Bladder Urothelial Carcinoma with Peritoneal Involvement: Benefit of Continuous Maintenance Chemotherapy

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Abstract. *Aim: We investigated bladder urothelial carcinoma with peritoneal involvement. Patients and Methods: Inclusion criteria were: pathology-confirmed urothelial carcinoma; peritoneal spread identified on computed tomographic (CT) scans performed initially or after either cystectomy or concomitant chemoradiotherapy (CCRT), and absence of visceral metastases; and chemotherapy administered after peritoneal spread was diagnosed. Results: Forty-seven cases included initial modes of therapy with chemotherapy in 24 patients (51%), cystectomy in 17 (36%), and CCRT in six (13%), only given as a result of under-staging. After local therapy, these patients received a continuous maintenance chemotherapy regimen of 5-fluorouracil, leucovorin, cisplatin, and gemcitabine. The overall response rate was 85%, and the side-effects were mild and tolerated. The median survival time was 28 months. The survival time of cases initially treated only with chemotherapy was not statistically different to that of those with local disease. Conclusion: Bladder urothelial carcinomas with peritoneal involvement can benefit from continuous maintenance chemotherapy.*

The bladder is a sub-peritoneal organ, and the peritoneum covers its posterosuperior surface. Along its lateral margins, the peritoneum attaches to the lateral walls of the pelvis, and the anterior, lateral, and lower parts of the posterior surface of the bladder are not connected to the peritoneum. The peritoneum consists of two layers: the visceral and the parietal peritoneum. The parietal peritoneum is attached to the abdominal and pelvic walls (1). The pelvic peritoneal space is defined by the inferior reflection of the peritoneum over the fundus of the urinary bladder and the front of the rectum at the junction of the middle and lower thirds of the rectum (1). When disease spreads from the subperitoneal space to the peritoneal cavity *via* the peritoneal lining, transperitoneal spread can occur. According to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM system, stage T4b bladder cancer describes a tumor that has spread to the pelvic or abdominal wall (2). Tumors can enter the abdominal wall from the bladder dome, and the peritoneum (3) and can invade the pelvic sidewall from the posterolateral bladder wall or involve the peritoneal reflexion (4, 5). Spread of bladder urothelial carcinoma to the peritoneum is frequently encountered (4-8).

Computed tomographic (CT) scans are useful for determining the stage and extent of bladder cancer, and can also detect peritoneal metastasis (6-9). However, identifying peritoneal spread before treatment to determine the best course of action is difficult. Black *et al.* reported that long-term survival can be achieved in some patients with cT4b bladder cancer undergoing chemotherapy and extirpative surgery (10). However, Liberman *et al.* mentioned that radical cystectomy of patients with pT4b disease had higher cancer-specific mortality (11).

In this case series study, we investigate the clinical course of bladder urothelial carcinoma with peritoneal involvement, and discuss diagnosis and management, especially chemotherapy.

Patients and Methods

Study population. This retrospective case series study was conducted using data collected from patients with bladder cancer who were admitted to the Oncology wards of Chang-Gung Memorial Hospital, Taoyuan, Taiwan, between January 2010 and December 2016. The majority of patients had urothelial carcinomas, and a medical oncologist specializing in urological cancer provided most of the

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data. The criteria for inclusion were: pathology-confirmed diagnosis of urothelial carcinoma; peritoneal spread identified by CT scans performed initially or after either radical/partial cystectomy or concomitant chemoradiotherapy (CCRT), and an absence of metastases in the visceral organs; and chemotherapy was administered after the diagnosis of peritoneal spread.

Of the 206 patients with bladder cancer assessed, 47 (23%) met the criteria for inclusion in this study. Initial treatment included chemotherapy, radical or partial cystectomy, or CCRT. The bladder cancer stage was determined from CT scans (12,13) according to the seventh edition of the AJCC TNM system (2), and the treatment response assessment for bladder cancer was based on the RECIST criteria (14).

Chemotherapy regimens included 5-fluorouracil, leucovorin, cisplatin, and gemcitabine (Gemmis; TTY, Taipei, Taiwan, ROC). The original dosage was 50 mg/m^2 cisplatin by intravenous infusion for 3 hours on day 1, plus 1,000 mg/m^2 gemcitabine intravenous infusion for 30 minutes on days 1, 15 and 22 in combination with a continuous intravenous infusion of 1000 mg/m^2 5-fluorouracil and 100 mg leucovorin for 46 h every 28 days. When renal function impairment was observed (serum creatinine value >2 mg/dl), cisplatin was changed to 150 mg/m^2 carboplatin intravenous infusion for 2 hours. The schedule was modified during the chemotherapy course in the case of challenging admissions. Generally, we administered an inpatient chemotherapy regimen of 5-fluorouracil and leucovorin plus cisplatin with or without the gemcitabine regimen every 4 weeks, and gemcitabine was administered in the Outpatient Department every 2 weeks. Treatment strategies were initially aggressive, but were slowed down based on stable or improving condition and the results of imaging studies. We lengthened the chemotherapy interval or administered gemcitabine only if the patient was too old, had a severe comorbidity, or a poor performance status. Continuous maintenance chemotherapy was administered until tumor progression was detected, or the patient or doctor decided to discontinue therapy. Follow-up CT scans were performed every 3 months to assess tumor response.

Schedule of initial CCRT with combined radiotherapy and chemotherapy. The radiotherapy dose administered was 44-45 Gy in 22-26 fractions delivered to the whole pelvis, followed by a booster to the bladder, to a total dose of 60-61.2 Gy. The chemotherapy regimen was 5-fluorouracil, leucovorin, and cisplatin: 50 mg/m^2 cisplatin intravenous infusion for 3 hours on day 1, combined with a continuous intravenous infusion of 1,500 mg/m^2 5-fluorouracil and 150 mg leucovorin for 46 hours every 28 days. The post-cystectomy CCRT radiotherapy dose was 45 Gy in 25 fractions to the pelvis, then a booster to the bladder fossa, up to a total dose of 54 Gy, in 30 fractions.

Identification of inflammatory cytokines in patients with bladder cancer is necessary (15) due to paraneoplastic syndromes related to cytokine production, including thromboembolism complications, cachexia, and neoplastic fever, during the disease course (16, 17). Enoxaparin (Sanofi-Aventis) was administered to treat thromboembolism complications, medroxyprogesterone acetate for cancer cachexia, and naproxen for neoplastic fever.

Statistical methods. Continuous data (presented as the mean±standard deviation) were used to determine the number of chemotherapy cycles delivered by inpatient and outpatient services. The survival time was calculated from the start of therapy to death,

Table I. *Characteristics of the 47 patients with bladder cancer with peritoneal involvement.*

Characteristic	Value
Median age (range), years	67 (40-85)
Gender	
Male/female	34/13
Tumor extent, no./total no. (%)	
Iliac lymph nodes*	19/47 (40)
Abdominal wall	8/47 (17)
Pelvic sidewalls	3/47 (6)
Prostate, uterus, or rectum	6/47 (16)
Entire bladder wall	5/47 (11)
Performance status, no./total no. (%)	
0-1	44/47 (94)
≥2	3/47 (6)
Initial understaging (<T4), no./total no. (%)	
Yes	24/47 (51)
No	23/47 (49)
Initial mode of therapy, no./total no. (%)	
Chemotherapy	24/47 (51)
Surgery	17/47 (36)
CCRT	6/47 (13)

CCRT: Concomitant chemoradiotherapy. *Two cases with tumors extending to the para-aortic lymph nodes; two cases with tumors extending to the para-aortic and supraclavicular lymph nodes.

Table II. *Treatment response rate following chemotherapy and paraneoplastic syndromes reported.*

	No. of patients (%)
Response	
Overall response	46/47 (85)
Complete response	2/47 (4)
Partial response	44/47 (81)
Stable disease	2/47 (4)
Progressive disease	6/47 (11)
Paraneoplastic syndrome	25/47 (53)
Cachexia	24/47 (51)
Thromboembolic complications	22/47 (47)
Neoplastic fever	3/47 (6)

and the survival curves were determined using the Kaplan–Meier method. Significant differences between survival curves were measured using the log-rank test.

Results

Forty-seven consecutive bladder cancer patients met the inclusion criteria for this study, including 34 men and 13 women (median age=67 years; range=40-85 years). The patients' clinical characteristics are shown in Table I. All patients had peritoneal involvement, and a range of tumor
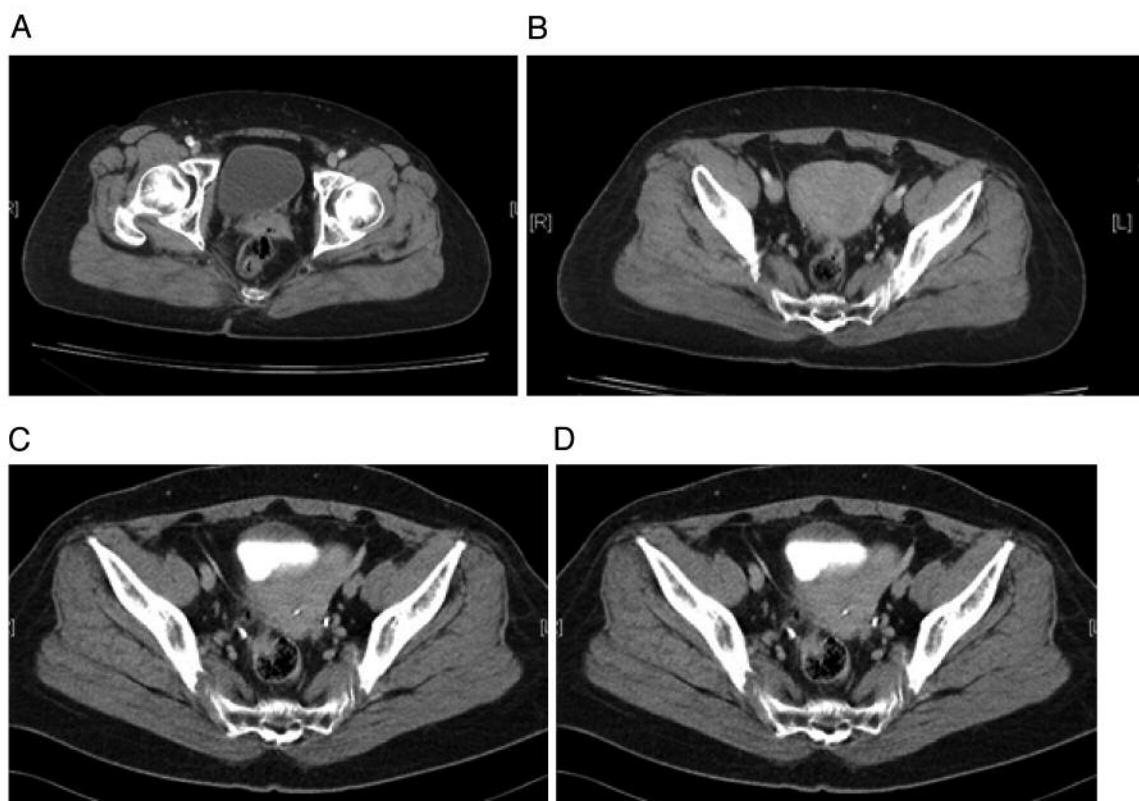
Figure 1. *A 60-year-old woman with bladder urothelial carcinoma with peritoneal spread. The initial clinical stage was T4N1M1. She underwent continuous maintenance chemotherapy for four years. A and B: Computed tomographic scans showing tumor spread from the left posterolateral aspect of the bladder to the peritoneum. C and D: Computed tomographic scans after she had received continuous maintenance chemotherapy showed tumor regression.*

extents was represented: 19 patients (40%) had a tumor involving iliac lymph nodes, including two involving para-aortic lymph nodes and two involving the supraclavicular lymph nodes; eight (15%) had superior and anterior invasion into the abdominal wall; three (6%) had tumors extending to the pelvic sidewall; six (13%) had posterior invasion of the prostate, uterus, or rectum; and five (11%) had circumferential tumors that surrounded the entire bladder wall. Forty-three patients (94%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Two had simultaneous bladder and renal pelvis urothelial carcinomas, and three had undergone nephroureterectomy for a previous upper urinary tract urothelial carcinoma (two cases involving the renal pelvis and one involving the ureter). Two cases had prior renal transplantation. Initial understaging (less than T4) on CT scans occurred for 22 patients (44%).

Initial modes of therapy were chemotherapy in 24 patients (51%), radical or partial cystectomy in 17 (36%), and CCRT in six (13%). The clinical staging before surgery was T1 in

two patients, T2 in twelve, T3 in two, and T4 in one. The clinical staging before CCRT was T2 in five patients, and T1 in one. Inpatient chemotherapy regimens included 5-fluorouracil, leucovorin, and cisplatin, with or without gemcitabine every 4 weeks. Five cases experienced renal function insufficiency (serum creatinine level >2.0 mg/dl) – three initially and two during chemotherapy – and were given carboplatin instead of cisplatin. The outpatient chemotherapy regimen was gemcitabine monotherapy every 2 weeks. The mean number of inpatient chemotherapy cycles was 10±6 (range, 1-24 cycles) and the mean number outpatient chemotherapy cycles was 21±16 (range, 0-83 cycles). After a period of inpatient and outpatient chemotherapy, 13 patients chose to rest. There were nine patients who did not agree to long-term chemotherapy, three stopped chemotherapy based on their doctors' advice, and one ceased chemotherapy due to comorbidity.

The overall chemotherapy response rate was 85%, including complete response in 4%, partial response in 81%, stable disease in 4%, and progressive disease in 11%
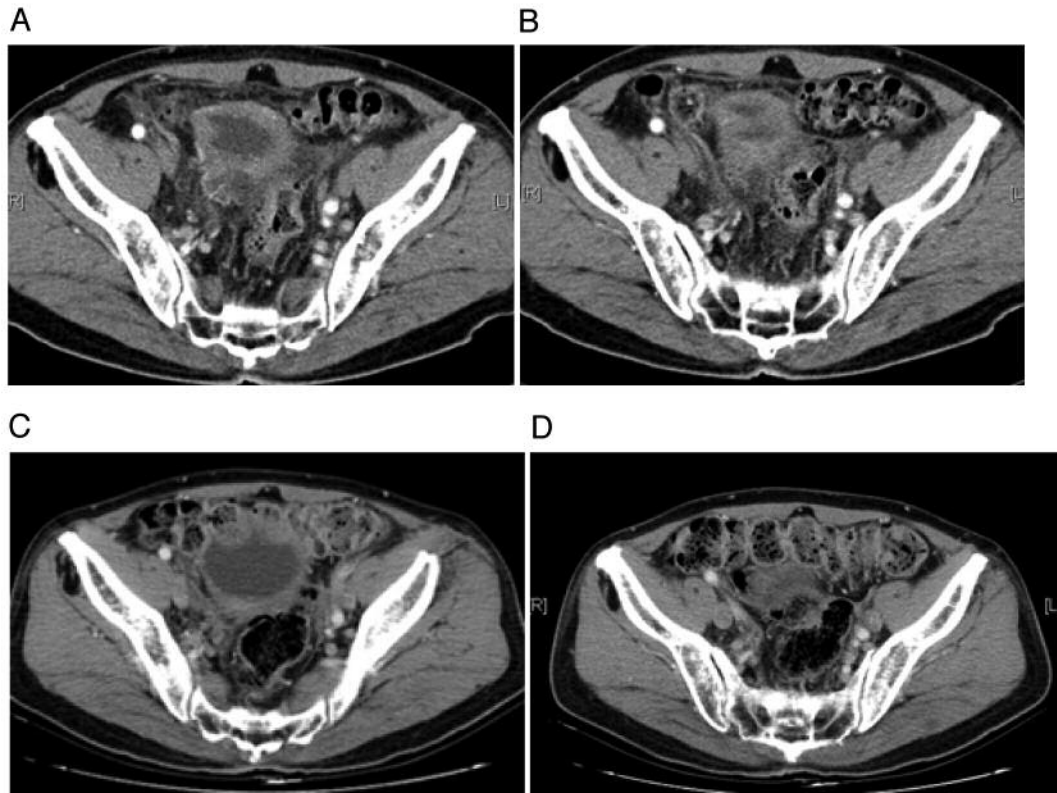
Figure 2. *An 80-year-old man with bladder urothelial carcinoma with peritoneal spread. The initial clinical stage was T2N0M0. The patient underwent concomitant chemoradiotherapy (CCRT). Two months later, the tumor had progressed rapidly, with increased peritoneal lesions and lung metastases. A and B: Computed tomographic scans showing tumors infiltrating the entire bladder wall and spreading from the bladder dome to the peritoneum. C and D: Computed tomographic scans showing tumor progression with increased peritoneal extension following CCRT.*

(Table II). The response evaluation sites were the bladder tumors, lymph nodes, and peritoneal lesions; however, thick or dirty lesions over the peritoneum made it difficult to assess the level of treatment response. Figure 1 shows a bladder tumor that exhibited a good partial response after chemotherapy only.

The side-effects of the chemotherapy were mild and tolerated, and sepsis occurred in only one patient during chemotherapy. During the treatment course, 25 patients (53%) developed paraneoplastic syndrome. Thromboembolic complications detected by imaging were iliofemoral venous obstruction in nine patients, inferior vein thrombosis in four cases, pulmonary vein obstruction in three, and cerebral thrombosis in two.

The overall response rate for the 24 patients in the initial-chemotherapy-only group was 92%, including complete response in 8%, partial response in 83%, stable disease in 4%, and progressive disease in 4%. The mean number of inpatient chemotherapy cycles was 10±5 (range=1-20 cycles), and of outpatient chemotherapy cycles was 21±18 (range=0-83

cycles). One patient underwent radical cystectomy after one cycle of inpatient and four cycles of outpatient chemotherapy. Six patients elected for chemotherapy to be tapered off after some time. One patient received 11 cycles of inpatient and 83 cycles of outpatient chemotherapy, which was then tapered based on the doctor's advice; unfortunately, locoregional tumor recurrence over the whole bladder region occurred 17 months later. Another patient with pathology-proven urothelial carcinoma experienced tumor recurrence after receiving 10 cycles of inpatient and eight cycles of outpatient chemotherapy, with a weaning-off interval of 12 months. One patient received radiotherapy following the cessation of chemotherapy, and the continuous maintenance chemotherapy of another, who had pathology-proven urothelial carcinoma, involved 20 cycles of inpatient and 42 cycles of outpatient chemotherapy.

Of the six patients who received CCRT, none exhibited a positive tumor response; in fact, three experienced tumor progression following CCRT (see Figure 2). Of the 17 patients who underwent cystectomy, 13 underwent radical
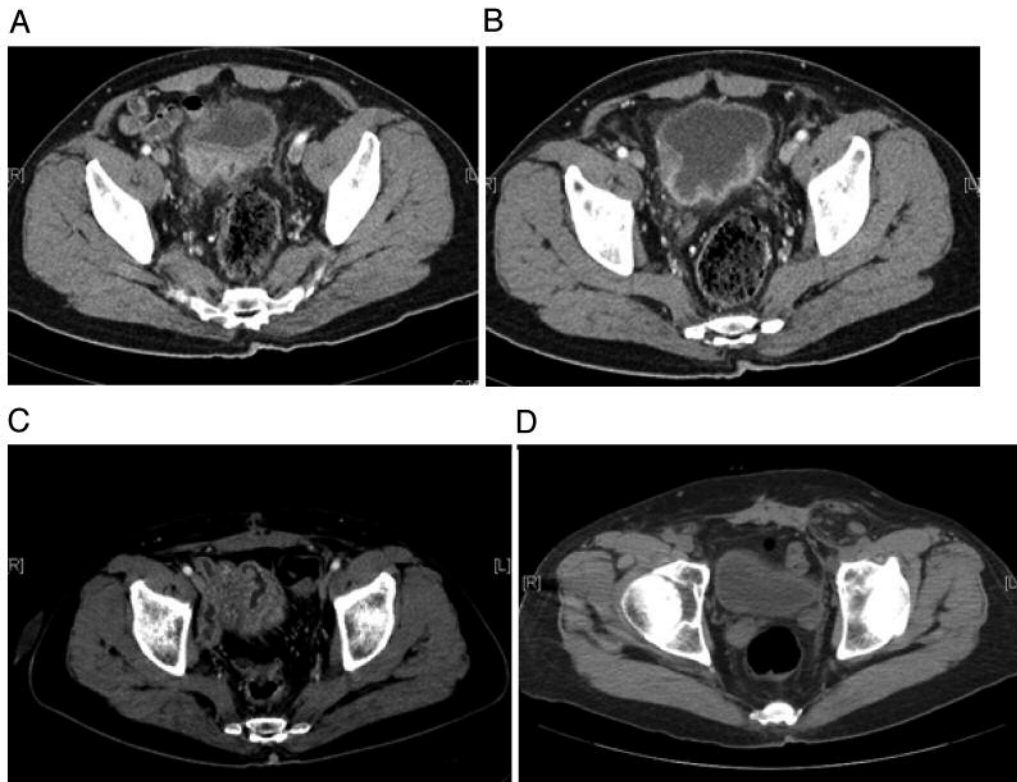
Figure 3. *A 56-year-old man with bladder urothelial carcinoma with peritoneal spread. The initial clinical stage was T2N0M0. The patient underwent radical cystectomy and the pathological stage of the specimen was T3bN0M0. Postoperatively, the patient received concomitant chemoradiotherapy (CCRT) followed by continuous maintenance chemotherapy for 3.5 years. A and B: Computed tomographic scans showing tumors spreading from the right anterolateral bladder wall and dome to the peritoneum and the right abdominal wall. C: Computed tomographic scan showing right pelvic peritoneal thickening and abdominal wall invasion 3 months after surgery. D: Computed tomographic scan showing tumor regression after the patient had received CCRT and continuous maintenance chemotherapy.*

cystectomy and four underwent partial cystectomy. Eight cases received postoperative therapy when the CT scan showed evidence of a recurrent peritoneal tumor or they became symptomatic; 14 received chemotherapy and three received CCRT. The mean duration of therapy following surgery was 4.4±2.8 months (range=1-10 months). Figure 3 shows an example of tumor regression after CCRT and subsequent continuous maintenance chemotherapy following radical cystectomy. Nine cases, including eight chemotherapy and one CCRT. Figure 4 shows an example of tumor regression after chemotherapy only, following evidence of peritoneal tumor recurrence on CT scans after partial cystectomy. The partial response rate after chemotherapy for these 23 patients was 74%, the stable disease rate was 4%, and the progressive disease rate was 22%. The mean number of inpatient chemotherapy cycles was 11±7 (range=2-24 cycles) and the mean number of outpatient chemotherapy cycles was 20±14 (range=0-51

cycles). Seven patients elected to rest. Three patients experienced an inguinal hernia (probably related to tumor invasion of the abdominal wall; Figure 4D), of whom two underwent herniorrhaphy but showed abdominal-wall regional tumor progression with peritoneal seeding following the procedure.

The follow-up period ranged from 3 to 80 months. Twenty-six patients were followed-up until their death; two were lost to follow-up. Nineteen patients were still alive at the time of writing. The median survival time was 28 months (range of 3 to >80 months). The median survival time was 26 months for the initial-chemotherapy-only group *versus* 32 months for the group treated with initial-cystectomy or CCRT, According to a log-rank test (p=0.51), the survival time of the two groups was not statistically different (Figure 5). Of the mortalities, death resulted from loss of consciousness in 25 cases and respiratory failure in one.
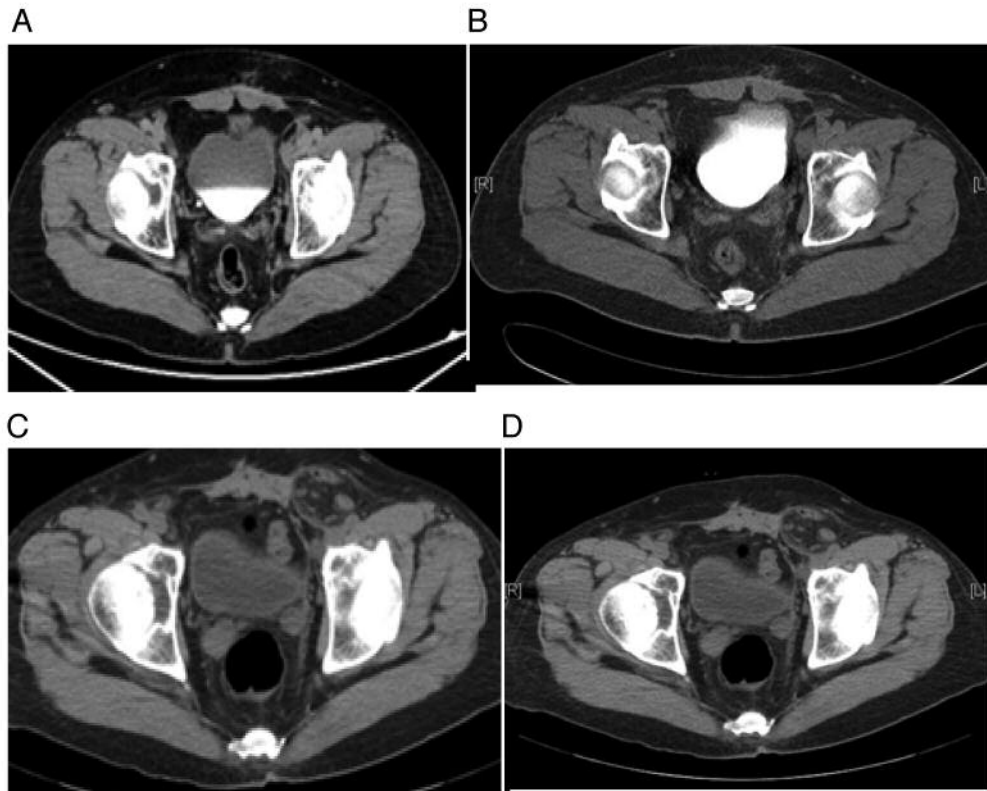
Figure 4. *A 59-year-old man with bladder urothelial carcinoma with peritoneal spread. The initial clinical stage was T3N0M0. The patient underwent partial cystectomy; the pathological stage of the specimen was T1N0M0. Six months postoperatively, tumor recurrence was noted with peritoneum and left-abdominal-wall spread. The patient received continuous maintenance chemotherapy for three years. A and B: Computed tomographic scans showing show tumors extending from the anterior bladder wall to the peritoneum and the left abdominal wall. Computed tomographic scan showing tumor regression (C) and the formation of an inguinal hernia (D) after the patient had received continuous maintenance chemotherapy.*

Discussion

CT scans play an important role in the diagnosis of peritoneal spread (7, 8), and understanding the anatomical relationship between the peritoneum and the bladder is crucial (1, 2). Tumors can progress to anterior invasion from the superior or the anterior side, from the bladder dome to the abdominal wall, can spread anterolaterally or posteriolaterally to the pelvic peritoneum, and can attach circumferentially to the peritoneum and surround the entire bladder wall. Forty percent of our patients had tumors that extended to the iliac lymph nodes. Peritoneal spread, iliac lymph node involvement, and T4b lesion staging based on the seventh edition of the AJCC TNM system were all classified as stage 4 disease.

The chemotherapy regimen used in our study included 5-fluorouracil, leucovorin, cisplatin, and gemcitabine. Combination chemotherapy with gemcitabine plus cisplatin,
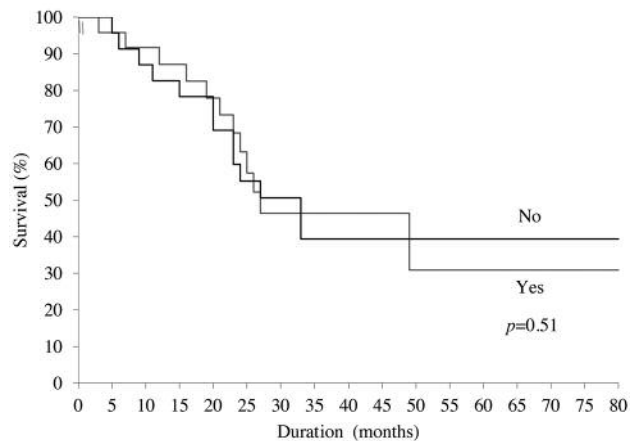

Figure 5. *The survival time for the groups treated with initial chemotherapy only and those with initial cystectomy or concomitant chemoradiotherapy. According to the log-rank test, median survival (28 months versus 32 months) did not differ significantly between groups.*

or 5-fluorouracil and leucovorin plus cisplatin are both considered aggressive treatment for advanced or metastatic bladder urothelial carcinoma (18, 19). However, patients with bladder cancer are usually older and have renal function impairment with a post-unilateral or renal transplant status (20-22). Administration of 50 mg/m^2 cisplatin every 4 weeks can prolong its use and reduce its toxicity (23) indeed, significantly improved survival of patients with metastatic colorectal cancer can be achieved using continuous maintenance chemotherapy (24, 25). Karogirou *et al.* reported that maintenance monotherapy with gemcitabine following primary cisplatin-based combination chemotherapy in patients surgically treated for advanced urothelial carcinoma significantly improved treatment outcomes (26). In our patients, the overall response rate was 85%, and the median survival time was 28 months.

The disease status of the initial-chemotherapy-only patients usually involved obvious peritoneal lesions. Their overall treatment response rate was over 90%, with a median survival time of 26 months. Only one patient underwent radical cystectomy after chemotherapy. We, therefore, support the use of neoadjuvant chemotherapy for muscle-invasive bladder cancer (27). However, a subset of patients receiving chemotherapy will still experience disease progression (28).

In this study, initial treatment with cystectomy or CCRT was related to understaging. Initial-cystectomy patients generally did not exhibit obvious peritoneal lesions. We also excluded patients with visceral metastases at the time of the diagnosis of peritoneal metastases. While immediate *versus* deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder showed no difference in outcome (29), early initiation of chemotherapy following complete resection of advanced ovarian cancer has been shown to be associated with improved survival (30). Those of our patients who received initial CCRT showed no positive treatment response, and some even exhibited tumor progression. This is inconsistent with our previous study, which suggested that CCRT is a feasible and promising treatment for invasive bladder cancer (31). This is probably due to the presence of peritoneal lesions outside the radiation field. Patients treated with initial cystectomy or CCRT had an overall response rate of 74% with chemotherapy, however. The median survival time from initial cystectomy or CCRT was 32 months, and there was no significant difference in survival time between the groups treated with initial chemotherapy only and those treated with initial cystectomy or CCRT in our study.

The tumor microenvironment has been shown to affect tumor progression, and has been detected in bladder cancer tissues (32). Evidence suggests that critical elements of the tumor microenvironment are immune and inflammatory cells, blood and lymphatic vascular networks, fibroblasts, and the extracellular matrix (33). Cytokine production and alteration of hemostasis in cancer can promote tumor progression (16). Cancer cachexia, thromboembolic complications, and neoplastic fever are all linked to cytokine production by inflammatory cells (34-36), although thromboembolic complications are also associated with vascular disorders. Anti-cytokine therapy, such as progesterone acetate, non-steroidal anti-inflammatory drugs, and low-molecular-weight heparin, can improve these complications, probably by modifying the tumor microenvironment to prevent tumor growth (37).

Cancer-associated fibroblasts (CAFs), a major component of the cancer stroma, have a prominent role in the progression, growth, and spread of cancers (38, 39), and can be involved in angiogenesis and the response to injury. CAFs are thought to be derived from mesothelial cells *via* mesothelial-to-mesenchymal transition in peritoneal metastasis (40). The extracellular matrix either represents a defense mechanism by non-malignant host cells against invading cancer cells, or promotes tumorigenesis. Formation of the extracellular matrix is essential for processes such as growth, wound healing, and fibrosis (41). In our patients, chemotherapy was able to reduce the peritoneal tumor burden and facilitate peritoneal wound healing in order to prevent tissue damage. A dirty and thickened peritoneum represented cancer cells in the peritoneum following chemotherapy; however, the number of cancer cells and their fibrotic tissue could not be determined. These phenomena are probably linked to the presence of fibroblasts, since fibrotic tissue can prevent tumor progression. Some patients were able to stop chemotherapy for a period of time and remain in a stable condition. Two of our patients who underwent herniorrhaphy to repair a hernia sac exhibited abdominal-wall and regional peritoneal progression after surgery. Although the true etiology of a dirty and thickened peritoneum is not known, CAFs and the extracellular matrix may have played an important role in our patients.

Our study has several important limitations. Firstly, the data were collected from a retrospective case cohort from a single center, mainly from one physician. Secondly, the in-patient and out-patient chemotherapy duration was not uniform. Thirdly, the diagnoses of peritoneal involvement and further investigations lacked histological confirmation.

Conclusion

Bladder urothelial carcinomas with peritoneal involvement can benefit from chemotherapy. Continuous maintenance chemotherapy can prolong patient survival for more than 2 years. Pre-therapy staging based on CT scan is important, especially for detecting tumors with peritoneal involvement. Understanding the concept of the tumor microenvironmement can help to treat these patients.

Ethics Statement

The Authors declare that an Institutional Review Board/Ethics Committee determined that patient informed consent was not required. The study was approved by the Chang Gung Medical FoundationInstitutional Review Board. IRB No.: 201700764B0.

Disclosure

The Authors declare that they have no conflict of interest regarding the publication of this article.

Acknowledgements

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