival (OS) rate of approximately 50%.[6–8] With a more aggressive approach, cytoreductive surgery (CRS), combined with hyperthermic intraperitoneal chemotherapy (HIPEC), as proposed by Sugarbaker,[9] several centres report a 5-year OS of 75–95%.[10–13] However, after these procedures, morbidity and mortality rates can be high. Furthermore, there have been few comparisons between these two surgical treatment strategies regarding morbidity, mortality and overall and disease-free survival.

The aim of this study was, therefore, to compare debulking surgery and CRS with respect to efficacy and morbidity in patients with PMP.

Patients and methods

Patients' characteristics

Between September 1993 and December 2008, all 152 patients registered in the Uppsala University hospital, Uppsala, Sweden PMP database (71 men, 81 women, mean

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age 55 years, range 21–79) were included in the study. Two patients were classified as "open and close" and were excluded from the comparison. The remaining 150 patients were scheduled for debulking surgery followed by intraperitoneal chemotherapy (IPC) or CRS and IPC formed the basis for this follow-up study. The regional ethics committees approved the study, and informed consent was obtained from each patient. The eligibility requirements for treatment were: confirmed clinical, radiological and/or histological diagnosis of PMP; no distant metastasis; adequate renal, haematopoietic and liver functions, and a WHO performance status of $\leq$2. Histopathology was classified according to Bradley[14] as low or high grade mucinous carcinoma peritonei (MCP-L or MCP-H).

Adverse events were recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v 3.0 (CTCAE).

During the study period, treatment strategy shifted from debulking surgery and IPC to the more aggressive CRS and IPC procedure. The organization of the two groups in this report is based on the treatment philosophy, i.e. the intention to treat principle. The debulked group consisted of 40 patients treated with debulking surgery and sequential postoperative intraperitoneal chemotherapy (SPIC) or HIPEC. The CRS group consisted of 110 patients scheduled for the CRS who also received either SPIC or HIPEC treatment (Table 1).

Quantitative prognostic indicators

Quantitative prognostic indicators – Prior Surgical Score (PSS) and the Peritoneal Cancer Index (PCI)[15,16] – were retrieved from the medical records in the debulked group and recorded prospectively in the CRS group. PSS estimates the extent of abdominal and pelvic dissection performed before definitive cytoreductive surgery. The extent of tumour load in the abdominal cavity was assessed by PCI score (range 1–39), which is calculated by summing lesion size scores (0–3) in 13 different regions of the abdomen. For the purpose of this analysis, the PCI score was

Table 1
Patient characteristics.

Variable	Debulking group, *n* (%)	CRS group, *n* (%)	Total, *n* (%)	*P*
No of patients	40	110	150	
Sex				0.061
Men	24(60)	47(43)	71(47)	
Women	16(40)	63(57)	79(53)	
Mean age (years)	55(21–79)	55(24–76)	55(21–79)	0.832
BMI	24.5(16.2–38.3)	24.9(17.6–37.8)	24.7(16.2–38.3)	0.429
Histopathology				0.002
MCP-L	10(25)	59(54)	69(46)	
MCP-H	30(75)	51(46)	81(54)	
Previous systemic chemotherapy				0.644
	9(23)	21(19)	30(20)	
ASA classification				0.351
10	15(38)	49(45)	64(43)	
20	21(53)	52(47)	73(49)	
30	4(10)	9(8)	13(9)	
WHO performance status				0.008
0	28(70)	101(92)	129(86)	
1	6(15)	7(6)	13(9)	
2	3(8)	1(1)	4(3)	
3	1(3)		1(1)	
MD	2(5)	1(1)	3(2)	
PCI				0.918
0–10	6(15)	17(15)	23(15)	
11–20	10(25)	24(22)	34(23)	
21–39	24(60)	69(63)	93(62)	
PSS				0.012
0	12(30)	30(27)	42(28)	
1	9(23)	31(28)	40(27)	
2	13(33)	13(12)	26(17)	
3	6(15)	36(33)	42(28)	
Mean operation time	6:14(1:40–17:00)	9:47(2:00–15:20)	8:45(1:40–17:00)	<0.001
Mean operative bleeding (ml)	2744(0–14500)	2031(50–16500)	2198(0–16500)	0.533
Mean blood products/first 24 h (ml)	2407(0–11700)	2374(0–18300)	2355(0–18300)	0.616
Mean IVA stay (h)	16.5(0–205)	30.5(0–592.5)	26.4(0–592.5)	<0.001
Mean hospital stay (days)	15.6(7–32)	18.9(7–56)	18.0(7–56)	0.006

BMI = body mass index, MCP-L = low grade mucinous carcinoma peritonei, MCP-H = high grade mucinous carcinoma peritonei, PCI = peritoneal cancer index, PSS = prior surgical score. n.s = not significant.

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simplified into three categories PCI-I (PCI 1–10); PCI-II (PCI 11–20); and PCI-III (PCI 21–39). The completeness of the cytoreduction was scored at the end of surgery as no residual macroscopic tumour (R1) or macroscopic residual tumour (R2), as defined by the International Union Against Cancer.[17]

Surgical treatment

Debulking surgery

The definition of debulking surgery was when the scope of the surgical technique limited the removal of macroscopic tumour from the abdominal cavity, especially from the upper abdomen. Between 1993 and 2002, no attempt was made to remove the tumour if the peritoneal surface of the upper abdomen (right and left upper quadrant, lesser omentum and duodenal-hepatic ligament) was involved. Instead, tumours on these sites were superficially treated by 70 W electrocautery. Between 2003 and 2008, 16 patients were scheduled for debulking surgery. Selection was based on patients' performance status and peroperative findings, thus CRS technique existed, and these patients are grouped in the debulking group.

Cytoreductive surgery

Between 2003 and 2008, CRS was performed using a ball-tip electro surgical hand piece and a high voltage of 200/300 W, as described by Surgarbaker.[18]

Intraperitoneal chemotherapy

During the study period, 31 patients from the debulked group and ten CRS patients were treated with SPIC. Seven patients from the debulked group and 98 patients from the CRS group were treated with HIPEC with or without early postoperative intraperitoneal chemotherapy treatment (EPIC). Four patients did not receive any intraperitoneal chemotherapy.

Sequential intraperitoneal chemotherapy

SPIC treatment was given as described by previously.[19] SPIC started the day after surgery with 5-fluorouracil (5-FU; 550 mg/m^2 day) dissolved in 500 ml of 0.9% saline. Sixty minutes after the start of IPC infusion, an intravenous (IV) infusion of leucovorin (LV) (60 mg/m^2) was administered. The 5-FU dose was selected as a result of previous findings.[20] The SPIC treatment was given sequentially for six days with 4–6 weeks intervals up to a maximum of eight courses, provided there was acceptable tolerance and no clinical tumour progression. All treatment-related symptoms and side effects were recorded.

Hyperthermic and early postoperative intraperitoneal chemotherapy

HIPEC was given according to the Coliseum technique[21] with one inflow catheter in the caudal end of the incision and four outflow catheters, one in the left subphrenic cavity, one under the liver and two at the superficial pelvic level. Chemotherapy was heated to an intra-abdominal target temperature of 42 °C (range 41–43). Mitomycin-C was given to 96/105 patient. Between October 2003 and February 2005, mitomycin-C was given in doses of 10–12 mg/m^2 for 90 min. Thereafter, based on a report by van Ruth et al., the dose changed to 30–35 mg/m^2.[22] Three patients received oxaliplatin for 30 min at a dose of 460 mg/m^2, following the findings of Elias et al.[23] These patients also received concomitant intravenous 5.FU (500 mg/m^2) and LV (60 mg/m^2). Six patients received a combination of cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) over 90 min. The rationale for using cisplatin and doxorubicin was based on previous reports on their favourable *in vitro* test drug sensitivity for PMP.[24]

HIPEC perfusion was delivered using a Medtronic BioPump with a heater/cooler (Jostra, Bio-pump BPX80, Bio.probe DP38, Medtronic 3/8 hose 2 × 2 m M999133C) with Dideco heat exchanger D720A Helios reference number 05328 and Quickprime tubing reference number S0641. Before perfusion, the patients were cooled to 34 °C with a cooling blanket (Allon®). The four outflow catheters remained in place after surgery, allowing EPIC to be administered during the first five postoperative days.

Statistical methods

To test differences between the groups, the Mann–Whitney *U* test or Kruskal Wallis was used for quantitative variables and Fisher exact or chi square test for categorical variables. Postoperative adverse events (AE) were only analyzed for the index operation. The influences of variables (sex, histopathology, PCI, PSS, treatment strategy, surgical outcome, IPC and postoperative complications) on survival between the groups were tested with the log rank test as well with a Cox proportional hazard model. The latter method was also used to assess the influence of a variable on survival while simultaneously adjusting for the effects of other variables. The Kaplan–Meier method was used to evaluate overall and cancer-specific survival according to intention to treat, starting at the date of the first operation and using 15 October 2010 as a reference date. A *p*-value below 0.05 was considered statistically significant.

Results

Base-line comparison between debulked and CRS groups

The two groups were well balanced regarding gender, age, BMI, ASA classification and PCI (Table 1). MCP-H histopathology was more common in the debulked group 30/40 patients (75%) than in the CRS group 51/110 patients (46%) and the performance status of the debulked group was worse than that of the CRS group (Table 1). The

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median of follow-up was 40 (5–90) months for the CRS group and 41 (2–199) months for the debulked group.

Debulked group

In the debulking group, R1 resections were achieved in ten patients (25%) and 30 patients (75%) had R2 surgery. Serial debulking, defined as multiple operations due to persisting tumour, was performed on 25 patients. In nine patients, R1 was accomplished at the repeat surgery whereas 16 patients had R2 resections.

CRS group

An R1 resection was achieved in 79/110 patients (72%) and R2 in 31 patients (28%). R1 surgery was more common in the CRS group compared to the debulking group ($P < 0.001$). The following surgical procedures were more common in the CRS group in comparison to the debulking group: greater and lesser omentectomy, left and right diaphragm stripping, anterior resection, splenectomy, gastric resection, cholecystectomy, bladder and pelvic peritonectomy. Several variables were associated with the surgical outcome (Table 2).

Intraperitoneal chemotherapy treatment

SPIC was given to 41/150 patients (27%), with a median of 6 (range 0–8) cycles. Twenty-one completed the planned eight cycles of treatment. The main reasons for not fulfilling all planned courses were: progressive disease ($n = 4$), lack of widespread distribution in the abdominal cavity ($n = 4$), and abdominal infection ($n = 4$).

Table 2
Association between categorical clinical variables and surgical outcome (R2).

	n	*P*[a]	OR (95% CI)	*P*[b]
Histopathology		<0.001		
MCP-L	69		0.300 (0.125–0.722)	0.007
MCP-H	81			
PCI		<0.001		
0–10	23		0.091 (0.016–0.533)	0.008
11–20	34		0.124 (0.033–0.465)	0.002
21–39	93			
PSS		0.031		
0	42		1.092 (0.370–3.222)	0.874
1	40		0.463 (0.135–1.593)	0.222
2	26		0.456 (0.101–2.065)	0.308
3	42			
Surgery		<0.001		
Peritonectomy	110		0.059 (0.016–0.214)	<0.001
Debulking	40			

MCP-L = low grade mucinous carcinoma peritonei, MCP-H = high grade mucinous carcinoma peritonei, PCI = peritoneal cancer index, PSS = prior surgical score.
[a] Chi square test.
[b] Logistic regression model.

Among the 105/150 patients (70%) receiving HIPEC, 75 (71%) were also treated with EPIC. Four patients (3%) were not treated with IPC for the following reasons: too little tumour burden (one patient), small bowel obstruction (two patients), massive perioperative bleeding (one patient).

In the debulking group, 31 patients were treated with SPIC, seven patients with HIPEC and two patients received no IPC. In the CRS group, ten patients were treated with SPIC, 98 patients received HIPEC and two patients had no IPC treatment. One patient in the CRS group had an anaphylactic reaction to mitomycin C at the start of HIPEC so the treatment was terminated at 6 min.

Mortality and morbidity

In total, one patient (1%) died within the first 90 postoperative days. One debulking patient with poor performance score died of progressive disease.

During the hospital stay, a total of 114 Grade II–IV adverse events (AE) were recorded in 64 patients (43%). Grade II was recorded in 16 patients and 48 had Grade III–IV.

Ten patients in the debulked group (29%), and 54 patients in the CRS group (47%) experienced an AE of Grade II–IV ($P = 0.053$). Grades III–IV AE were recorded for nine debulked patients (23%) and 39 CRS patients (35%) ($P = 0.227$). The main non-surgical morbidities were: neutropenia Grade 1 (one patient), neutropenia Grade 2 (eight patients), neutropenia Grade 3 (seven patients), pleural effusion (13 patients) and sepsis (ten patients). Surgical complications occurred in 24/150 patients (16%) and 18/150 (12%) needed a re-laparatomy. Surgical complications occurred in six debulked patients (15%) and 18 CRS treated patients (16%) ($P = 0.900$). Re-laparatomy was needed for four debulked patients (10%) and for 14 CRS patients (13%) ($P = 0.800$). Bleeding (six patients, 4%), and perforations (five patients, 3%) were the most common reasons for re-laparatomy.

There was no increased risk of surgical complications in patients receiving HIPEC ($P = 0.466$). However, more frequent medical/infectious complications were observed in patients undergoing HIPEC ($P = 0.003$) (Grade 2 ($P = 0.005$)). For complications in total, an increased risk in HIPEC patients was seen only in Grade 2 ($P = 0.013$).

Survival

The overall survival (OS) at three years was 79% and 62% at five years. For the debulked group, median survival is 39.3 months and the lower quartile is 25.5 months. For the CRS group, the lower quartile is 51.0 months and median survival has not yet been reached. Macroscopic radical surgery had a significant impact on OS: 5-year OS was 94% for R1 resections and 28% for R2 ($P < 0.001$). Patients who underwent CRS had a better 5-year OS (74%) than those with debulking (40%, $P < 0.001$). Patients with

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a high grade malignant tumour (5-year OS 51%) had a poorer outcome than patients with a low grade malignant tumour (5-year OS 80%) ($P < 0.001$). For the entire study population, a difference in survival between the PCI groups ($P = 0.002$) was recorded, and this could be seen in the debulking group ($P = 0.004$) but not in the CRS group ($P = 0.105$). After adjusting for prognostic factors (sex, histopathology, PCI, PSS, IPC, type of surgery and surgical outcome) using a Cox proportional hazard model, only surgical outcome had an impact on survival.

Patients in the debulked group had a 3-year OS of 65% and a 5-year OS of 40%. In the CRS group, OS at 3 years was 85% and 74% at 5 years.

Surgical outcome had a significant impact: the 5-year OS for R1 was 93% and 38% for R2 ($P < 0.001$) in the CRS group. In the debulked group, the 5-year OS for R1 resections was 100% and for R2 resections was 19% ($P = 0.001$) (Fig. 1). No differences in OS were seen when comparing patients with R1 surgery from the two treatment strategies.

Histopathology had an impact on the 5-year OS for patients in the CRS group. For patients with low grade malignant tumour the 5-year OS was 88% and for those with high grade malignant tumour it was 60% ($P = 0.001$). No difference in OS was seen in the debulked group between the two histopathological types (Fig. 2).

Disease-free survival at five years was 67% and histopathological types made a difference in median time to relapse: MCP-L (54 patients) lower quartile have not been reached and MCP-H 29.9 months (35 patients) ($P < 0.001$) (Fig. 3), and in OS of patients with R1 surgery ($P = 0.048$). During the entire study period, complications (both surgical and non-surgical) had no impact on survival.

Discussion

As one of the first studies comparing the outcomes between debulking and CRS for patients with PMP, the findings from this single institution seem to confirm that CRS should be considered as the treatment of choice for patients with PMP, since the likelihood of achieving R1 surgery is higher if CRS is performed. The frequency of adverse effects is high in both groups and a trend towards an increased risk of AE was seen in the CRS group ($P = 0.053$).

This report has several limitations that could weaken its conclusions, one of which is the longer treatment period and the differences in patients characteristics between the two groups. Ideally, a randomized trial would be preferable. However, it is always difficult to run randomized trials in surgical oncology, were surgeons are supposed to do suboptimal procedures in every second case. Therefore, due to this circumstances and the fact that PMP is a rare condition, we believe that this data analysis is appropriate. Moreover, PMP is a heterogeneous disease especially for the histopathology sub-type. Therefore, considering PMP as a benign disease is unjustified since it could worsen the

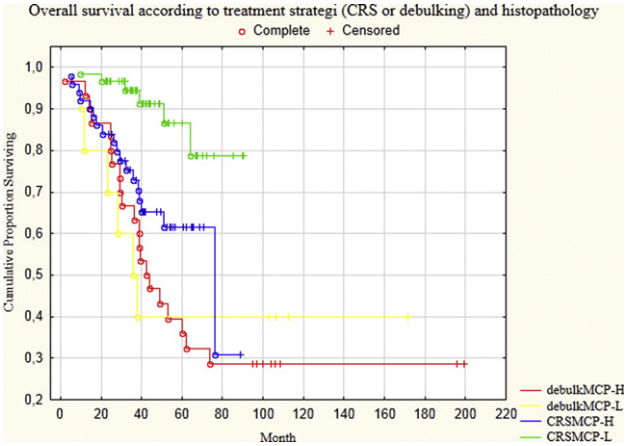

Figure 2. Overall survival according to treatment strategy (peritonectomy or debulking) and histopathology.

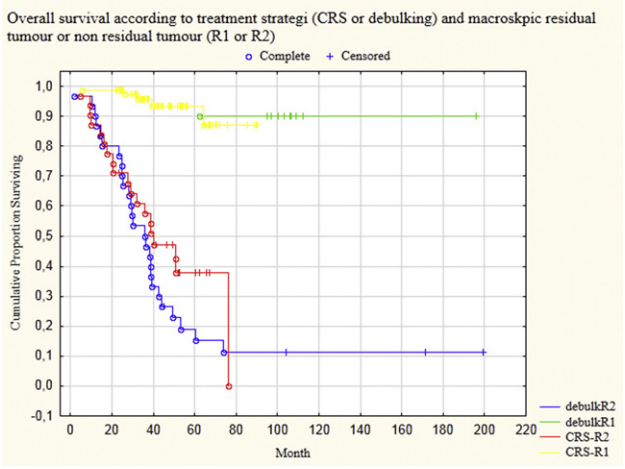

Figure 1. Overall survival according to treatment strategy (peritonectomy or debulking) and macroscopic residual tumour or non residual tumour.

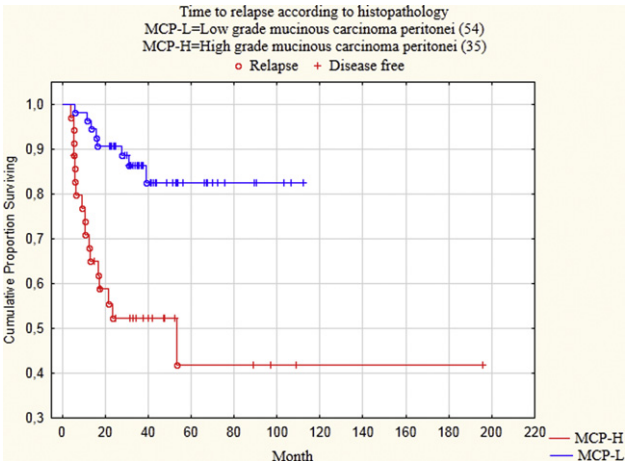

Figure 3. Time to relapse according to histopathology.

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survival options of patients, especially those with high grade PMP.

The overall 5-year survival rate for debulked patients in this study (40%) was lower than previous debulking-based reports on PMP.[6,8] The inferior survival rate observed in debulked patients in this study could be due to the presence of extensive tumour burden i.e. higher PCI in a combination with a higher frequency of patients with the histopathology subtype of MCP-H. Therefore, advocating debulking surgery for PMP patients could be biased if histopathology subtypes and tumour burden (PCI) are not considered. Järvinen et al.[8] report a 5-year survival rate of 67% in their latest study of debulked patients. This result could be affected by patient selection, in that a majority of the patients have a favourable histopathology i.e. MCP-L. Both Ronnett et al. and Bradley et al.[3,14] have reported a poorer outcome for patients with MCP-H, so most of these patients may not have been considered for multiple surgical procedures. Since the two groups in our study were comparable in that both groups received IPC, treatment extent and philosophy could be one of the explanations for the survival benefit presented by CRS, although the role of IPC cannot be addressed by this study, previous study[25] on HIPEC and SPIC comparison has demonstrated better survival in patients treated with HIPEC.

An attempt has been made to treat PMP patients with systemic chemotherapy.[6] However, patients treated with this approach had inferior long-term survival rates than those treated with CRS.[26] As PMP has extensive mucus and a less invasive nature, the rationale for using a systemic treatment in this disease seems week. However, the IPC route could be advantageous as chemotherapy is administered locally. In order to benefit from IPC, the tumour burden should be limited to a few millimetres as the penetration of the drug to the tumour nodules is limited to a few millimetres.[27] Therefore, the use of IPC in debulked patients with a high tumour volume left in situ is questionable.

During the early stages of treating patients with PMP, debulking surgery was the standard in our centre, since the attempt was only to reduce tumour burden. This was due to a suboptimal surgical technique. However, four patients had R1 resection even under these circumstances, but these patients only had tumours localized in the mid and lower abdomen. As CRS became the standard of care in our centre for patients with PMP, and as the surgical team's experience increased, more patients had R1 outcomes after surgery. Our current policy is to perform CRS in order to achieve R1 resection. The introduction of an advanced procedure, such as CRS, often results in an increased rate of both surgical and non-surgical complications. Although the morbidity rate was high at 44%, it was within the range suggested by earlier reports.[28,29]

In conclusion, data from this single hospital series suggest that CRS is more efficient than debulking surgery. Therefore, if surgically possible, CRS should be considered as the treatment of choice in patients with PMP since CRS prolongs survival and offers the possibility of cure, albeit probably with a slightly increased risk of AE. However, debulking surgery may still be performed for palliative purposes on selected patients.

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Conflict of interest statement

All authors declare no conflict of interest.

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