Introduction

Malignant bowel obstruction (MBO) is a common complication of cancer; it occurs in 10–20% of colorectal cancer patients and 20–50% of ovarian cancer patients [1–3]. Malignant small bowel obstruction (MSBO) poses the greatest challenge for clinical care. The outcomes for surgical intervention are generally poor, with several studies demonstrating a low likelihood of meaningful clinical benefit [4–6]. In part, this relates to the frequent multifocality of small bowel involvement in the context of peritoneal carcinomatosis and the poor nutritional status of patients. Therefore, a conservative management approach consisting of bowel rest is considered standard treatment for symptomatic episodes of MSBO. It has been reported that 36% of cases with MBO achieve symptomatic relief with conservative treatment [7]. However, those failing such strategies have goals of care that are typically palliative in nature and preclude the continuation or initiation of anti-cancer therapy.
Supplemental total parenteral nutrition (TPN) has not been shown to improve outcomes in patients with terminal cancer [8]. Outcomes from the use of supplemental TPN among patients with MBO are poor, with the median overall survival (OS) duration ranging from 53 to 140 days [9–13]. Studies have reported even worse outcomes for patients with MBO in the context of peritoneal carcinomatosis, with median OS durations of 40–74 days with TPN [14–16]. Though studies have frequently noted that a small subpopulation appears to benefit from TPN, recognizing members of this subgroup ahead of treatment has, thus far, proven difficult [16–19].

The use of systemic chemotherapy in conjunction with TPN to manage MSBO is an aggressive approach that has not been well studied. Several small retrospective studies have included patients who have undergone this regimen [11, 17, 20–22], but no study has yet attempted to report on a large multitumor dataset. Because recent improvements in systemic chemotherapy have resulted in improved outcomes for patients with peritoneal carcinomatosis, a clearer understanding of the risks and benefits of aggressive TPN and chemotherapy treatment is needed [23, 24]. In this study, we examine a large, single-institution dataset to describe outcomes associated with concurrent TPN and systemic chemotherapy for persistent MSBO after conservative management.

Methods

Patient selection and data collection

We queried The University of Texas MD Anderson Cancer Center’s pharmacy administration database to identify all patients treated concurrently with intravenous chemotherapy and TPN between January 2005 and December 2013 (n = 442). We excluded patients on the basis of nonsolid tumor histology (n = 219), age ≤16 years old (n = 12), administration of TPN for ≤8 days (n = 10), duodenal obstruction as cause of MSBO (n = 7), lack of radiographic or surgical confirmation of SBO (n = 111), and lack of peritoneal carcinomatosis (n = 1). The final study population consisted of 82 patients. The Institutional Review Board at MD Anderson Cancer Center approved this study.

Two physicians (J. C. and R. G.) retrieved from the database retrospective data on patient demographics, tumor characteristics, laboratory indices, chemotherapy and surgical treatments, TPN supplementation, frequency of hospitalization, and duration of stay in the inpatient setting. TPN-related complications included in this study were line infections and hyperbilirubinemia. Line infection was defined as a positive blood or catheter-tip culture from the patient’s TPN line, and hyperbilirubinemia was defined as a total bilirubin level >1.5 times the upper limit of normal (1.0 mg/dL) that was unexplained by hepatic metastases, biliary obstruction, or prior hepatobiliary disease. Best response to chemotherapy was categorized semiquantitatively as stable disease, disease progression or disease stabilization based on a retrospective review of the patient’s radiographic records and the treating physician’s assessment of them. MSBO resolution was defined as a patient tolerating an oral diet without the need for additional intravenous nutritional supplementation for ≥60 days.

### Table 1. Patient demographic baseline characteristics (N = 82).

| Variable                                                | N    | Percentage or range |
|---------------------------------------------------------|------|---------------------|
| Median age, years                                       | 55   | 17–85               |
| Median initial body mass index (kg/m²)                  | 23.9 | 14.3–38.0           |
| Median initial albumin (g/dL)                           | 2.8  | 1.6–4.4             |
| Female sex                                              | 51   | 62.2                |
| Caucasian race                                          | 53   | 64.6                |
| Median duration of metastasis prior to TPN/chemotherapy, months | 6.9  | 0–115               |
| Extraperitoneal metastasis                              | 48   | 58.5                |
| Previous abdominal surgery                              | 59   | 72                  |
| Tumor histology                                         |      |                     |
| Carcinoma                                               | 71   | 86.6                |
| Noncarcinoma                                            | 11   | 13.4                |
| Primary site                                            |      |                     |
| Gastrointestinal                                        | 49   | 59.8                |
| Colorectal                                              | 20   |                     |
| Appendix                                                | 6    |                     |
| Pancreas                                                | 6    |                     |
| Other¹                                                  | 11   |                     |
| Gynecological                                           | 18   | 22.0                |
| Ovarian/Primary Peritoneal                              | 16   |                     |
| Uterine                                                 | 2    |                     |
| Other²                                                  | 15   | 18.3                |
| Line of chemotherapy                                    |      |                     |
| 1st                                                     | 38   | 46.3                |
| 2nd                                                     | 15   | 18.3                |
| ≥3rd                                                    | 29   | 35.3                |
| First chemotherapy regimen                               |      |                     |
| 5-FU                                                    | 32   | 39                  |
| Taxane                                                  | 15   | 18.3                |
| Other³                                                  | 35   | 42.7                |
| New chemotherapy start during TPN                       | 58   | 70.7                |

TPN, total parenteral nutrition.

¹Stomach (5); gastrointestinal cancer of unknown primary (1); gallbladder (1); small bowel carcinoid (2); small bowel adenocarcinoma (1); and intra-abdominal desmoid tumor (1).

²Sarcoma (4); melanoma (4); cancer of unknown primary (3); bladder (2); urachus; (1); and prostate (1).

³5-FU + taxane (5); doxorubicin (6); gemcitabine (2); irinotecan (5); platinum-based therapy (7); Carmustine (1); anti-EGFR therapy (2); pemetrexed (1); IL-2 (2); topotecan (2); and bevacizumab.
Statistical analysis

Comparisons of relevant factors were made using analysis of variance (ANOVA), chi-square tests, or log-rank test. Kaplan–Meier curves were used to calculate time to event analyses, and were calculated from the initial date where TPN supplementation and chemotherapeutic intervention coincided until the date of last contact or occurrence of a relevant indicated event.

Multivariate Cox proportional hazard models were created and included any variable with a P-value <0.10 in univariate analysis. Multivariate Cox proportional hazard modeling was conducting using a stepwise selection approach. A pool of candidate predictor variables consisting of ten covariates (age, body mass index, duration of metastatic disease, sex, site, histology, peritoneum only metastases, chemotherapy regimen, new chemotherapy start on TPN, and line of therapy) were offered to the model. Factors significant at the 0.10 level were allowed to enter the model, but significance at the 0.05 level was required to stay in the model. A P-value of 0.05 was considered statistically significant. All analysis was performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics and clinical course

Among the 82 patients with MSBO secondary to peritoneal carcinomatosis who met the inclusion criteria (Table 1), the median age was 55 years. The most common primary tumor types were gastrointestinal (59.8%) and gynecologic (22.0%); extra-peritoneal metastases were present in 48 (58.5%) patients. The median follow-up time was 89.5 days (range, 4–2117 days).

The median duration of metastatic disease prior to the administration of concurrent systemic chemotherapy and TPN was 6.9 months (range, 0–115 months). The initial systemic chemotherapy was the first-line therapy for metastatic disease in 38 (46.3%) patients. Twenty-four (29.3%) patients continued to receive the same chemotherapy regimen after the initiation of TPN. The median duration of chemotherapy prior to TPN initiation was 8.5 days (range, 4–2117 days), with only one patient having more than 2 cycles of chemotherapy prior to TPN initiation.

Response to chemotherapy was assessed radiographically in 54 (65.9%) patients (Table 2). The remaining 28 (34.1%) patients demonstrated clinical decline and did not undergo further radiographic imaging. Of the 54 patients with radiographic assessments, 19 patients showed a radiographic response, 9 had stable disease, and 26 had progressive disease (Table 2).

The median duration of TPN was 45 days (range, 9–639). TPN-related complications (i.e., line infections or hyperbilirubinemia) occurred in 27 (32.9%) patients. Bowel perforation occurred rarely, in only 4 (4.9%) patients. Sixty-three (76.8%) patients required hospitalization after the initiation of systemic chemotherapy and TPN, with 23 (28.1%) patients admitted to the intensive care unit. The median number of hospitalizations was 2 (range, 1–11), and the median time spent hospitalized was 26.5 days (range, 4–167 days). On average, patients spent 38% (range, 1–100%) of their remaining lives in the hospital.

Resolution of MSBO

MSBO resolution was observed in 10 (12.2%) patients (Table 2; Fig. 1). As shown in Figure 1, resolution of MSBO was attributable to surgery in 3 cases and chemotherapy in 5 cases, while an additional two cases had MSBO resolution without either surgery or a chemotherapy response. Recurrence of the MSBO obstruction occurred in 6 of the 10 patients, at a median time of 5.3 months (range, 2–90 months) after the initial resolution. Surgery with the goal of correcting the MSBO was attempted infrequently (6 cases, 7.3%) with the median time from
Chemotherapy and TPN for MSBO

initiation of systemic chemotherapy and TPN to MSBO surgery of 35.5 days (range, 6–217 days).

On univariate analysis, surgery (odds ratio [OR] 9.86; 95% confidence interval [CI], 1.66–58.40, \( P = 0.01 \)) and radiographic response to treatment (OR 6.37; 95% CI, 1.63–24.85, \( P = 0.007 \)) were found to be predictors of MSBO resolution (Table 3). On multivariate modeling that did not include subsequent treatment variables of radiographic response or surgery for MSBO—no factors were found to be significant predictors of MSBO resolution. With the inclusion of the two subsequent-treatment factors, only radiographic response correlated with an increased rate of MSBO resolution (OR 6.81; 95% CI, 1.68–27.63, \( P = 0.007 \)).

Overall survival

The median OS duration for our patient cohort was 3.1 months (range, 0.03–69.4 months), with a 1-year OS rate of 12.2% (Fig. 2A). Among the 54 patients who underwent radiographic assessments, those with a radiographic response to therapy showed longer OS than those with no response (median OS 9.2 vs. 4.7 months, \( P = 0.018 \)) (Fig. 2B). The median OS was 1.7 months for patients who did not undergo radiographic evaluation. Of the 10 patients who lived longer than 1 year, three had favorable tumor types (desmoid, appendiceal adenocarcinoma and carcinoid) while the remaining 7 had ovarian/primary peritoneal (\( n = 4 \)), prostate (\( n = 1 \)), endometrial adenocarcinoma (\( n = 1 \)), and small bowel adenocarcinoma (\( n = 1 \)). The median time spent inpatient was 49 days (range 7–126 days) and SBO resolution occurred in 5 patients (2 following surgery and 3 following chemotherapy). Of the seven patients with unfavorable tumor types, four underwent frontline chemotherapy and all had either a response or stable disease to chemotherapy.

On univariate analysis, only radiographic response to chemotherapy showed a statistically significant correlation with OS (OR 0.36; 95% CI, 0.20–0.65, \( P = 0.0007 \)) (Table 4). Multivariate modeling that excluded the subsequent-treatment variables showed no statistically significant factors. With the inclusion of radiographic response and MSBO surgery in the multivariate analysis, radiographic
response (OR 0.30; 95%, 0.16–0.56, \( P = 0.004 \)) and initiation of new systemic chemotherapy during TPN (OR 0.55; 95% CI, 0.33–0.94, \( P = 0.026 \)) were correlated with improved OS.

**Discussion**

The treatment approach for cancer patients with MSBO after conservative management with bowel rest is poorly defined. Studies have shown limited benefit with either surgical intervention or supplemental TPN for this patient population [4–6, 9, 14, 16, 20]. Our study analyzed the largest available dataset evaluating the more aggressive approach of concurrent systemic chemotherapy and TPN. We conclude that the outcomes of this aggressive approach are poor, yielding a median OS duration of 3.1 months.

In addition, we observed significant treatment-related morbidity; 76.8% of patients were rehospitalized, and on average they spent approximately 38% of their remaining lives in the hospital. Although a radiographic response to chemotherapy predicted MSBO resolution in our multivariate analysis, only 5 of the 19 patients with a radiographic response (6% of the entire cohort) experienced MSBO resolution attributable to the use of systemic chemotherapy. These results demonstrate that the aggressive treatment of MSBO secondary to peritoneal carcinomatosis with systemic chemotherapy and concurrent TPN supplementation provided minimal benefit to our patient population.

Several previous studies, with populations ranging from 4 to 31 patients, have reported on the palliative management of MBO with chemotherapy and TPN supplementation.

| Variable                                      | \( n \) | Univariate Odds ratio (95% CI) | \( P \)-value | Multivariate Odds ratio (95% CI) | \( P \)-value |
|-----------------------------------------------|--------|--------------------------------|--------------|---------------------------------|--------------|
| Age\(^1\)                                      | 82     | 0.96 (0.91–1.00)               | 0.06         |                                 |              |
| Albumin\(^2\)                                  | 79     | 1.06 (0.42–2.71)               | 0.90         |                                 |              |
| Body mass index\(^2\)                         | 81     | 0.98 (0.88–1.09)               | 0.68         |                                 |              |
| Metastatic disease duration ≥7 months          | 82     | 0.41 (0.10–1.69)               | 0.22         |                                 |              |
| New chemotherapy start during TPN              | 58     | 1.52 (0.33–6.94)               | 0.59         |                                 |              |
| Sex                                           |        |                                |              |                                 |              |
| Male                                          | 31     | Reference                      |              |                                 |              |
| Female                                        | 51     | 0.87 (0.24–3.23)               | 0.84         |                                 |              |
| Site                                          |        |                                |              |                                 |              |
| Gastrointestinal                              | 49     | Reference                      |              |                                 |              |
| Gynecological                                 | 18     | 1.23 (0.24–6.28)               | 0.81         |                                 |              |
| Other                                         | 15     | 2.27 (0.50–10.32)              | 0.29         |                                 |              |
| Histology                                     |        |                                |              |                                 |              |
| Carcinoma                                     | 71     | Reference                      |              |                                 |              |
| Noncarcinoma                                   | 11     | 4.78 (1.00–22.87)              | 0.051        |                                 |              |
| Extraperitoneal metastasis                    |        |                                |              |                                 |              |
| Yes                                           | 34     | Reference                      |              |                                 |              |
| No                                            | 48     | 0.97 (0.26–3.56)               | 1.00         |                                 |              |
| Chemotherapy regimen                          |        |                                |              |                                 |              |
| 5-FU                                          | 32     | Reference                      |              |                                 |              |
| Taxane                                        | 15     | 1.17 (0.21–4.50)               | 0.86         |                                 |              |
| Other                                         | 35     | 1.08 (0.26–4.50)               | 0.92         |                                 |              |
| Line of chemotherapy                          |        |                                |              |                                 |              |
| 1st                                           | 38     | Reference                      |              |                                 |              |
| 2nd                                           | 15     | 0.93 (0.18–4.75)               | 0.93         |                                 |              |
| ≥3rd                                          | 29     | 1.09 (0.21–5.69)               | 0.92         |                                 |              |
| Surgery for MSBO                              |        |                                |              |                                 |              |
| No                                            | 76     | Reference                      |              |                                 |              |
| Yes                                           | 6      | 9.86 (1.66–58.40)              | 0.01         |                                 |              |
| Radiographic response                         |        |                                |              |                                 |              |
| No                                            | 63     | Reference                      |              |                                 |              |
| Yes                                           | 19     | 6.37 (1.63–24.85)              | 0.007        | 6.81 (1.68–27.63)               | 0.007        |

CI, confidence interval; TPN, total parenteral nutrition; MSBO, malignant small bowel obstruction.  
\(^1\)\( P < 0.05 \) was considered statistically significant.  
\(^2\)Continuous variable used to calculate odds ratios.
Brard et al. [10] conducted one of the larger studies to specifically address the role of TPN and chemotherapy in the setting of MBO; they found no statistically significant difference between the median OS duration of 18 patients treated with chemotherapy and TPN compared and that of 7 patients treated with chemotherapy alone (72 vs. 42 days, $P = 0.09$) [10]. In contrast, Abu-Rustum et al. [23] reported, in a study of 21 ovarian cancer patients with MBO, that patients receiving TPN and chemotherapy had a significantly longer median OS than those treated with chemotherapy alone (80 vs. 62 days, $P = 0.031$) [21]. However, due to the retrospective nature of these studies and their relatively small sample sizes, no definitive conclusions can be drawn from them.

The frequency of MSBO resolution in our overall cohort (12.2%) was similar to that observed in two previous studies, which found MBO resolution in 1 (12.5%) of 8 and 2 (12.2%) of 11 ovarian cancer patients managed with an aggressive approach like the one examined in our study [20, 21]. Among our patient cohort, radiographic response was the only independent predictor of MSBO resolution. However, a discrepancy between treatment response and MSBO resolution did exist. Of 19 patients with radiographic tumor response, only 5 (26%) patients went on to have MSBO resolution that could be attributed to chemotherapeutic intervention. A relationship between chemotherapy response and MBO-resolution has not been well described in the literature, but was suggested in an examination of 39 ovarian cancer patients palliatively managed with chemotherapy and/or surgery. In this study, a platinum response disease was seen in 46% of patients with resolution of their MBO compared to only 27% of patients without resolution of their MBO, $P = 0.17$ [25].

Figure 2. Overall survival (OS) for (A) all patients ($n = 82$) and (B) patients who underwent radiographic tumor assessment ($n = 54$).
In addition, we identified no baseline factors that predicted either OS or MSBO resolution. Indeed, we were surprised that neither the line of chemotherapy used nor the tumor type predicted either outcome. It was also of interest that worse OS was seen in patients in whom the same chemotherapy administered prior to the development of MSBO was continued unchanged after the MSBO diagnosis. Given that treatment response was the only factor that correlated with both OS and MSBO resolution in our study, it is critical that, if this aggressive approach is attempted, the radiographic results from systemic chemotherapy are incorporated into clinical assessments of the risks and benefits of further treatment. However, the absence of any pretreatment factors that statistically correlated with improved outcomes poses a major limitation to the clinical application of this aggressive approach.

Though we were unable to assess quality of life measures due to our study’s retrospective nature, our analyses suggest that the aggressive treatment approach is associated with high morbidity rates. In particular, 23 (28.1%) patients required admission to the intensive care unit, and 27 (32.9%) developed TPN-related complications. In part, these findings may reflect the well-known increased risks of infections and iatrogenic complications from the concurrent use of supplemental TPN in patients treated with chemotherapy [8]. Most importantly in terms of quality of life, patients spent an average of 38% of their remaining lives in the hospital.

Although we examined the largest population of patients with MSBO treated with concurrent chemotherapy and TPN of any study to date, our study, like others, was limited by its relatively small cohort size and its

### Table 4. Univariate and multivariate analyses of factors correlating with overall survival.

| Variable                        | n  | Univariate Hazard ratio (95% CI) | P-value<sup>1</sup> | Multivariate Hazard ratio (95% CI) | P-value<sup>1</sup> |
|---------------------------------|----|---------------------------------|---------------------|-----------------------------------|---------------------|
| Age<sup>2</sup>                 | 82 | 1.00 (0.98–1.01)                | 0.70                |                                   |                     |
| Albumin<sup>2</sup>             | 79 | 0.94 (0.68–1.30)                | 0.71                |                                   |                     |
| Body mass index<sup>2</sup>     | 81 | 1.01 (0.97–1.04)                | 0.68                |                                   |                     |
| Metastatic disease duration ≥7 months | 82 | 0.99 (0.98–1.00)                | 0.94                |                                   |                     |
| New chemotherapy start during TPN | 58 | 0.77 (0.47–1.28)                | 0.3                 | 0.55 (0.33–0.94)                  | 0.026               |
| Sex                             |    |                                 |                     |                                   |                     |
| Male                            | 31 | Reference                       |                     |                                   |                     |
| Female                          | 51 | 0.90 (0.56–1.44)                | 0.67                |                                   |                     |
| Site                            |    |                                 |                     |                                   |                     |
| Gastrointestinal                | 49 | Reference                       |                     |                                   |                     |
| Gynecological                   | 18 | 0.70 (0.49–1.27)                | 0.20                |                                   |                     |
| Other                           | 15 | 1.01 (0.56–1.83)                | 0.97                |                                   |                     |
| Histology                       |    |                                 |                     |                                   |                     |
| Carcinoma                       | 71 | Reference                       |                     |                                   |                     |
| Noncarcinoma                    | 11 | 0.93 (0.56–1.83)                | 0.84                |                                   |                     |
| Extraperitoneal metastasis      |    |                                 |                     |                                   |                     |
| Yes                             | 34 | Reference                       |                     |                                   |                     |
| No                              | 48 | 0.92 (0.58–1.44)                | 0.70                |                                   |                     |
| Chemotherapy regimen            |    |                                 |                     |                                   |                     |
| 5-FU                            | 32 | Reference                       |                     |                                   |                     |
| Taxane                          | 15 | 0.58 (0.30–1.14)                | 0.16                |                                   |                     |
| Other                           | 35 | 1.09 (0.65–1.84)                | 0.74                |                                   |                     |
| Line of chemotherapy            |    |                                 |                     |                                   |                     |
| 1st                             | 38 | Reference                       |                     |                                   |                     |
| 2nd                             | 15 | 1.19 (0.64–2.21)                | 0.58                |                                   |                     |
| ≥3rd                            | 29 | 1.38 (0.72–2.62)                | 0.33                |                                   |                     |
| Surgery for MSBO                |    |                                 |                     |                                   |                     |
| No                              | 76 | Reference                       |                     |                                   |                     |
| Yes                             | 6  | 0.67 (0.32–1.39)                | 0.28                |                                   |                     |
| Radiographic response           |    |                                 |                     |                                   |                     |
| No                              | 63 | Reference                       |                     |                                   |                     |
| Yes                             | 19 | 0.36 (0.20–0.65)                | 0.0007              | 0.30 (0.16–0.56)                  | 0.0004              |

CI, confidence interval; TPN, total parenteral nutrition; MSBO, malignant small bowel obstruction.

<sup>1</sup>P < 0.05 was considered statistically significant.

<sup>2</sup>Continuous variable used to calculate odds ratios.
retrospective nature. In addition, while our study population was representative of clinical practice patterns for the treatment of solid tumors, heterogeneity in the patient population and in tumor types prevented us from undertaking a more detailed investigation of the prognostic significance of various subgroups. Additionally, while better performance status has previously been reported to predict longer OS in patients with MBO [12, 16, 26], we were unable to evaluate this relationship due to a lack of documentation of performance status for hospitalized patients. Because the aggressive treatment approach may have only been considered for more functionally robust patients, it is possible that the population we studied reflects a highly selected cohort. A final limitation involves the definition of unresolving MSBO. By requiring more than 8 days of TPN, we designed our study criteria to identify patients with an unresolving MSBO that was likely not amenable to surgical intervention; nevertheless, a small subset of patients went on to have palliative surgical procedures, and 2 patients were observed to have spontaneous resolution of their MSBOs.

In conclusion we recommend against that the use of systemic chemotherapy and TPN for patients with MSBO secondary to peritoneal carcinomatosis. Though a small subset of the studied patients did gain a modest benefit, the lack of predefined factors that could identify this population in advance makes it clinically challenging to apply this aggressive approach, especially in light of the significant treatment-related morbidity we observed.

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Conflict of Interest
None declared.

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Chemotherapy and TPN for MSBO

J. Chouhan et al.

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