

Retrospective Cohort Study

Gastric peritoneal carcinomatosis - a retrospective review

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Abstract**AIM**

To characterize patients with gastric peritoneal carcinomatosis (PC) and their typical clinical and treatment course with palliative systemic chemotherapy as the current standard of care.

METHODS

We performed a retrospective electronic chart review of all patients with gastric adenocarcinoma with PC diagnosed at initial metastatic presentation between January 2010 and December 2014 in a single tertiary referral centre.

RESULTS

We studied a total of 271 patients with a median age of 63.8 years and median follow-up duration of 5.1 mo. The majority ($n = 217$, 80.1%) had the peritoneum as the only site of metastasis at initial presentation. Palliative systemic chemotherapy was eventually planned for 175 (64.6%) of our patients at initial presentation, of which 171 were initiated on it. Choice of first-line regime was in accordance with the National Comprehensive Cancer Network Guidelines for Gastric Cancer Treatment. These

patients underwent a median of one line of chemotherapy, completing a median of six cycles in total. Chemotherapy disruption due to unplanned hospitalizations occurred in 114 (66.7%), while cessation of chemotherapy occurred in 157 (91.8%), with 42 cessations primarily attributable to PC-related complications. Patients who had initiation of systemic chemotherapy had a significantly better median overall survival than those who did not (10.9 mo *vs* 1.6 mo, $P < 0.001$). Of patients who had initiation of systemic chemotherapy, those who experienced any disruptions to chemotherapy due to unplanned hospitalizations had a significantly worse median overall survival compared to those who did not (8.7 mo *vs* 14.6 mo, $P < 0.001$).

CONCLUSION

Gastric PC carries a grim prognosis with a clinical course fraught with disease-related complications which may attenuate any survival benefit which palliative systemic chemotherapy may have to offer. As such, investigational use of regional therapies is warranted and required validation in patients with isolated PC to maximize their survival outcomes in the long run.

Key words: Peritoneal carcinomatosis; Gastric cancer

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Core tip: We present a retrospective review of the clinical course and treatment outcomes of patients with gastric peritoneal carcinomatosis. It carries a poor prognosis with a clinical course fraught with disease-related complications which disrupts planned systemic palliative chemotherapy in the majority of patients. Such disruptions attenuate the benefits of systemic chemotherapy and decrease overall survival. Patients with isolated peritoneal disease may as such benefit from investigational loco-regional therapies pending further studies and validation.

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INTRODUCTION

Gastric cancer is the fifth most common cancer across the world, accounting for 723000 deaths per year, the third most frequent cause of cancer-related deaths^[1-3]. In Singapore, gastric cancer ranks as the seventh and ninth most common cancers, but accounts for the fourth and fifth most frequent cancer deaths amongst males and females respectively^[4]. The poor prognosis of gastric cancer has in part been attributed to the high incidence of advanced disease at presentation, with up to 39% harboring disseminated disease at diagnosis^[5]. Metastatic gastric cancer carries a grim prognosis

with a median overall survival of approximately four months and five-year survival rates of 3%-6%^[1,6,7]. Although palliative systemic chemotherapy has been demonstrated in numerous trials to improve survival amongst patients with metastatic gastric cancer to a median of 7.5-12.3 mo^[8-11], whether such a benefit accrues equally to all sites of gastric cancer metastases is unclear.

Peritoneal carcinomatosis (PC) is recognized as an independent poor prognostic factor and is known to have a penchant for causing a wide range of troubling clinical symptoms including symptomatic ascites, intestinal obstruction, perforation and obstructive uropathy^[12]. This can result in repeated hospitalizations, therapeutic interventions and rapid deterioration of a patient's performance status, which may serve to interrupt and prematurely terminate any planned palliative systemic chemotherapy regime a patient might be on. There is a paucity of literature on the characteristics of patients with gastric PC^[5], with virtually no studies examining the clinical and treatment course of these patients. The advent of studies examining the role of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of gastric PC was borne from the concept of peritoneal metastases being a loco-regional disease extension rather than a true systemic dissemination of gastric cancer^[13-18]. Should patients with gastric PC be less likely to complete planned courses of palliative systemic chemotherapy and hence perform relatively poorly, it would further bolster the case for studying CRS and HIPEC for a select group of patients with gastric PC to maximize their survival.

As such, we aim to characterize patients with gastric PC and their typical clinical and treatment course to glean a better understanding of how well this subset of metastatic gastric cancer patients are doing with palliative systemic chemotherapy as the current standard of care.

MATERIALS AND METHODS

We performed a retrospective review of all patients with metastatic gastric cancer managed at the National Cancer Centre Singapore, the largest tertiary referral centre for cancer treatment locally, over a 5-year period between January 2010 and December 2014. All patients with gastric adenocarcinoma with peritoneal metastasis diagnosed at initial metastatic presentation, with or without other concomitant distant sites of metastasis, were included in our study. Patients with isolated positive peritoneal cytology were excluded. Electronic records were reviewed for various patient characteristics including patient demographics, gastric cancer characteristics, treatments administered and subsequent clinical course through each patient's follow-up duration.

All patients included in the study had computed tomography scans of the thorax, abdomen and pelvis performed for initial staging following the diagnosis of

Table 1 Baseline patient demographics

Characteristic	n (%)
Median age (range) (yr)	63.8 (26.9-89.0)
Ethnicity	
Chinese	203 (74.9)
Indian	13 (4.8)
Malay	20 (7.4)
Others	35 (12.9)
Gender	
Male	134 (49.4)
Female	137 (50.6)
ECOG status	
0	89 (32.8)
1	135 (49.8)
2	28 (10.3)
3	11 (4.1)
4	8 (3.0)
ASA score	
1	107 (39.5)
2	128 (47.2)
3	36 (13.3)
Comorbidities	
Diabetes mellitus	56 (20.7)
Hypertension	124 (45.8)
Cardiac comorbidities	43 (15.9)
Respiratory comorbidities	15 (5.5)
Chronic renal impairment	10 (3.7)
Central nervous system comorbidity	19 (7.0)
Previous cancer	27 (10.0)
Cigarette smoking	58 (21.4)
Regular alcohol use	31 (11.4)

ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anaesthesiology.

gastric adenocarcinoma. Patients without radiological evidence of metastatic disease then underwent staging laparoscopy with intra-operative frozen section assessment of peritoneal deposits.

Palliative systemic chemotherapy was offered as the standard of care in our institution to all patients with metastatic gastric cancer in close discussion with each patient. The first-line palliative systemic chemotherapy regime for each patient was chosen in accordance to the National Comprehensive Cancer Network Guidelines for Gastric Cancer Treatment with consideration to each patient's performance status and preferences, favoring two to three-agent chemotherapy combinations over single-agent chemotherapy where possible^[19]. Trastuzumab was additionally offered in cases which were positive for Her2/Neu overexpression. Chemotherapy regime was switched or discontinued based on clinician discretion during the course of follow-up if patients experienced unacceptable levels of toxicity or had clinical evidence of disease progression. Chemotherapy was also put on hold or stopped entirely in the event of acute deteriorations in patients' functional and/or medical conditions. Other therapeutic interventions including surgery, endoscopic therapy and radiotherapy were also undertaken where clinically indicated. Follow-up duration of each patient is calculated in months beginning from initial diagnosis till the last follow-up or death at the point

of data collection.

Statistical analysis

Statistical analysis was performed using SPSS Statistics Version 19.0 (Armonk NY: IBM Corp). Continuous and categorical variables and survival data were analyzed using the Student's *t*-test, χ^2 test and Kaplan-Meier analysis respectively, with a statistical significance level of 5% used.

RESULTS

Demographics and baseline characteristics

We studied a total of 271 patients with gastric adenocarcinoma with PC diagnosed at initial metastatic presentation with a median follow-up duration of 5.1 mo (IQR: 2.2-11.7). Patient characteristics are summarized in Table 1. The median age was 63.8 years (range 26.9-89.0), with relatively equal gender proportions (49.4% male) and a predominant Chinese ethnicity (74.9%). The majority of patients had good functional and medical conditions at the point of diagnosis, with Eastern Cooperative Oncology Group (ECOG) performance status ratings of 0-1 in 82.6% and American Society of Anaesthesiology (ASA) scores of 1-2 in 86.7%.

The bulk of our patients ($n = 258$, 95.2%) had peritoneal metastasis diagnosed at initial gastric cancer diagnosis, while the remaining 13 (4.8%) cases of PC were diagnosed as a metastatic recurrence of previously treated gastric cancer. In our cohort, 217 (80.1%) patients had the peritoneum as the only site of metastasis at initial presentation, while 54 (19.9%) had other concomitant distant site(s) of metastasis. Approximately half of the diagnosis of PC was made radiologically ($n = 134$, 49.4%) while the remainder was made intra-operatively. Other gastric cancer-related characteristics of our cohort are summarized in Table 2. Of note, when comparing patients with peritoneal metastasis only to patients with other concomitant distant sites of metastasis, there was a higher proportion of females (53.9% vs 37.0%, $P = 0.026$) and diffuse histology (57.1% vs 33.3%, $P = 0.002$), and a lower proportion of HER2/Neu overexpression (16.4% vs 33.3%, $P = 0.029$).

Palliative systemic chemotherapy

Palliative systemic chemotherapy was offered as standard of care in all patients with metastatic gastric cancer in our institution in close discussion with each patient, with 175 (64.6%) patients eventually planned for systemic chemotherapy following initial metastatic presentation. The subsequent chemotherapy-related clinical course of these patients is summarized in Figure 1. Expectedly, the baseline functional and medical status of patients planned for systemic chemotherapy were significantly better than those who opted for best supportive care upfront, with ECOG ratings 0-2 in 98.9% vs 82.3% ($P < 0.001$) and ASA scores of 1-2 in 92.0% vs 77.1% ($P = 0.001$). Four patients planned for systemic chemotherapy

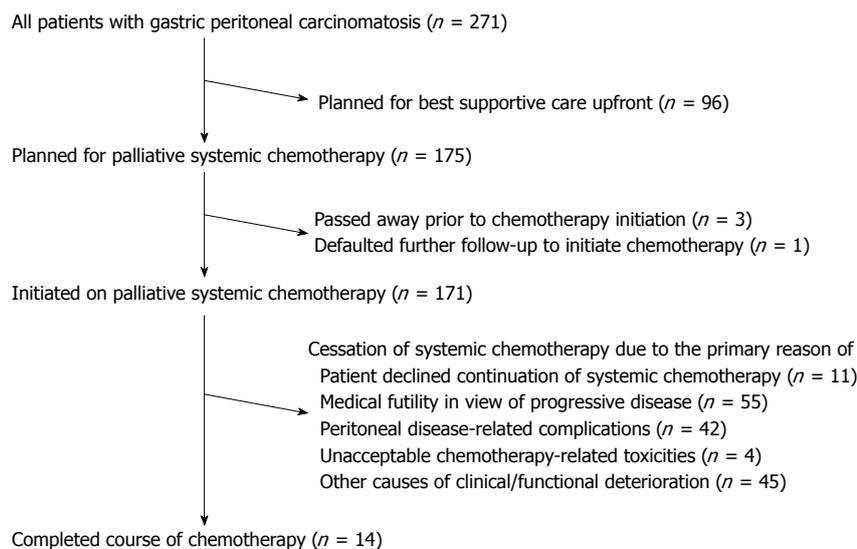


Figure 1 Chemotherapy-related clinical course.

Table 2 Baseline gastric cancer-related characteristics

Characteristic (n = 271)	n (%)
Presentation of peritoneal metastases	
At initial gastric cancer diagnosis	258 (95.2)
Recurrence of treated gastric cancer	13 (4.8)
Site of metastases	
Peritoneal only	217 (80.1)
Peritoneal and distant site(s)	54 (19.9)
Primary gastric cancer location	
Gastroesophageal junction	23 (8.5)
Proximal gastric	16 (5.9)
Gastric body	101 (37.3)
Distal gastric	103 (38.0)
Linitis plastica	28 (10.3)
Lauren's classification	
Intestinal	129 (47.6)
Diffuse	142 (52.4)
c-erb-B2 receptor status (n = 195)	
Positive	37 (19.0)
Negative	158 (81.0)

Table 3 First-line chemotherapy regime

Chemotherapy regime (n = 171)	n (%)
Anthracycline + platinum-based agent + nucleotide analogue	13 (7.6)
Examples	
epirubicin + cisplatin + 5-fluorouracil	
epirubicin + oxaliplatin + 5-fluorouracil	
Platinum-based agent + nucleotide analogue	97 (56.7)
Examples	
cisplatin + 5-fluorouracil	
oxaliplatin + capecitabine	
cisplatin + S-1	
Nucleotide analogue monotherapy	30 (17.5)
Examples	
5-fluorouracil	
capecitabine	
S-1	
FOLFOX (5-fluorouracil + leucovorin + oxaliplatin)	24 (14.0)
Other regimes (e.g., Docetaxel + cisplatin + 5-fluorouracil)	7 (4.2)

did not eventually initiate chemotherapy as three passed away prior to chemotherapy initiation due to cancer-related complications while one defaulted further follow-up for chemotherapy initiation.

The most common first-line chemotherapy regimes utilized in our cohort are summarized in Table 3. Notably, of the 171 patients who eventually initiated chemotherapy, 138 (80.7%) patients received two or three-agent chemotherapy regimes as first-line therapy. Our patients underwent a median of one line of chemotherapy (IQR 1-2), completing a median of six cycles in total (IQR 3-11). Chemotherapy was disrupted in 114 (66.7%) cases due to unplanned hospitalizations, with a median duration of disruption of two weeks (IQR 1-2.25) each time. Chemotherapy-related toxicity was documented in 81 (47.4%) of cases, most commonly affecting the gastrointestinal (n = 28, 34.6%), neurological (n = 23, 28.4%) and hematological (n = 22, 27.2%) systems.

Cessation of systemic chemotherapy occurred in

157 (91.8%) of patients due to a variety of reasons as delineated in Figure 1. Of note, slightly over a quarter (n = 42, 26.8%) of cessations were primarily attributable to peritoneal disease-related complications. Eventually, only 14 (8.2%) patients completed their courses of chemotherapy with subsequent close clinical surveillance.

Clinical course and therapeutic interventions

Through the course of follow-up, 201 (74.2%) patients required unplanned hospitalizations (median number of hospitalizations = 2, IQR 1-3) following initial diagnosis for various disease and/or treatment-related complications including symptomatic ascites, sepsis, gastric outlet obstruction and gastrointestinal tract bleeding (Table 4). 242 (89.3%) patients required some form of therapeutic intervention in an outpatient and/or inpatient setting including surgery, endoscopic stenting, feeding tube insertion and radiotherapy (Table 5). Median overall survival of our patient cohort was 8.7 mo (95%CI: 7.3-10.1) with a trend towards longer survival amongst

Table 4 Reasons requiring unplanned hospitalizations

Reason (n = 201)	n (%)
Symptomatic ascites	64 (31.8)
Sepsis	64 (31.8)
Gastric outlet obstruction	60 (29.9)
Bleeding GIT	60 (29.9)
Intestinal obstruction	59 (29.4)
Chemotherapy-related toxicity	23 (11.4)
Obstructive jaundice	17 (8.5)
Obstructive uropathy	17 (8.5)
Tumour perforation	7 (3.5)

Table 5 Therapeutic interventions required

Treatment category	Treatment	n (%)
Surgery n = 89 (32.8%)	Palliative gastrectomy	32 (36.0)
	Surgical bypass	46 (51.7)
	Open gastrostomy	2 (2.2)
	Feeding jejunostomy	5 (5.6)
	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	1 (1.1)
	Others	3 (3.3)
Endoscopic intervention n = 57 (21.0%)	Feeding tube insertion only	45 (78.9)
	Stenting only	8 (14.0)
	Feeding tube insertion and stenting	4 (7.0)
Radiotherapy n = 35 (12.9%)	Radiotherapy to gastric tumour	29 (82.9)
	Radiotherapy to other sites	6 (17.1)

patients with peritoneal metastasis only as compared to those with other concomitant distant sites of metastasis (median survival 8.9 mo vs 7.0 mo, $P = 0.061$). The 171 patients who initiated systemic chemotherapy, when compared to the rest of the patients who received best supportive care upfront, had a significantly better median overall survival of 10.9 mo vs 1.6 mo ($P < 0.001$) (Figure 2). Of these patients who initiated systemic chemotherapy, the ones who experienced any disruptions to chemotherapy due to unplanned hospitalizations had a significantly worse median survival compared to those without chemotherapy disruptions (8.7 mo vs 14.6 mo, $P < 0.001$) (Figure 3).

DISCUSSION

Existing literature on gastric cancer has largely evaluated metastatic gastric cancer as a homogeneous, undifferentiated entity, with clinical features, prognostic factors, treatment outcomes and overall survival examined as a single patient group^[1-3]. In a similar vein, treatment for metastatic gastric cancer has also been predominated by palliative systemic chemotherapy and supportive care^[20]. There has been a growing interest in the treatment of PC with the advent of CRS and HIPEC especially in colorectal and appendiceal malignancies. The idea of peritoneal metastasis representing loco-regional disease extension as opposed to systemic

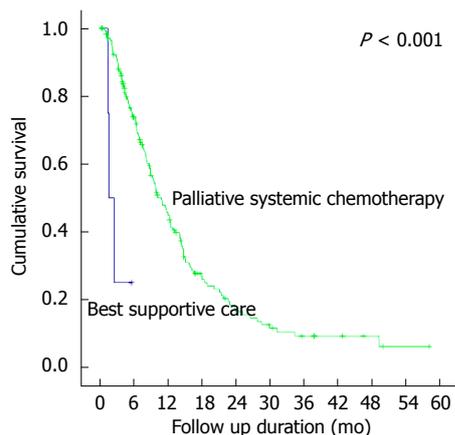


Figure 2 Overall survival of patients initiated on palliative systemic chemotherapy vs patients who received best supportive care upfront.

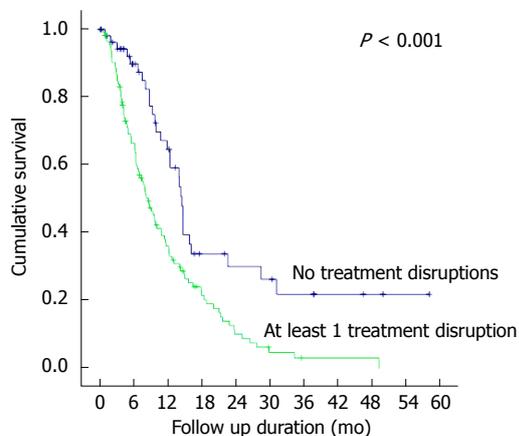


Figure 3 Overall survival of patients initiated on palliative systemic chemotherapy who had treatment disruptions vs without treatment disruptions.

dissemination in other sites of metastasis has likewise encouraged ventures at examining the benefit of CRS and HIPEC in the treatment of PC of other primaries, including gastric cancer^[21]. Our understanding of the clinical characteristics of this subgroup of metastatic gastric cancer patients with PC and how they fare with the current gold standard of treatment - palliative systemic chemotherapy - remains limited, a knowledge gap we sought to address through this study.

Gastric PC was reported by Thomassen *et al.*^[5] to account for a sizeable 35.0% of metastatic disease at presentation, with PC as the only site of metastasis in 68.6% of cases, comparable to 80.1% of cases in our cohort. It similarly represents 36.0%-45.9% of metastatic recurrences after previous curative treatment for gastric cancer^[22,23]. Several studies have reported clinical characteristics predictive of peritoneal metastasis at presentation or recurrence including a younger age, female gender, serosal involvement of primary tumor and a diffuse histology. We found the female gender, diffuse histology and absence of HER2/Neu overexpression to be associated with PC as the sole site of metastatic disease in gastric cancer^[5,23].

Palliative systemic chemotherapy has been well established as the current standard of care for patients with metastatic gastric cancer. A recent meta-analysis of 35 trials involving 5726 patients demonstrated that, in terms of overall survival, systemic chemotherapy achieves superior outcomes compared to best supportive care, and that combination chemotherapy is superior to single-agent chemotherapy with the trade-off of increased incidence of chemotherapy-related toxicity^[20].

Despite the fact that the subgroup of our patient cohort planned for systemic chemotherapy had highly optimal baseline functional and medical statuses (98.9% with ECOG ratings of 0-2 and 92.0% with ASA scores of 1-2) with a large proportion (80.7%) undergoing two to three-agent combination chemotherapy regimes upfront, only a mere 14 (8.2%) patients eventually completed their chemotherapy regimes with subsequent close clinical surveillance. This could be attributed to several reasons.

Firstly, a significant proportion of patients who initiated chemotherapy had clinical evidence of progressive disease in spite of treatment, and even after a trial of second, third or fourth-line regimes in a handful of patients, 32.2% eventually opted for supportive care in view of treatment futility. The poor response of PC to conventional systemic chemotherapy could in part be accounted for by the poor penetration of peritoneal deposits by chemotherapeutic agents administered systemically^[24]. This has spurred efforts at studying the efficacy of a combined bidirectional intravenous and intraperitoneal route of chemotherapy administration for PC, which has been proven to confer survival benefit in ovarian cancer, and has been tested in several phase 2 trials for gastric PC with encouraging results^[25,26].

Secondly, a large proportion of our cohort (74.2%) required unplanned hospitalizations due to disease and/or treatment-related complications, each of which could significantly accelerate the process of clinical deterioration. The median number of hospitalizations each of these patients required was 2, for a variety of complications including those attributable to PC including symptomatic ascites, bowel obstruction, obstructive uropathy and obstructive jaundice. Besides resulting in unforeseen breaks in systemic chemotherapy occurring in 66.7% of our patients who underwent chemotherapy, these acute clinical events also directly contributed to significant clinical and functional decline necessitating premature cessation of chemotherapy in a quarter of cases (Figure 1). Considering that a sizeable proportion of patients who ceased chemotherapy due to other causes of clinical/functional deterioration were attributable to nosocomial infections contracted during admissions for peritoneal disease-related complications, the inadvertent impact of PC on cessation of systemic chemotherapy in these patients may indeed be even greater. The consequent impact on survival outcomes is evident from our finding of a significantly worse overall survival amongst patients on systemic chemotherapy who experienced treatment disruptions (Figure 3).

We report an overall survival of 8.7 mo in our cohort, comparable to survival outcomes of 7.5-12.3 mo achieved by patients on systemic chemotherapy in several trials^[8-11]. Stratified analysis revealed a trend towards improved survival in patients with isolated peritoneal metastasis, in keeping with findings of Thomassen *et al*^[5] which reported median survival of 4.6 and 3.3 mo in patients with isolated peritoneal metastasis and peritoneal plus other concomitant distant sites of metastasis respectively. This is consistent with proposed theories of isolated PC as a loco-regional disease extension rather than a true systemic dissemination of metastatic disease, which further lends support to the investigational use of aggressive loco-regional treatment with CRS and HIPEC in at least selected cases to maximize survival outcomes.

While we recognize the limitations inherent to the retrospective nature of our study, it is, to the best of our knowledge, the only study after Thomassen *et al*^[5] to examine the demographic and disease characteristics of gastric PC, and the first study to examine the clinical and treatment course of these patients.

Looking ahead, further studies could examine and compare the clinical course and outcomes of gastric cancer patients with different groups of metastatic sites (*e.g.*, peritoneal metastasis vs isolated liver metastasis vs other distant sites of metastasis). Additionally, delving further into gastric PC, further work could be put into determining if the extent of peritoneal involvement affects clinical course and outcomes, which could in turn help better define a patient subgroup which may best benefit from aggressive loco-regional treatment options.

Conclusion

Gastric PC carries a grim prognosis with a clinical course fraught with disease-related complications which may attenuate any survival benefit palliative systemic chemotherapy has to offer. As such, investigational use of regional therapies is warranted and required validation in patients with isolated PC to maximize their survival outcomes in the long run.

COMMENTS

Background

Systemic palliative chemotherapy is the current standard of care for all metastatic gastric cancers, including cases with peritoneal carcinomatosis (PC). Gastric PC is known to cause symptoms requiring repeated hospitalizations which may interrupt and terminate planned palliative systemic chemotherapy. There exists a paucity of literature examining the clinical course of patients with gastric PC. The authors aimed to characterize patients with gastric PC and their typical clinical and treatment course with palliative systemic chemotherapy as the current standard of care.

Research frontiers

While systemic palliative chemotherapy has been established as the standard of care through several randomized controlled trials demonstrating survival benefit, the overall prognosis of metastatic gastric cancer remains poor. Investigational loco-regional treatment options such as intraperitoneal chemotherapy and cytoreductive surgery are currently being studied and validated as alternative treatment of patients with gastric PC.

Innovations and breakthroughs

This is, to the best of the knowledge, the only study after Thomassen *et al* to examine the demographic and disease characteristics of gastric PC, and the first study to examine the clinical and treatment course of these patients.

Applications

The authors demonstrated that patients with gastric PC have a grim prognosis, with frequent disease-related complications requiring unplanned hospitalizations which disrupt and terminate planned palliative systemic chemotherapy. As such, patients with gastric PC may benefit from investigational loco-regional treatment options as an alternative.

Peer-review

The authors present a retrospective study of a cohort of patients with gastric cancer and peritoneal metastases treated in a single oncology center. The rationale for the study is important as the prognosis remains poor in this group of patients. The study derives a lot of clinical data describing patients' baseline characteristics and their course during palliative therapy. The results are consistent with those presented in previous studies.

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