

# Palliative care in patients with ovarian cancer and bowel obstruction

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## Abstract

**Objective** Malignant bowel obstruction (MBO) is usually a pre-terminal event in patients with ovarian cancer. However, because of the lack of data in literature, decisions around surgical intervention, non-resectional procedures, or medical treatment of MBO in patients with ovarian cancer cannot be lightly undertaken. We analyzed medical and surgical procedures, performance status, nutritional status, cachexia, and their prognostic value in this group of patients.

**Methods** We retrospectively selected all consecutive patients with recurrent ovarian cancer who received medical or surgical treatment for MBO between October 2008 and January 2014 at the Academic Department of Gynecological Oncology of Mauriziano Hospital of Turin (Italy).

**Results** We found 40 patients: 18 of them underwent medical treatment and 22 of them were submitted to surgery. In the group of surgery, the hospitalization was shorter ( $p$  0.02), the pain reduction was more effective ( $p$  0.001), the number of chemotherapy lines was higher ( $p$  0.03), and re-obstruction was more rare ( $p$  0.02). Between the two groups, we did not find any differences in post-palliation episodes of vomit ( $p$  0.83), type of diet ( $p$  0.34), ability to return home ( $p$  0.72),

and death setting ( $p$  0.28). Median survival after palliation was longer in the group of surgery ( $p$  0.025). Cachexia, low performance status, and poor nutritional status were significant predictors of worse survival after MBO, independently by the treatment.

**Conclusions** Surgery has to be considered in patients without serious contraindications; otherwise, a medical protocol, including antisecretory drugs, is the standard of care in frail patients.

**Keywords** Malignant bowel obstruction · Palliative care · Ovarian cancer

## Introduction

Bowel obstruction is defined as the situation in which the normal intestinal transit is abnormally delayed or completely stopped. It is a common complication in patients with end-stage cancer, and it is estimated that malignant bowel obstruction (MBO) involves 3 % of the patients admitted in hospice. The reported frequency varies from 25 to 50 % in patients with advanced ovarian cancer [1]. Survival is generally poor, with a reported median survival of 1–3 months, but some studies have demonstrated survival of up to 1 year.

In the patients with advanced ovarian cancer, more often the intestinal occlusion is due to the diffuse peritoneal carcinomatosis. MBO may be sometimes the consequence of the cancer treatment: adhesions from previous surgery, radiation enteritis, chronic ischemia, neurotoxicity from Vinca Alkaloids, or narcotic intestinal syndrome from the use of opioids.

Bowel obstruction can be partial or complete and can occur at single or multiple sites. Small bowel obstruction is more common than large bowel obstruction (61 vs 33 %), and both sites are involved in >20 % of patients [2].

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Therapy directed at MBO must achieve certain goals, such as allowing the patient to return home, restoration of oral intake, and relief of abdominal distension and pain. Once the obstruction is relieved, a small proportion of patients is suitable for further treatment with chemotherapy.

Although bowel obstruction in advanced ovarian cancer presents quite commonly, its management still remains a challenge, mainly because it has been the focus of very few clinical trials. Because of the lack of the evidences in literature, decisions around surgical intervention, non-resectional procedures, or medical treatment of malignant intestinal obstruction cannot be lightly undertaken. The survival benefit from the different strategies is difficult to validate because of the heterogeneity of the populations studied in various trials, particularly with respect to the primary cancer type. Studies so far have measured peri-operative mortality and morbidity but have not taken the quality of life (QOL) into account when measuring the success of any procedures [3].

The aim of the study was to describe and to compare the two different strategies, medical and surgical, in the management of MBO in ovarian cancer patients. We evaluated if operative and conservative approaches produce an effective and durable palliation in terms of QOL and survival. Furthermore, we investigated the prevalence of low performance status, poor nutritional status, and cachexia in this group of patients and whether the results correlated with overall survival.

## Material and methods

All consecutive patients with recurrent ovarian cancer who experienced bowel obstruction between October 2008 and January 2014 at the Academic Department of Gynecological Oncology of Mauriziano Hospital of Turin (Italy) were identified through the discharging program of the Division. We excluded patients with MBO for other gynecological malignancies, non-epithelial or borderline ovarian cancer, patients with bowel obstruction for benign causes, patients with a history of previous or concurrent malignancy, and patients with concomitant recto-vaginal fistula.

The diagnosis of MBO was based on history, signs and symptoms, physical examination, and radiological findings. At the moment of hospital admission, all patients underwent some laboratory tests and a chest-abdominal computed tomography (CT) to identify the site of bowel occlusion and to restage the disease. Because the location of the MBO can determine the treatment options, we distinguished the site of obstruction in large, small, and both small and large bowel.

The selected patients received medical or surgical treatment.

Medical management of the patients with MBO considered the following protocol:

- Morphine sulfate 60 mg, haloperidol 1.5 mg, octreotide 0.3 mg [4] through continuous subcutaneous pump infusion per day
- Dexamethasone 8 mg intravenous per day
- Stop oral intake
- Parenteral liquids

Surgical management consisted of the less invasive and most conservative interventions to palliate symptoms and to restore intestinal function.

The significance of the palliative treatment was largely explained to the patients, and for the surgical procedures, an informed consensus was signed by the patient and by the surgeon. Patients and their families during the palliative care for the MBO were followed by the team of gynecological oncology, a nutritionist, a palliative care physician, a group of three colorectal surgeons, and a nurse expert in ostomy management. All patients were visited by all the specialists during the process of care. At discharge, patients underwent chemotherapy, if indicated, or palliative care at home or in hospice.

We collected the following data on the history of the patients relative to three stages:

- I- *Before MBO*: stage of the ovarian cancer at diagnosis (FIGO), date of the end of the primary treatment, date of the recurrence, platinum sensitivity, number of chemotherapy lines, secondary surgery, and radiotherapy
- II- *Time of MBO*: performance status (Karnofsky scale), nutritional status (PG-SGA) [5, 6], cachexia (CCSG) [7], body mass index (BMI (kg/m<sup>2</sup>)), comorbidities, date of MBO, vomit, pain (NRS), palpable abdominal mass, CT scan findings (peritoneal carcinomatosis, abdominal, or extra-abdominal disease, ascites >2 L, and the site of obstruction), serum sodium (mEq/L) serum kalium (mEq/l), calcium (mg/dl), serum creatinine (mg/dl), total serum protein (g/dl), serum albumin (mg/dl), hemoglobin (g/dl), C-reactive protein (mg/l), medical or surgical management, type of surgical procedure, surgical morbidity and mortality, and duration of the hospitalization (days)
- III- *After MBO*: pain (NRS), vomit, type of diet at discharge (oral, oral and parenteral, or parenteral), ability to return home, accesses to emergency department and re-hospitalization for re-obstruction and successive medical or surgical intervention, number of chemotherapy lines, death setting (hospital, hospice, or home), and survival

The range from the end of the primary treatment and the diagnosis of relapsed cancer was defined disease-free interval

(DFI), and the recurrent disease was considered platinum sensitive when it reappeared after a DFI >6 months.

The study was approved by the local ethics committee.

### Statistical analysis

Differences in the groups were analyzed using the Student's *t* test for continuous variables or the *U* Mann–Whitney test when a normal distribution was not assumed (non-parametric test); the Pearson chi-square test was adopted to compare frequencies. Overall survival curves were plotted according to the Kaplan–Meier product limit method and analyzed by the log-rank test. Multivariate analysis was performed using the Cox's proportional hazards logistic regression. Alfa level of less than or equal to 0.05 were considered statistically significant.

## Results

### Patients' characteristics

Between October 2008 and January 2014, 53 patients were hospitalized in our division with the admission diagnosis of intestinal occlusion. Thirteen patients with MBO for endometrial, non-epithelial, or borderline ovarian cancer, five patients with bowel obstruction for benign causes, two patients with a history of previous or concurrent malignancy, and three patients with concomitant recto-vaginal fistula were excluded. Data from the remaining 40 patients with concomitant recurrent epithelial ovarian cancer and malignant bowel obstruction were collected. At ovarian cancer diagnosis, 4 patients were stage I–II and 36 patients were stage III–IV, according to FIGO. All patients underwent debulking surgery, and all patients, except one, received neoadjuvant or first-line platinum-based chemotherapy. Median DFI was 10 months (range 3–96 months). In three cases, the diagnosis of recurrent disease was concomitant to MBO. Before MBO, the median number of chemotherapy line was three lines (range 1–7). One patient was submitted to radiotherapy for a muscle-skeletal recurrence of the ileo-psoas region, and one patient received radical secondary cytoreductive surgery. The median interval from the diagnosis of ovarian cancer to MBO was 26 months (range 3–149 months). The median age at first episode of MBO was 63 years (range 24–79 years). Nineteen patients suffered from at least one comorbidity, and the most frequent was hypertension. Eighteen patients underwent medical treatment, and 22 patients were submitted to surgery. Data of the patients at the moment of hospital admission for MBO are summarized in Table 1. We found 4 clinical factors, amongst the 12 analyzed, who resulted significantly different between the two groups: performance and nutritional status, pain (NRS $\geq$ 7), and

ascites. Considering the laboratory tests, only the levels of serum albumin were significantly higher in the group undergoing surgery ( $p$  0.01). At hospital admission, after the radiological restaging (chest-abdomen CT), 32 patients were classified stage FIGO III C (macroscopic peritoneal metastasis beyond the pelvis more than 2 cm), three patients were classified FIGO IV A (pleural effusion), and five patients were classified FIGO IV B (three patients with liver metastasis, one with pulmonary hilum lymph nodes metastasis, and one with muscle-skeletal metastasis). On the basis of the FIGO staging, no difference has been found between the two groups.

### Medical treatment

The medical protocol controlled symptoms within 4 days (range 1–9 days), and the median hospitalization duration was 8 days (range 3–25 days). No side effects were reported. Data about diet, re-obstruction, vomit, and chemotherapy after MBO are reported in Table 2. Median survival after MBO for the group of medical treatment was 5.7 months (range <1–8.4 months). At the moment, 17 patients died, 4 (22.2 %) in hospital, 3 (16.7 %) in hospice, 10 (55.5 %) at home, and 1 patient is still alive with disease.

### Surgical treatment

Surgical procedures included four (18.9 %) bowel resection and anastomosis, nine (40.9 %) bowel resection and ostomy (two colostomy and seven ileostomy), eight (36.4 %) exclusive ostomy (one colostomy and seven ileostomy), and one (4.5 %) positioning of colonic stent. One patient (4.5 %), who underwent large bowel resection and anastomosis, had a post-operative recto-vaginal fistula and required a re-intervention and ileostomy. The mortality within 30 days from surgery was 4.5 % (one case), who died from progression of tumor. Five patients (22.7 %) underwent surgery within 24 h from the hospital admission, but there were no more complications or longer hospitalization in this group. Median hospitalization was 14 days (range 8–30 days). Data about diet, re-obstruction, vomit, and chemotherapy after MBO are reported in Table 2. The median survival after MBO for the group of surgical treatment was 13.6 months (10.1–17.0 months). Nineteen patients died of disease, six (27.3 %) in hospital, four (18.9 %) in hospice, nine (40.9 %) at home, and three (13.6 %) patients are still alive with disease.

### Comparison of treatments

Median hospitalization was shorter for the medical than for the surgical treatment ( $p$  0.02). Pain reduction 1 week after palliation was significantly more effective in the surgical group ( $p$  0.001).

**Table 1** Characteristics of patients at time of MBO

Characteristic	Medical treatment				Surgical treatment				<i>p</i>
	0	1	2	3	0	1	2	3	
Performance status (WHO)	0	6	10	2	3	18	1	0	<b>0.0001</b>
Nutritional status (SGA)	A	B		C	A	B		C	<b>0.02</b>
	3	8		7	5	16		1	
Cachexia (CCSG)	Y		N		Y		N		0.69
	8		9		7		13		
BMI (kg/m <sup>2</sup> )	<20		≥20		<20		≥20		0.71
	3		15		3		19		
Platinum sensitivity	Sensitive		Resistant		Sensitive		Resistant		0.18
	11		7		17		5		
Pain (NRS)	<7		≥7		<7		≥7		<b>0.004</b>
	10		8		1		21		
Vomit	Y		N		Y		N		0.8
	10		8		11		11		
Palpable abdominal mass	Y		N		Y		N		0.33
	4		14		8		14		
Peritoneal carcinomatosis	Y		N		Y		N		0.9
	15		3		18		4		
Stage IV according to FIGO	Y		N		Y		N		0.8
	4		14		4		19		
Ascites	Y		N		Y		N		<b>0.02</b>
	7		11		2		20		
Site of obstruction	L	S	LS		L	S	LS		0.19
	1	10	7		6	9	7		

Bold values are statistically significant

*L* large, *S* small, *LS* large and small

The number of accesses to emergency department and re-hospitalization for re-obstruction was significantly higher in the group of medical treatment, and in these patients, the medical protocol was applied or reapplied (*p* 0.02) (Table 2). After intestinal occlusion, the number of chemotherapy lines was higher in the surgical group (*p* 0.03). Between the two groups, we did not find any difference in post-palliation episodes of vomit (*p* 0.83), type of diet (*p* 0.34), ability to return home (*p* 0.72), and death setting (*p* 0.28). The median survival after palliation was longer in the group of surgery (*p* 0.025) (Fig. 1).

In the group of surgery, patients had a better performance and nutritional status, but no differences were shown about

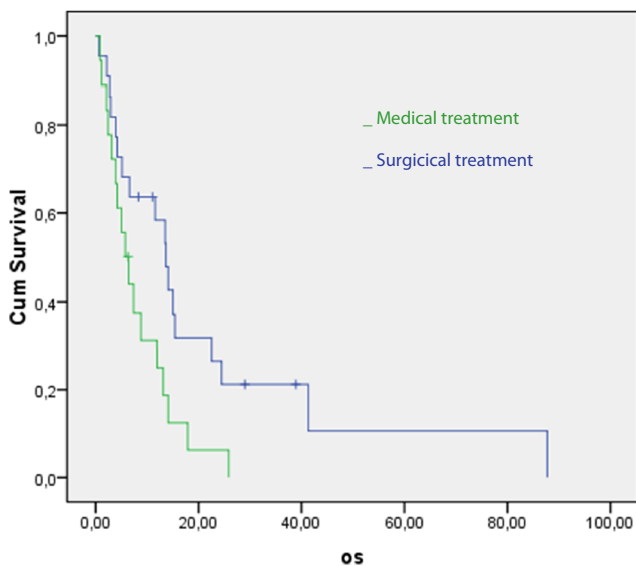
cachexia (Table 1). Cachexia, defined by the CCSG criteria, increased the risk of death with an odds ratio of 3.2 (95 % C.I. 1.5–6.6) (*p* 0.001), the performance status amplified the risk of death with an odds ratio of 2.3 (95 % C.I. 1.4–3.7) (*p* 0.0001), and having a poor nutritional status (SGA-C) enlarged the risk of death with an odds ratio of 4.7 (95 % C.I. 1.4–14.9) (*p* 0.008), compared to well-nourished patients (SGA-A).

In the multivariate logistic regression analysis (Cox proportional hazard model), including as co-variables all the considered variables, CCSG cachexia and performance status resulted independent prognostic factors (*p* 0.0001) (Table 3).

**Table 2** Outcomes after palliation

	Medical treatment			Surgical treatment			<i>p</i>
	Oral	Oral+parenteral	Parenteral	Oral	Oral+parenteral	Parenteral	
Diet	9	3	6	15	1	6	0.346
Re-obstruction	Y	N		Y	N		<b>0.02</b>
	13	5		8	14		
Vomit	Y	N		Y	N		0.83
	2	16		2	20		
Chemotherapy	Y	N		Y	N		<b>0.03</b>
	10	8		15	7		

Bold values are statistically significant



**Fig. 1** Survival after palliation for MBO

## Discussion

Bowel obstruction is usually a pre-terminal event in patients with ovarian cancer. For this reason, the relief of symptoms is the first aim of the treatment of these patients, but the clinical management is not completely defined. Many treatment options, medical approaches, endoscopic procedures, and surgical interventions have been proposed, but current evidences do not provide a standard of care. Modern medical protocols include the use of somatostatine analogs (octreotide) that inhibits the release of gastrointestinal secretions and regularizes the intestinal motility [4]. Surgery remains a discussed issue in patients with advanced cancer.

In patients with MBO, the major perplexities concern the success of conservative treatment and the safety of operative management. Tang et al. reported that only 3.8 % of complete obstruction resolved with conservative management [8]. In a

later study, 43 % of 329 patients were successfully treated conservatively but with a re-obstruction rate of 40.5 % [9]. On the other hand, palliative surgery was associated with a reported morbidity of 5–49 % and mortality of 5–15 % [10–12]. Major operative complications are fistulas, anastomotic leaks, and sepsis. In our study, the postoperative morbidity and mortality were low (4.5 % each). We registered only one case of recto-vaginal fistula, which required a re-intervention and ileostomy, and one case of death within 30 days from surgery due to tumor progression. In similar recent studies, Kolomainen et al. found an operative mortality and morbidity rate of 18 and 27 %, respectively [13], and Perri et al. described a mortality rate of 14.7 % within 30 days [14]. Medina-Franco et al. described a hospital mortality rate of 10.8 % and a postoperative morbidity of 16.2 %, and the factors associated with a significant increase of surgical mortality were advanced patient age, hypoalbuminemia, ovarian neoplasms, and poor performance status [14].

In patients with MBO and recurrent ovarian cancer, the reported median survival is 3–6 months after palliation [15, 16]. More recent series reported a median survival of 11.4–12.6 months in patients undergoing surgery for MBO versus 3.7–3.9 months for non-surgical patients [17]. In our study, the median survival after palliation was 13.6 months for the group of surgery and 5.7 months for the group of medical treatment. Mangili et al. also found a longer survival in the surgical group [18], and Kolomainen et al. reported a median overall survival after surgical management of MBO around 3 months (range 2 days–6 years) [13]. Table 4 compares the reported survival after palliation in the literature.

In the present study, amongst the analyzed factors, the two groups of treatment showed five significant differences: performance status, nutritional status, pain, ascites, and albumin. There were not any differences between the two groups in terms of age, FIGO stadition, number of previous chemotherapy lines, DFI, time from ovarian cancer diagnosis and MBO, and time from the last chemotherapy infusion. In the group of surgery, the number of chemotherapy lines after MBO was higher, 15 patients (68.2 %) received at least one line and 5 patients (22.7 %) completed more than one line ( $p$  0.03).

In our series, many QOL criteria were considered in the analysis. Pain reduction was more effective in the surgical

**Table 3** Survival after palliation

Factor	Survival (months)	<i>p</i>
Treatment	Overall 8 years Medical 5 (3–8) Surgical 13 (10–17)	0.025
CCSG cachexia	Present 4 (2–5) Absent 13 (12–14)	0.002
Nutritional status	SGA-A 22 (7–37) SGA B 8 (2–15) SGA C 3 (<1–6)	0.015
Performance status	0, 24 (21–27) 1, 13 (11–15) 2 3 (1–5) 3, 5 (1–6)	0.001

**Table 4** Survival after palliation—comparison of the literature

Study	Surgical treatment (months)	Medical treatment (months)
Current study	13.6	5.7
Kolomainen et al.	3.0	–
Mangili et al.	Significantly longer	–
Li et al.	12.6	3.7

group, and re-obstruction was more frequent in the group of medical treatment. Between the two groups, we did not find any difference in post-palliation episodes of vomit, type of diet, and ability to return home. As reported, two essential QOL factors, pain reduction and re-obstruction, were significantly improved by surgical palliation. In case of re-obstruction, all patients received medical treatment. Two reports, each describing a small series of ovarian cancer patients who underwent exploratory laparotomy for recurrent bowel obstruction, reported successful palliation in 30 % of cases [2, 3]. In accordance with the cited studies, because of the high morbidity rate, the rapid development of subsequent bowel obstructions, and the limited survival, we agree that a non-surgical approach is probably preferable for patients who experience repeated bowel obstruction. Because of the retrospective design, we lack data from some overall QOL questionnaires [18, 19].

Considering some selection bias, our data suggest that patients who underwent palliative surgery achieve more effective survival and QOL improvements, but because of the reported implications, the decision to proceed with surgical palliation in patients with ovarian cancer and MBO has to be carefully evaluated for each individual patient.

Several studies have focused their attention to the identification of some prognostic factors for the selection of patients who may benefit from surgery. Mangili et al. suggested that the surgical approach seems to be useful for patients with life expectancy greater than 2 months [20]. Studies identified age, ascites, previous radiotherapy, multiple bowel obstructions, carcinomatosis, palpable masses, and short interval from diagnosis to obstruction as clinical indicators of poor prognosis after surgery [13, 21–24]. Henry et al. proposed a nomogram of four identified risk factors: carcinomatosis on imaging, leukocytosis, normal albumin, and non-gynecologic cancer that revealed which patients with complete small bowel obstruction might benefit from surgery [25]. However, because only 17 % of the included patients had gynecologic malignancies, their findings might not be fully applicable to gynecological oncology. Finally, in the study of Perri et al., a four-variable score was correlated with the 30 and 60 days overall survival after surgical palliation for MBO in gynecologic malignancies, 2.7 and 5.4 %, respectively (score 0–1), and 40 and 73.3 %, respectively (score 3–5). The score includes age above 60, ascites of more than 2 L, non-ovarian primary tumor, and albumin <2.5 g/dl [3]. The first three factors were assigned a value of 1 if present and 0 if not. Albumin <2.5 mg/dl was assigned a value of 2 if present and 0 if not. The proposed scoring system is easy to apply and might facilitate decision of the health-care team and information of patients and families. The major limitation of this score is that it does not take into account information about performance status.

Different tools have been proposed for cancer malnutrition and wasting assessment. They have been largely confirmed in

gastrointestinal cancer patients, but they have never been validated in ovarian cancer neoplasm. We designed the second part of the study to identify the role of performance status, nutritional status, and cachexia in ovarian cancer patients with MBO and their association with survival after palliation, independently by the treatment. Thirteen patients (32.5 %) had a low performance status and, finally, in accordance with PG-SGA classification, eight patients (20 %) were “severely malnourished”. Low performance status, CCSG cachexia, and poor nutritional status were all significant predictors of worse survival after MBO. To the best of our knowledge, the present study is the first that applied these assessment tools in such homogeneous group of patients with advanced ovarian carcinoma. The CCSG definition of cachexia was first introduced in a study of patients with pancreatic carcinoma in which cachexia was found to be related to the patients’ survival [26]. In that study, 60 % of the patients had cachexia and the HR for overall survival was 2.23, close to our findings. These observations suggest that the CCSG definition of cachexia should be applicable also in advanced ovarian carcinoma. In this study, CCSG cachexia and low performance reached statistical significance in both unadjusted and adjusted survival analyses and were the most powerful predictors of survival. The sample size of the study was limited, and further investigations are required to confirm the prognostic value of the nutrition and cachexia assessments.

In our report, especially for the group of surgery, the long prognosis, the low rates of postoperative morbidity and mortality, and the high number of patients who received chemotherapy after MBO probably reflect the good performance status of the patients. Furthermore, previous reports date back several decades and so they do not take into account the substantial improvements of the current medical protocols, surgical techniques, and anesthesia. On the basis of our experience, we support the hypothesis that performance and nutritional status and cachexia may address the choice of the treatment.

All series, including ours, are retrospective and include a small number of patients, but our study solely comprised ovarian cancer patients treated in a relatively short period. In the analysis, we focused specific attention to QOL outcomes. Moreover, our results come from a single institution and patients were assessed by a multidisciplinary team.

In the setting of palliative care, a randomized trial is challenging [27]. A trial comparing therapies for MBO will help to define therapy and identify selection criteria. Until now, no comparative trials have been performed on the role of the therapeutic strategies for MBO. To prove the effects of any given treatment, hundreds of patients would need to be recruited. A trial in this scenery is hampered by many individual differences between patients and by the myriad of advanced medical and surgical protocols. Currently, in the absence of a shared protocol, it is our intention to validate our findings in a prospective study.

In conclusion, malignant bowel obstruction represents a common end-of-life event in ovarian cancer patients. Because of its complexity and frailty of involved patients, a multidisciplinary and collaborative approach is mandatory for an optimal clinical management and palliation of MBO. In a palliative setting, the most important goal is to identify the patient's expectations, because they are largely subjective for each individual patient [28]. For these reasons, patients, and eventually their families, must be informed about their health and life expectancy. Surgery has to be considered in patients without serious contraindications; otherwise, a combination of opioids, anti-emetics, corticosteroids, and antisecretory drugs is the mainstay in patients with poor general conditions.

**Conflict of interest** The authors have no financial and personal relationships with other people or organizations that could inappropriately influence this work. They have full control of all primary data, and they agree to allow the journal to review data if requested.

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