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Safety and Efficacy of the Metabolic Profiling of the BIMRT Utilizing 18F FDG PET-CT

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Abstract

Aim: This study aims to evaluate the safety and efficacy of fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) guided intensity-modulated radiation therapy (IMRT) for patients with peritoneal metastases. **Patients and Methods:** A total of 55 patients with peritoneal metastases were treated with 18F-FDG-PET/CT-guided IMRT (BIMRT) from January 2012 to January 2019. They were prescribed with a fraction of the median dose of 2 Gy to a total dose of 50.4 Gy. The multivariate analysis was used the Cox proportional hazard model and the Kaplan-Meier plot was used to perform local control rate (LCR), progression-free survival (PFS), and overall survival (OS) analysis. **Results:** The 1-year, 2-year, and 3-year LCR were 72.7%, 36.4%, and 9.1%, respectively; the 1-year, 2-year, and 3-year PFS were 69.1%, 30.9%, and 7.3%, respectively, and the median PFS time was 18 months. The 1-year, 3-year and 5-year OS were 70.9%, 28.7%, and 4.2%, respectively. Based on the multivariate analysis using the Cox proportional hazard model, the Karnofsky performance status (KPS) score and radiotherapy joint chemotherapy (RJC) method were independent prognostic-related indicators ($P < 0.0001$). **Conclusion:** BIMRT may be a safe and effective treatment for patients with peritoneal metastases, especially for patients who cannot undergo surgery. In addition, the results indicated that the patient's KPS score and RJC method were independent prognostic-related indicators for patients survival time.

Keywords

peritoneal metastasis, intensity-modulated radiation therapy, fluorodeoxyglucose positron emission tomography/computed tomography, 3D-conformal radiotherapy, cavity radiosurgery

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Introduction

A gastrointestinal tumor advanced in an organ or parietal layer surface is disseminated to peritoneal metastases (PM), which has been considered as the terminal stage of the tumor in the traditional view, with 3 to 7 survival months.[1-3] Ovarian malignant tumor is not easy to diagnosis in the early stage, 75% of patients are found at a late stage (FIGO III-IV), with tumor involving the peritoneum or distant metastasis, 5 years survival rate is less than 20%,[4] and 70% of patients have recurrence as peritoneal metastatic carcinoma.[5] Once, the patients have PM, the prognosis is extremely poor, and traditional surgery and/or systemic adjuvant chemotherapy cannot improve patients' survival time or quality of life. With the research progress of tumor biological behavior and the progress of clinical diagnosis and treatment technology, people's understanding of PM

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changed fundamentally in the late 20th century, They believe that PM is a kind of local and regional disease with the main lesion scope limited to peritoneum.[6-9] And for different patients, an individualized treatment plan is particularly important.

18F-fluorodeoxyglucose PET/CT is the preferred imaging method for diagnosing PM, which can detect the presence of cancer lesions based on cellular glucose uptake to avoid false-negative results.[10] In order to determine the exact location and area of peritoneal metastasis, PET/CT provides better accuracy, especially compared with MRI and CT.[11] Many studies[12,13] have introduced BIMRT for the treatment of ovarian cancer. Du et al.[12] demonstrated that using 18F-FDG PET/CT for the design of the IMRT plan for recurrent retroperitoneal lymph nodes of ovarian cancer can improve the accuracy of tumor volume (GTV) and improve the clinical curative effect. Dang et al.[13] reported a case of a 68-year-old woman with ovarian cancer and large abdominal metastases (stage FIGO III) who did not receive surgery but received BIMRT. The patient did not develop any significant acute or chronic radiation reactions. Subsequently, after 4 cycles of chemotherapy, all lesions disappeared and the levels of cancer antigens Ca-125, Ca-19, and oncogenic antigen were reduced to normal levels. The patient experienced no recurrence for 3 years. In this study, 55 patients with peritoneal metastatic undergone BIMRT were retrospectively analyzed and the efficacy and acute or chronic radiation reactions were observed to evaluate the clinical effect.

Materials and Methods

Patients

From January 2012 to January 2019, 55 patients with peritoneal metastatic cancer from the 986 hospital of the PLA air force received BIMRT treatment (Elekta Oncology Systems, Shanghai, China), (Table 1). The inclusion criteria was that patients diagnosed as malignant tumors with peritoneal metastasis by pathology or imaging; age range from 12 to 90 years. The exclusion criteria was that patients were systematically assessed through laboratory examinations (blood and urine) and clinical imaging results to exclude any possible inflammation and bleeding. Among them, 43 patients relapsed after surgery, and 12 patients could not tolerate or reject surgery, so that they received 5 to 10 cycles of chemotherapy with different regiments according to their respective pathological types, including 40 mg of cisplatin peritoneal infusion, and systemic chemotherapy. Tumor stage, lesion size, and radiotherapy localization were determined by 18F-FDG PET/CT (SIEMENS, Germany).The patients underwent 6 cycles of systemic chemotherapy according to efficacy and systemic tolerance after radiotherapy. The study protocol was approved by the Ethics Committee of the Institute of 986 hospital of People's Liberation Army Air Force. All patients' written informed consent was obtained.

Table 1. Patients Characteristics and Demographics.

Items	N (%)
Median age (range), years	65 (45-86)
KPS score, n (%)	
≥70	35 (64)
<70	20 (36)
Radiation dose (median, range)	50 (30-60)
≥50 Gy, n (%)	36 (65)
<50 Gy, n (%)	19 (35)
Cancer site	
Gastric cancer	8 (14.5)
Colon cancer	21 (38.2)
Ovarian cancer	26 (47.3)
Group, n (%)	
Chemotherapy + radiotherapy	47 (85.5)
Radiotherapy	8 (14.5)
Abdominal effusion n (%)	
YES	26 (47.3)
NO	29 (52.7)

Abbreviations: KPS, Karnofsky performance status.

Treatment Process

All patients underwent 18F-FDG-PET/CT examination. Gross tumor volume (GTV) was positioned by image contour simulation (Huiheng system, Shenzhen, China) with standard uptake value (SUV) of 3.0. The clinical target volume (CTV) was 5 mm outside the GTV boundary, and the planned target volume (PTV) around the CTV did not need to be expanded. The organs at risk included regional liver, kidney, small intestine, and bladder. The patients were treated with a median prescription dose of 5,040 cGy (ranging from 4,500 to 5,500 cGy), with a median dose of 200 cGy per fraction (ranging from 180 to 220 cGy) once a day and 5 times a week. After 10-14 days of treatment, the patients had rest for 1 to 2 weeks. After that, the BIMRT was performed to complete all the plans. We designed endangers organ planning limitations: the volume of the kidney, liver, and small intestine V40 <30%, rectum V40 <60%, bladder V45 <50%, lung V20 <20%, heart V25 <25%.

Toxicity Evaluation

The common term standard for adverse events (CTCAE) V4.03[13,14] was used to monitor patients for acute and late toxicity. The patient's disease status and the emergence of acute and advanced toxicity were assessed on the basis of the patient's history, physical examination, and above laboratory and radiological examination.[12] Acute toxicity was defined as events occurring within 28 days after completion of radiotherapy, while late toxicity was defined as events occurring ≥28 days after completion of radiotherapy. After completion of radiation therapy, patients were followed up by radiologists for an average of 5 years.

Statistical Analysis

All patients were followed up for a total of 5 years, and once every 3 months after radiotherapy, then after 2 years, once

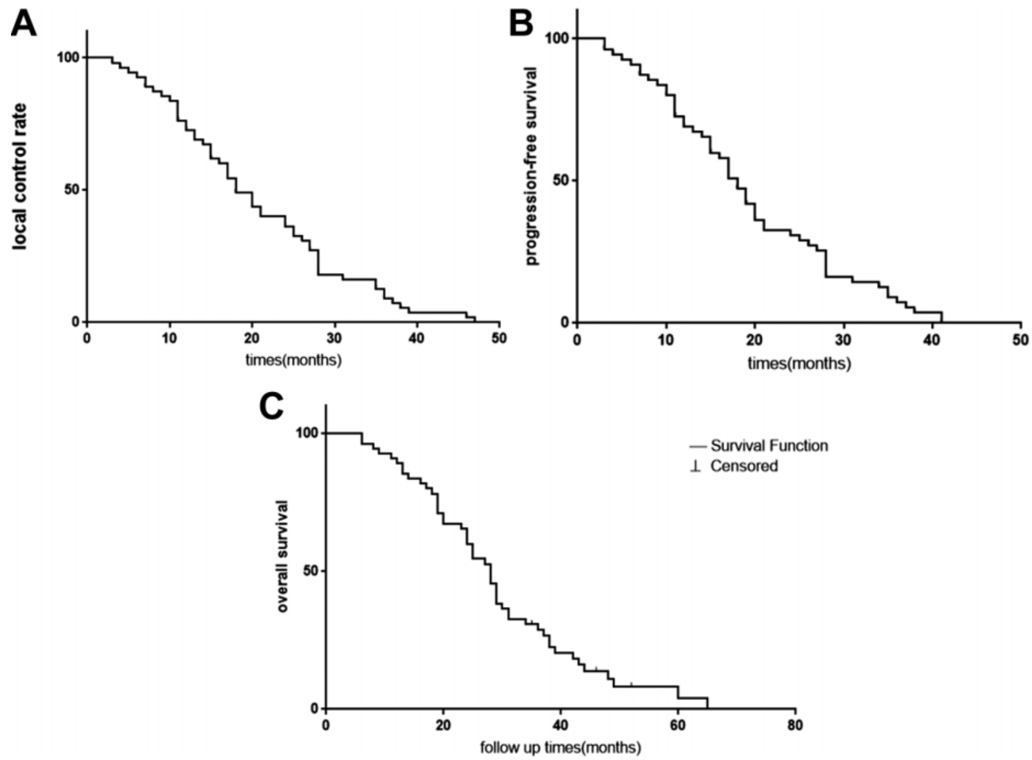

Figure 1. Survival evaluation of LC, PFS and OS (A) Kaplan-Meier plot of 1-, 2- and 3-year local control rates of 72.7%, 36.4%, and 9.1%, respectively; (B) Kaplan-Meier plot of 1-, 2-and 3-year PFS rates of 69.1%, 30.9% and 7.3%, respectively, and a median PFS time of 18 months. (C) Kaplan-Meier plot of 1-, 3-, and 5-year overall survival rates of 70.9%, 28.7%, and 4.2%, respectively.

every 6 months. To evaluate the improvement of clinical symptoms, the KPS score, LCR, PFS, and OS were performed by Kaplan-Meier analyzed. Statistical comparisons used univariate and multivariate Cox proportional hazard models to assess the impact of clinical factors. The Kaplan-Meier method was used to perform PFS and OS. Survival data were analyzed using logarithmic rank test. All data were represented mean ± standard deviation and conducted with SPSS 19 software (IBM Corporation, Armonk, NY, USA) and $P < 0.0001$ was considered a statistically significant difference.

Results

Survival Evaluation

After radiotherapy, the LCR, PFS, and OS were improved. The 1-year, 2-year and 3-year LCR were 72.7%, 36.4% and 9.1%, respectively (Figure 1A). PFS in 1 year, 2 years and 3 years were 69.1%, 30.9% and 7.3% respectively, and the median PFS time was 18 months (Figure 1B). OS of 1 year, 3 years and 5 years were 70.9%, 28.7% and 4.2%, respectively (Figure 1C).

Toxicity Evaluation and Adverse Reactions

The incidence of acute and advanced toxicity is low. All patients were observed for acute gastrointestinal and hematologic reactions during radiotherapy. 90.9% of the gastrointestinal reactions were lower than grade 2, and only 9.1% of the gastrointestinal reactions were around grade 3. Although the lesions were large and widespread, there were no signs of intestinal obstruction or intestinal bleeding. Gastrointestinal reactions were reversed by symptomatic treatment or 3 days after the termination of radiotherapy. Acute toxicity of the blood is considered acceptable; 92.8% of patients had less than grade 2 of hematologic responses and 7.2% of patients had less than grade 3 (Table 2).

Table 2. Acute Toxicities.

	Grade	
Acute toxicities	≤2	3
Gastrointestinal, n (%)	50 (90.9)	5 (9.1)
Hematological, n (%)	51 (92.8)	4 (7.2)

The incidence of late toxic side effects was only 41.8%, and patients were able to tolerate the side effects and use symptomatic treatment to alleviate them. No grade 3 gastrointestinal side effects. Only 1 patient (1.8%) had grade 3 hematologic side effects (Table 3).

Prognosis Analysis

Multivariate analysis showed that KPS score and radiotherapy combined chemotherapy were independent prognostic

Table 3. Late Toxicities.

Late toxicities	Grade	
	≤2	3
Gastrointestinal, n (%)	23 (41.8)	0 (0.0)
Hematological, n (%)	32 (58.2)	1 (1.8)

Table 4. Multivariate Analysis Using Cox's Proportional Hazard Model for Patients' Characters.

Variable	P-value	HR	95% CI	
			Min	Max
KPS	<0.0001	2.566	1.388	4.743
Age	0.65	0.8904	0.5247	1.511
Dose	0.13	1.484	0.8379	2.627
Abdominal effusion	0.2125	0.7286	0.4273	1.243
Treatment method	<0.0001	4.762	1.119	20.26

Table 5. Multivariate Analysis Using Cox's Proportional Hazard Model for PET Semiquantitative Values.

Variable	P-value	HR	95% CI	
			Min	Max
SUV_{max}	<0.0001	1.922	1.809	3.655
SUV_{mean}	0.26	0.786	0.430	1.776
MTV	0.112	0.5673	0.556	1.439
TLG	<0.0001	3.559	1.659	7.23

Note: Metabolic tumor volume (MTV); Total lesion glycolysis (TLG).

factors. Table 4 described multivariate analysis were performed for KPS score, total radiation dose, patient age, peritoneal effusion, as well as RJC treatment or radiotherapy alone. The results showed that the KPS score and RJC treatment were prognostic indicators (P <0.0001). Age, radiation dose and peritoneal effusion were not significantly correlated with prognosis. Table 5 described multivariate analysis of SUV_{max}, SUV_{mean}, metabolic tumor volume (MTV) and Total lesion glycolysis (TLG). The results showed that the SUV_{max} and TLG were prognostic factors (P < 0.0001).

Two Representative Cases of Curative Effect

The 2 representative patients that received BIMRT are provided in Figures 2 and 3.The first case is a 59-year-old female ovarian cancer patient with developed diffuse peritoneal and pelvic metastases, accompanied by massive peritoneal effusion and coronary heart disease (Figure 2A), which is in our previous study.[15] The patient with poor general condition refused to receive surgery and chemotherapy. Patients received PET/CT guided IMRT once a day and 5 times a week for a total of 14 cycles. After the first treatment, a review of PET/CT revealed abdominal and pelvic lesions decrease significantly and metabolism reduce (Figure 2B). After 2 weeks of rest, radiotherapy was continued for 11 times, with a total dose of 50 Gy. The PET/CT reexamination showed that peritoneal and pelvic metastatic cancer had completely disappeared (Figure 2C).

The second case, a 71-year-old patient with ovarian cancer presented with massive ascites and PET/CT showed extensive peritoneal implantation metastasis and retroperitoneal lymph node metastasis (Figure 3A). After ascites extraction, the patient received BIMRT once a day and 5 times a week for a total of 20 cycles, with a total dose of 50 Gy. At the same time, abdominal thermal perfusion chemotherapy was performed for 2 times (total perfusion of cisplatin was 100 mg), followed by 3 cycles TP regimen chemotherapy (paclitaxel 180 mg D1; D2-3, 40 mg Cisplatin and D4, 20 mg Cisplatin). After treatment, PET/CT showed a significant reduction of retroperitoneal metastatic carcinoma (Figure 3B).

Discussion

The 18F-FDG PET/CT technique has a high diagnostic value for the identification of peritoneal metastatic carcinoma.[15,16] In this study, BIMRT improved the delineation of GTV and reduced the possibility of incorrect treatment of tumor sites, thereby improving clinical results. Studies have shown that conventional CT can be obtained during free breathing without compensating for respiratory exercise, and this Radiation therapy plan (RTP) can lead to deformation and dislocation of tumor location. In some cases, fluoroscopy or slow CT may provide an overall impression of respiratory movements, but these methods are not sufficient for RTP procedures. Since the PET/CT period includes the complete respiratory cycle, the image obtained is blurred according to the respiratory movement, thus providing a good image of the shape and location of the tumor.[16,17] In addition, PET/CT can help distinguish the active and necrotic parts of mixed cystic and solid lesions. Compared with ordinary CT, the GTV target area outlined by PET/CT is larger, which is consistent with the findings reported by Mundt et al.[18] Most PC patients have a number of widely distributed lesions with large size and irregular shape, so it is difficult to determine the contour of GTV. Therefore, for the GTV boundary, the PET/CT SUV value of 3.0 image contour is set. The PTV target area should be adjacent to the tumor edge, so as to reduce radiation to the normal tissue area while covering all tumor areas. After 10-14 days of radiotherapy, patients are advised to rest for 1 to 2 weeks, and then to re-position PET/CT and redesign the treatment plan, and then complete the treatment. There are 3 reasons for the benefit of this treatment: i) the patient is in poor health. Many PM patients have a large number of ascites, with many lesions and wide distribution of metastasis. Many elderly patients have received one or more surgeries before. In addition, the large volume of radiation therapy results in relatively large doses of radiation to normal tissues. Prolonged treatment interval can reduce the acute toxicity of gastrointestinal and blood system caused by radiotherapy. ii) after rest, most patients showed abdominal lesions and significantly reduced abdominal water volume, and the location changed. Repositioning after rest is conducive to accurate

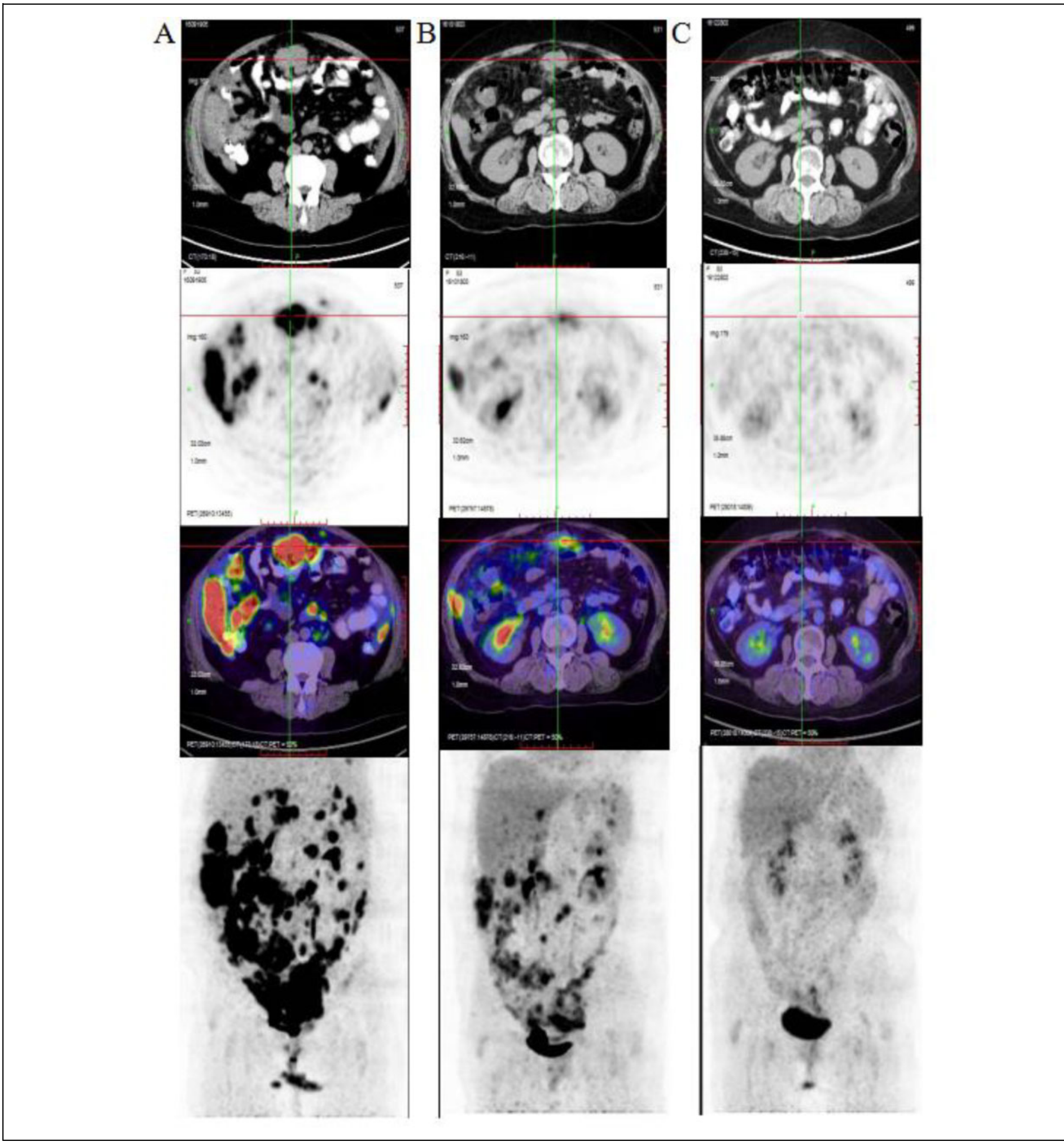

Figure 2. PET-CT scans of a 59-year-old female (A) prior to treatment, and following the (B) first and (C) second treatment. The results revealed that the metabolism of the lesions had disappeared. (Note: Part of Figure was cited from our previous study, Dang et al. 2018[15]).

treatment; iii) a few patients have new lesions after PET/CT localization, and repositioning therapy can improve the effect of the original treatment.

Before radiotherapy, nearly 50% of the patients had peritoneal metastasis accompanied by massive ascites. Due to the general biochemical indexes of most patients, the causes of ascites in this study were analyzed to be related to metastatic cancer. And a large amount of ascites causes peritoneal metastatic carcinoma drift in the abdominal cavity (Figure 4). In order to fix position of peritoneal metastatic to avoid moving in the ascites and reduce respiratory movement's influence on the position of metastasis, we released the peritoneal effusion

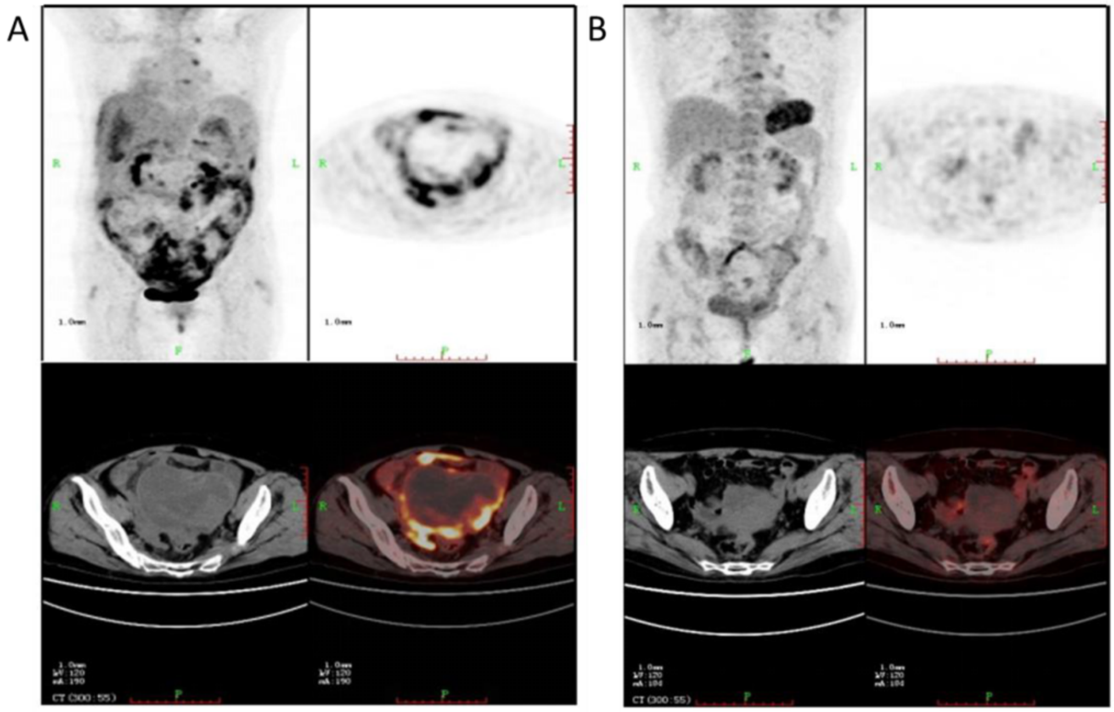

Figure 3. PET-CT scans of a 71-year-old female (A) prior to treatment, and following the treatment (B). The results revealed that the metabolism of the lesions was significantly decreased.

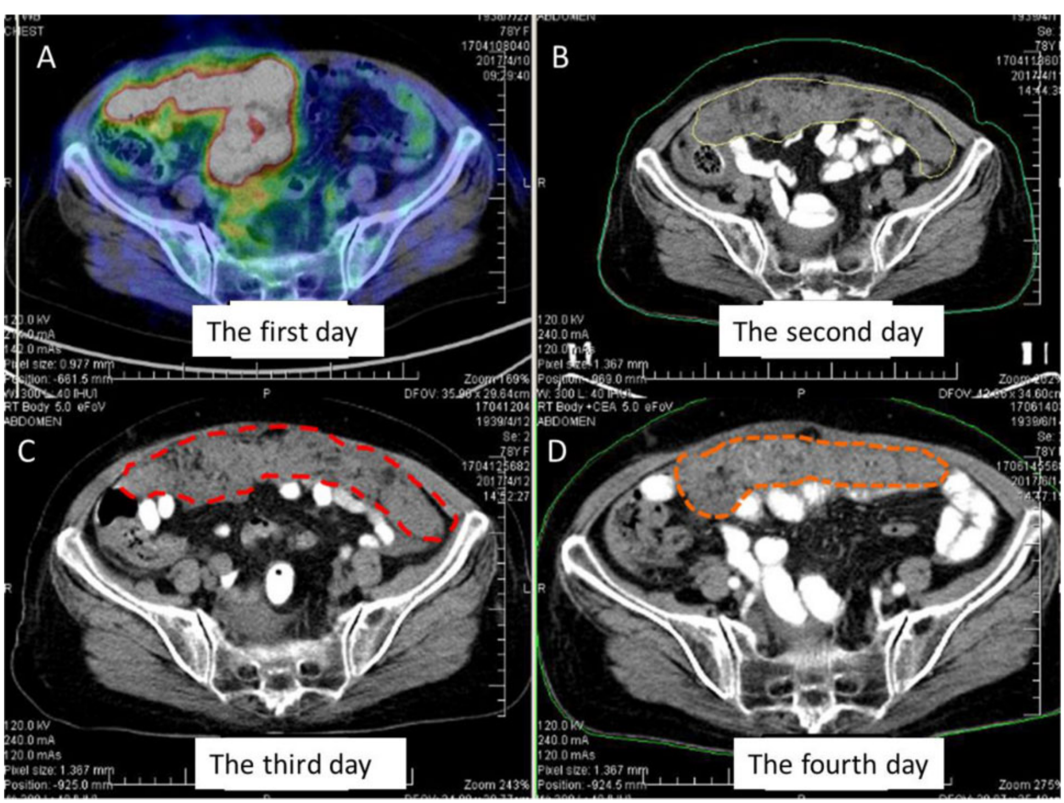

Figure 4. The position of peritoneal metastasis in the abdominal cavity has changed on (A) the first, (B) second, (C) third, and (D) fourth days.

patients before radiotherapy and used abdominal pressure plate during radiotherapy process, to avoid peritoneal movement in the process of radiation, This method both can be ensured radiotherapy accuracy and the convenience of the performing abdominal cavity perfusion chemotherapy.

Generally, good survival trends may be related to chemotherapy or the patient's health. Among the various factors assessed patient survival analysis, KPS was found to be one of the factors associated with survival. Good health is also the basis for chemotherapy. For the treatment of PM patients with BIMRT, the general condition of patients is very important. At the same time, radiotherapy combined chemotherapy is also one of the factors related to survival. Although almost all patients received chemotherapy in this study, we still believed that the involvement of chemotherapy can make the lesion eliminate more thorough in PM patients. The limit of this study is that the number of patients should be increased for future randomized controlled prospective studies.

Currently, for PM patients with good condition, the more common treatment is complete cell subtraction (CRS) combined with high-temperature intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy. The efficacy of this treatment was validated in 2003 by a randomized clinical trial, which they compared CRS joint HIPEC with systemic chemotherapy alone (median survival: 22.3 vs 12.6 months, $P = 0.032$).[9] Generally, complete CRS (CRS-r0) is a major prognostic factor, with the 5-year survival rate as high as 45%, but less than 10% when CRS is incomplete.[19] The general view is to transform extensive canceration into local and regional diseases and then adopt active CRS surgery for positive survival benefits. But for clinical in reality, the peritoneal metastatic patients were older, and had more heavy stomach and intestinal symptoms, even with an economic burden as early treatment fee spending. So, they were unable or unwilling to undergo surgery. But, untilizing PET/CT for the radiotherapy planning can be useful in the radiotherapy target volume definition[20] and improve radiotherapy effect. Mapelli P *et al* used FDG-PET/CT to predict outcome of oropharyngeal squamocellular cancer patients.[21] FDG-PET/CT took important role in prediction and diagnosis. In this study, we used FDG-PET/CT to guide radiotherapy, which provide a novel way to improve the target area definition. What's more, due to clinical differences in surgical technique, it is difficult to ensure the integrity of their cancer excision. Once the patients cannot receive a radical cure, they may bear double whammy with cancer and surgical trauma. As known to us, the overall survival outlook for PM patients is poor. When patients know they had peritoneal metastasis, they resisted accepting treatment because of fear, anxiety and losing cure hope. But, BIMRT has provided a new treatment method for some of these patients, possibly with better results and relatively higher quality of life.[22]

Conclusion

In summary, 18F-FDG-PET/CT-guided IMRT may be a safe and effective treatment for PM patients, especially for those who cannot undergo surgery. In addition, the KPS score and radiotherapy combination chemotherapy were 2 significantly prognosis index correlated with overall survival.

Authors' Note

Ya-Zheng Dang and Dong-Xian Zhang contributed equally to this work. The study protocol was approved by the Ethics Committee of the Institute of 986 hospital of People's Liberation Army Air Force (986LZ079). All patients' written informed consent was obtained.

Declaration of Conflicting Interests

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