Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastasis from Breast Cancer: A Preliminary Report on 4 Cases

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Research

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Abstract

Background: Breast cancer (BC) has the highest morbidity and the fifth mortality rate among women in China. Peritoneal metastases from BC is a rare disease and no guideline or international consensus for it.

Objective: To summarise our experiences in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) to treat breast cancer peritoneal carcinomatosis (BC PC).

Methods: 4 BC PC patients underwent CRS+HIPEC were enrolled in this study. The clinic-pathologic characteristics and overall survival (OS) were collected and analysed.

Result: The average age at CRS+HIPEC was 59.8 years. The average time of CRS+HIPEC was 8.8 h. The median number of resected organ areas was 7. OS from CRS+HIPEC were 31, 28, 16 and 52 months. There were no serious adverse events (SAEs) during the perioperative period.

Conclusions: The 4 cases provided evidence that integrated therapy with CRS+HIPEC may be a promising strategy to improve the outcome for BC PC patients.

Background

Breast cancer (BC) has been ranked as the first malignancy in incidence and the fifth mortality rate among women in China [1]. The five-year survival of BC has been increasing but the treatment of recurrent BC is a challenge [2–5]. Typical metastasis sites of BC in order of frequency were bones(67.8%), liver(47.8%), lungs(42.6%), brain(15.2%) and peritoneum (7.6%) [6–7]. Chemotherapy and estrogen therapy were the main treatments for peritoneal carcinomatosis from BC (BC PC), with the median OS was 28 months [4].

At present, for peritoneal carcinomatosis from gastrointestinal tumors or gynecological tumors, cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) have been recommended as the standard treatment. The detailed process and safety of CRS plus HIPEC in BC PC was the lack in the literature.

Here we report 4 BC PC cases with multiple therapeutic modalities, including CRS + HIPEC to determine the role of CRS + HIPEC in BC PC.

Patients And Methods

Clinical information

From January 2015 to March 2020, a total of 893 BC patients have underwent radical resection at Beijing Shijitan Hospital, 17 of which have progressive disease with PC. There are 4 BC PC patients who underwent CRS + HIPEC enrolled in this retrospective study. Another 13 patients with BC PC had exclusion

criteria or disagreed the CRS + HIPEC and were not enrolled. The diagnosis of BC PC is confirmed by pathology in all patients.

The study design was approved by the Ethical Committee of the Beijing Shijitan Hospital. All patients were introduced to the detailed process of CRS + HIPEC and signed informed consent.

CRS + HIPEC were the standard treatment for PC and had formed a standard clinical path, including detailed inclusion and exclusion criteria.

Inclusion criteria: (1) patients had a computed tomography of the abdomen with BC PC and pathological confirmation; (2) Karnofsky performance status (KPS) score ≥ 60; (3) liver function: bilirubin ≤ 2 × the upper limit of normal (ULN) and aspartic aminotransferase and alanine aminotransferase ≤ 2 × ULN; (4) renal function: serum creatinine ≤ 1.2 × ULN; and (5) cardiovascular pulmonary and other major organ functions could stand major operation.

Exclusion criteria: (1) bones, liver, lungs, brain or other distant metastases; (2) serum bilirubin, aspartic aminotransferase and alanine aminotransferase level > 2 × ULN; (3) serum creatinine level > 1.2 × ULN; (4) total gastrointestinal angiography indicating significant mesenteric contracture; (5) cardiovascular pulmonary and other major organ functions cannot stand major operation [8].

CRS + HIPEC procedure

All CRS + HIPEC were conducted by the same professional PC treatment team. Peritoneal cancer index (PCI) was evaluated through the nature of ascites, tumor size and location after cutting the abdominal cavity [9] (Fig. 1A). Subsequently, according to the peritonectomy procedures by Sugarbaker, the curative or palliative resection, peritonectomy, lymphadenectomy to maximal CRS [10]. Completeness of cytoreduction (CC) was evaluated based on residual tumor size [11] (Fig. 1B). HIPEC was carried out immediately after CRS intraoperatively. The HIPEC regimen consisted of docetaxel 120 mg plus cisplatin 120 mg. The HIPEC was conducted through the open Colliseum technique [8].Each drug was added to 3L saline and heated to 43 ± 0.5 ℃. The HIPEC time for each drug was 30 minutes and the flow rate was 400 ml / min. Gastrointestinal tract reconstruction, abdominal drainage tube placement and tension reduction suture incision were performed after HIPEC [12].

Study endpoint

The primary endpoint was the OS from CRS + HIPEC. The secondary endpoint was the perioperative safety of CRS + HIPEC in BC PC.

Definition

1. OS_1 was defined as the day from diagnosis BC to the day of death or related with BC PC or the last follow-up; OS_2 was defined as the day from CRS + HIPEC to the day of death or related with BC PC or the last follow-up.
2. The perioperative period was defined as 30 days after CRS + HIPEC [12].

3. Adverse events (AE) were defined according to the Clavier-Dindo classification system: Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions; Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications; Blood transfusions and total parenteral nutrition are also included; Grade III: Requiring surgical, endoscopic or radiological intervention; Grade IV: Life-threatening complication requiring intermediate care (IC)/ intensive care unit (ICU) management; Grade V: Death of a patient. SAEs were defined as the grade III-V AEs [13–14].

Follow-up

1) Patients were followed up every 3 months for the first 2 years and every 6 months thereafter; 2) Follow-up items included: physical examination, tumor markers, breast and gynaecological color Doppler ultrasound, chest and abdomen computed tomography (CT); 3) The last follow-up date was March 1, 2020, with the rate of 100%.

Results

Major clinicopathological characteristics

All 4 patients were female. The average age was 59.8 (50–65) years at CRS + HIPEC. In terms of pathology, there were 1 case with ILC and 3 cases with IDC. Molecular typing of primary tumors of all 4 cases was Luminal B. The major clinicopathological characteristics of primary BC and metastasis PC were shown in Table 1.

Table 1
Major clinicopathological characteristics of primary BC and metastasis PC

Characteristics	Case 1	Case 2	Case 3	Case 4
Age at diagnosis of breast cancer, years	50	60	53	50
Gender	Female	Female	Female	Female
Breast tumor localisation	Left	Right	Right	Left
Most extensively performed breast surgery	Modified radical mastectomy	Breast segment resection	Modified radical mastectomy	Modified radical mastectomy
Breast tumor histological subtype	ILC[1]	IDC[2]	IDC	IDC
Scarff-Bloom-Richardson grade			II	
Tumor stage	T_2	T_2	T_2	T_2
Nodal stage	N_2	N_2	N_0	N_0
Metastasis	0	1	0	1
TNM stage	IIIa	IV	IIa	IV
Estrogen receptor (Primary tumor/Metastasis tumor)	Positive / Positive	Positive / Positive	Positive / Positive	Positive / Positive
Progesterone receptor (Primary tumor/Metastasis tumor)	Positive / Positive	Positive / Negative	Negative / Negative	Negative / Positive
Her2/neu receptor (Primary tumor/Metastasis tumor)	Negative / Negative	Positive / Positive	Negative / Negative	Negative / Negative
Ki-67 (Primary tumor/Metastasis tumor) (%)	20/30	50/50	25/50	90/20
BRCA 1/2	Negative / Negative	Negative / Negative	Negative / Negative	Negative / Negative
Molecular subtypes (Primary tumor)	Luminal B	Luminal B	Luminal B	Luminal B
Postoperative pathology	ILC	IDC	IDC	IDC

Characteristics	Case 1	Case 2	Case 3	Case 4
Postoperative treatment of primary tumor	Cyclophosphamide + epirubicin + fluorouracil IV[3] Anastrozole	Docetaxel Trastuzumab Letrozole	Docetaxel + carboplatin IV + carboplatin IP[4]	Paclitaxel + carboplatin IP Chest wall radiotherapy Letrozole
Age at diagnosis of peritoneal metastases, years	64	60	65	50
Time between breast cancer and peritoneal metastases, months	174	0	120	0
Clinical presentation	Abdominal distension	Frequent urination, constipation and abdominal pain	Abdominal pain and abdominal distension	Left breast mass and abdominal distension
Diagnosis of peritoneal metastasis	Postoperative pathology	Postoperative pathology	Postoperative pathology	Needle biopsy

1. Invasive lobular carcinoma
2. Invasive ductal carcinoma
3. Intravenous
4. Intraperitoneal

Major characteristics of CRS + HIPEC

The average time of CRS + HIPEC was 8.8 h (range: 7–10.6 h). The median number of resected organs was 7 (range: 5–9). The average blood loss was 525 ml (range: 400–800 ml). The average ascites volume was 3,625 ml (range: 1,000–10,000 ml). In regard to HIPEC regimen, all 4 cases were with docetaxel 120 mg plus cisplatin 120 mg. The average PCI was 29.5 (range: 21–39). The case 1 and case 2 reached to CC 0. The case 3 and case 4 only reached to CC 3. The major clinicopathological characteristics of CRS + HIPEC were showed in Table 2.

Table 2
Major clinicopathological characteristics of CRS + HIPEC

Characteristics	Case 1	Case 2	Case 3	Case 4
Peritoneal cancer index (PCI)	39	28	21	30
Completeness of cytoreduction (CC)	3	3	0	0
Karnofsky performance status (KPS)	80	80	80	80
Blood loss (ml)	400	800	400	500
Rang of operation	Omentum, uterus, bilateral fallopian tubes, ovary, bladder tumor, hepatic round ligament, abdominal wall mass	abdominal wall tumor, intestinal repair, omentum, retroperitoneal tumor, breast segment	rectal, mesenteric, appendectomy, small bowel, diaphragm lesions, omentum lesion, total hysterectomy, bowel repair, omentectomy and pelvic lymphadenectomy	total uterus, double attachment, omentum, para-aortic lymph nodes, pelvic lymph nodes
Chemotherapy drugs for HIPEC	Docetaxel + Cisplatin	Docetaxel + Cisplatin	Docetaxel + Cisplatin	Docetaxel + Cisplatin
Operation duration (h)	7.0	10.6	9.0	8.5
HIPEC duration (min)	60	60	60	60
Ascites volume (ml)	10000	2000	1000	1500
Ascites properties	Light yellow slightly turbid	Light yellow	Yellow turbid	Light yellow
Postoperative treatment	Letrozole	Docetaxel Trastuzumab Letrozole	Docetaxel + carboplatin IV Letrozole	Paclitaxel + carboplatin IP Chest wall radiotherapy Letrozole
Operative complications	NO	NO	NO	NO

Characteristics	Case 1	Case 2	Case 3	Case 4
The average hospital stay after CRS + HIPEC (d)	15	10	21	12
Overall survival from diagnosis BC to last follow-up date (OS_1) (month)	205	28	136	52
Overall survival from CRS + HIPEC to last follow-up date (OS_2) (month)	31	28	16	52

OS and safety analysis

All 4 patients were alive and OS_2 were 31, 28, 16 and 52 months, respectively. OS_1 was 205, 28, 136 and 52 months, respectively. (Table 2)

Case 1 appeared incision liquefaction after CRS + HIPEC and no adverse events occurred in the other 3 cases. There were no SAEs such as gastrointestinal fistula, bleeding during the perioperative period.

Discussion

Our study introduces the detailed process of CRS + HIPEC and demonstrates that patients with BC PC can benefit from the treatment. CRS + HIPEC extends OS of BC PC patients. There are no SAEs during CRS + HIPEC perioperative period.

The most common metastasis sites of primary BC with invasive ductal carcinoma (IDC) include regional lymph nodes, lung, liver, bones, brain, and skin. BC with invasive lobular carcinoma (ILC) frequently affects bones, retroperitoneum, peritoneum, gynaecological organs, and gastrointestinal (GI) tract [15–16]. ILC accounts for less than 10% of all BCs and ICD accounts for more than 90%. However, the loss of E-cadherin expression on the surface of tumor cells in ILC patients leads to more diverse forms of metastasis. It prevents cell adhesion and promotes tumor cell migration [17]. Peritoneal metastasis can be diagnosed by CT or surgery. IDC patients account for only 3% while ILC patients account for 11% (P = 0.006). Regardless of IDC or ILC, PC is an important reason of morbidity and mortality [18]. In our study, there were 1 patient with ILC and 3 patients with IDC of the primary BC (Fig. 2–4). The metastasis tumor and the primary tumor had the same pathological type.

The prognosis of PC showed poor survival than other regional metastases from BC. The median survival time was 20.5 months from diagnosis of metastasis BC while the median survival of patients with BC PC was only 1.5 months [19]. Another study showed the OS was 5.8 months in patients with BC PC from the metastasis PC was diagnosed as compared to 22.6 months in patients with no metastasis PC. Patients with synchronous metastases have significantly better survival than those with metachronous metastases [20]. There were 2 cases with metachronous metastases and 2 cases with synchronous metastases in our study. The OS of the synchronous metastases' patients had reached 28 months and the longest OS of the metachronous metastases had reached 52 months to March 2020.

BC PC caused abdominal distension, abdominal pain or severe intestinal obstruction. And all patients in our study had at least one of the above symptoms. However, there were no effective treatments to relieve these symptoms and chronic malnutrition caused poor prognosis. The traditional treatment methods for BC PC were chemotherapy or radiotherapy but the effect of the treatment was unsatisfactory. The treatment of BC PC in our study was CRS + HIPEC combined with chemotherapy. To achieve radical CRS, the median number of resected organs were 7 and 2 patients reached CC 0. The tolerance to hyperthermia was higher in normal tissue than the tumor tissue. HIPEC could prevent the adhesion postoperatively, as well as decrease the accelerative effect of healing on tumor cell entrapment by killing the granulocytes and monocytes. The synergistic anti-cancer effect could be dramatically increased at 43°C. Hyperthermia could increase the response rates of cancer cells to HIPEC drugs, and the depth of HIPEC drugs into the tumor tissues. At last, loosening the adhesion of the intestine or ileostomy could relieve the intestinal obstruction. In our study, one case underwent loosening the adhesion of the intestine, and another underwent ileostomy, the abdominal distension or bowel obstruction of which relieved completely. All patients in our study received adjuvant chemotherapy and endocrine therapy pre- and post-CRS + HIPEC. The average OS reached 32 months better than literature [4].

Estrogen played an important role in the occurrence and prognosis of BC. The estrogen receptor (ER) was one of the important biomarkers to predict the prognosis of BC [21]. BC patients with ER- and progesterone receptor (PR)- positive had a better prognosis [22]. Human epidermal growth factor receptor 2 (HER-2) regulates cell proliferation, growth, and survival. HER-2 was a transmembrane tyrosine kinase receptor [23–24]. BC patients with high levels Ki-67 usually have a poor prognosis due to Ki-67 was a nuclear proliferation marker [25]. In our study, two patients with synchronous BC PC, one with Ki-67 80–90% and another with HER-2 positive, maybe one of the reasons for the early peritoneal metastasis. The other two cases received standard adjuvant therapy after the primary lesion. All patients received tamoxifen treatment for 5 years and metastasis occurred after 5 years of discontinuation (all 4 cases had positive estrogen receptors). It was necessary to receive estrogen therapy for hormone receptor-positive BC PC patients after CRS + HIPEC. At present, all the 4 patients had received letrozole orally after CRS + HIPEC and chemotherapy. No tumor progression occurred at the time of follow-up.

The average PCI was 29.5, which heralded the difficulty of CRS. The average operation duration was 8.8 h and average 7 organs were resected. The average blood loss was 525 ml and the average ascites volume was 3,625 ml. While there were no SAEs during the perioperative period and the average hospital stay was 15 d. The safety of CRS + HIPEC was accepted. It was important that a professional PC treatment team implemented standardised CRS + HIPEC. Otherwise, you maybe come to the opposite conclusion that CRS + HIPEC was not the treatment of choice [26]. This article provided new ideas and methods for the treatment of BC PC patients. This finding merits further investigation in larger studies.

The disadvantage of this study was that the number of patients was too small to perform statistical analysis. The follow-up time was short, no comparison with a control group and lack of questionnaires to evaluate quality of life (QoL). Therefore, these findings in this study required more confirmations from a large sample of evidence.

Conclusions

This paper reported 4 typical cases of BC PC successfully treated by a radical comprehensive treatments with CRS + HIPEC. These patients kept in good condition till now, with 32 months of mean OS_2. The 4 cases provided evidence that integrated therapy with CRS + HIPEC may be a promising strategy to improve the outcome for BC PC patients.

List Of Abbreviations

BC	Breast cancer
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
PC	Peritoneal carcinomatosis
BC PC	Breast cancer peritoneal carcinomatosis
SAEs	Serious adverse events
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
GI	Gastrointestinal
KPS	Karnofsky performance status
ULN	Upper limit of normal
PCI	Peritoneal cancer index
CC	Completeness of cytoreduction
OS	Overall survival
CT	Computed tomography
ER	Estrogen receptor
PR	Progesterone receptor
HER-2	Human epidermal growth factor receptor 2
IV	Intravenous
IP	Intraperitoneal
IC	Intermediate care
ICU	Intensive care unit
QoL	Quality of life

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the 4 patients for publication of this article and accompanying images. A copy of these written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jun-hui Yu organised the patient's medical records and was the major contributor in writing the manuscript.

Yu Feng, Xin-bao Li and Yan-Ping Li collected the patient's medical records.

Cheng-Yan Zhang and Feng Shi collected the patient's pathological pictures.

Song-Lin An, Gang Liu, Yan-Bin Zhang, Kai Zhang, Zhong-He Ji, Bing Li and Guo-Jun Yan conducted the procedures of CRS + HIPEC.

Yan Li designed the project, monitored project progress, and contributed to data evaluation of the manuscript.

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Not applicable.

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Figures

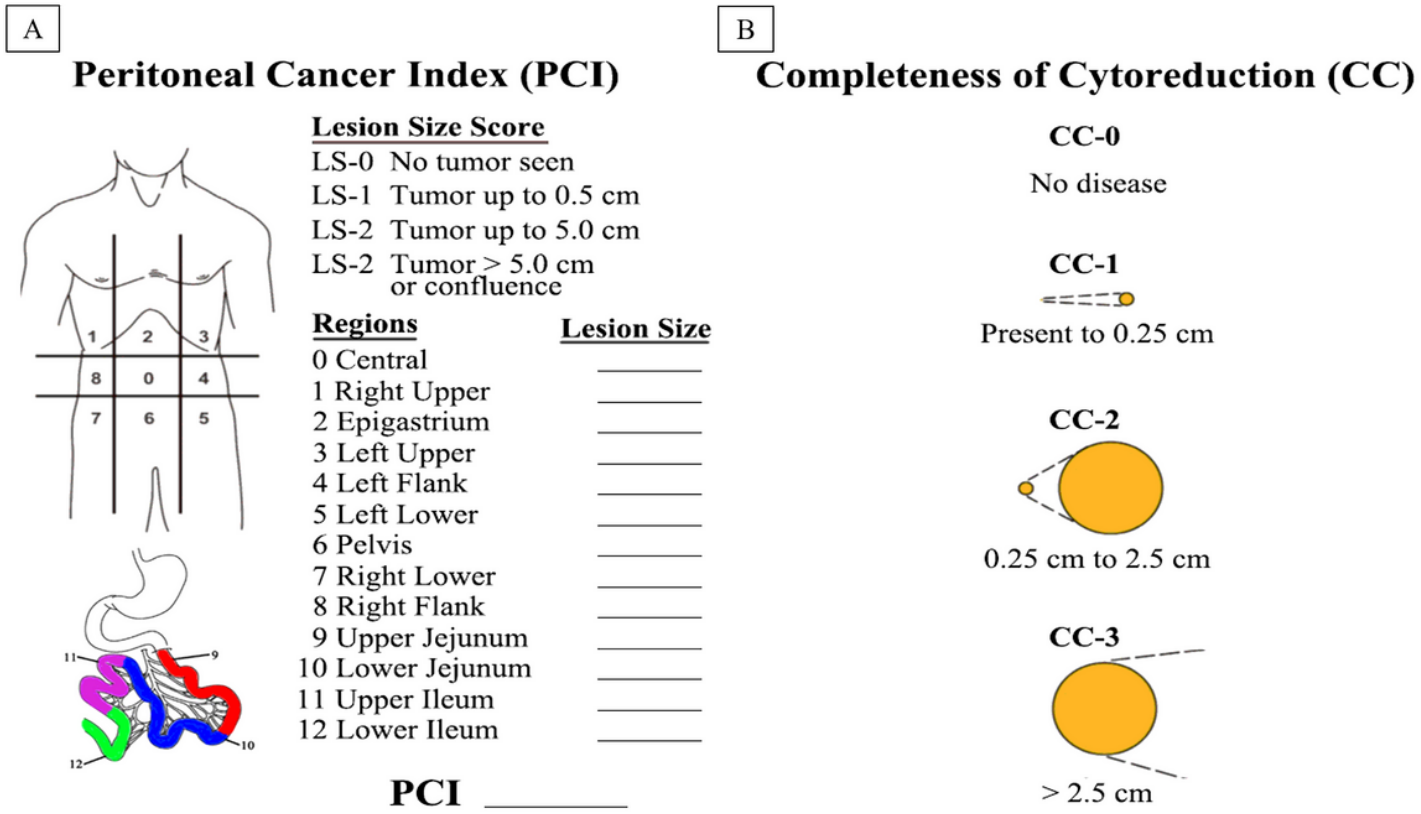

Figure 1

Peritoneal cancer index score (A) and completeness of cytoreduction score (B).

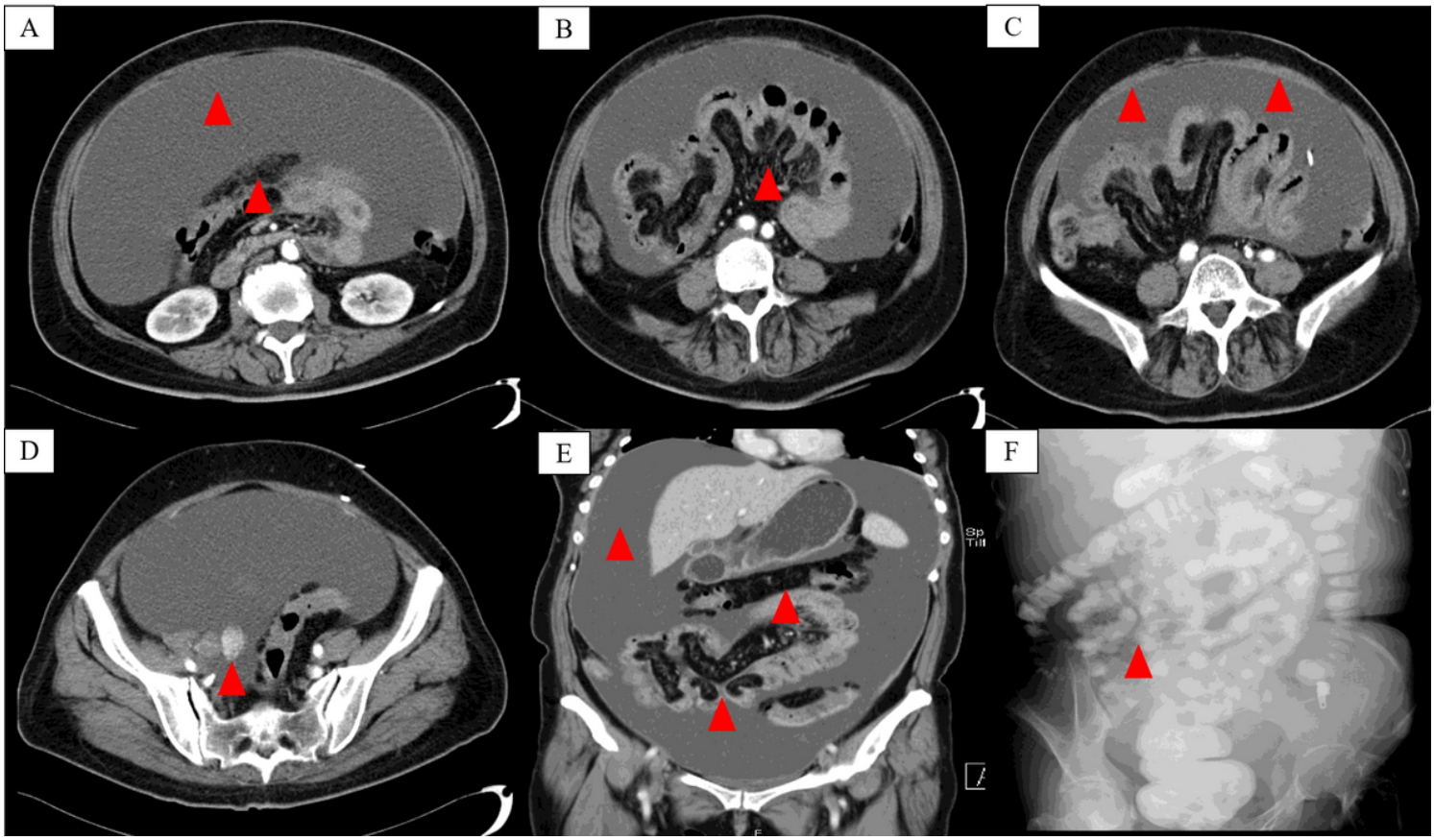

Figure 2

Preoperative image examination. A: Massive ascites and omentum contraction; B: Small intestine contraction; C: Peritoneal thickening; D: Pelvic tumor with contrast enhancement; E: Coronal showed Massive ascites; omentum contraction and small intestine contraction; F: Total gastrointestinal angiography showed the gathered small intestine.

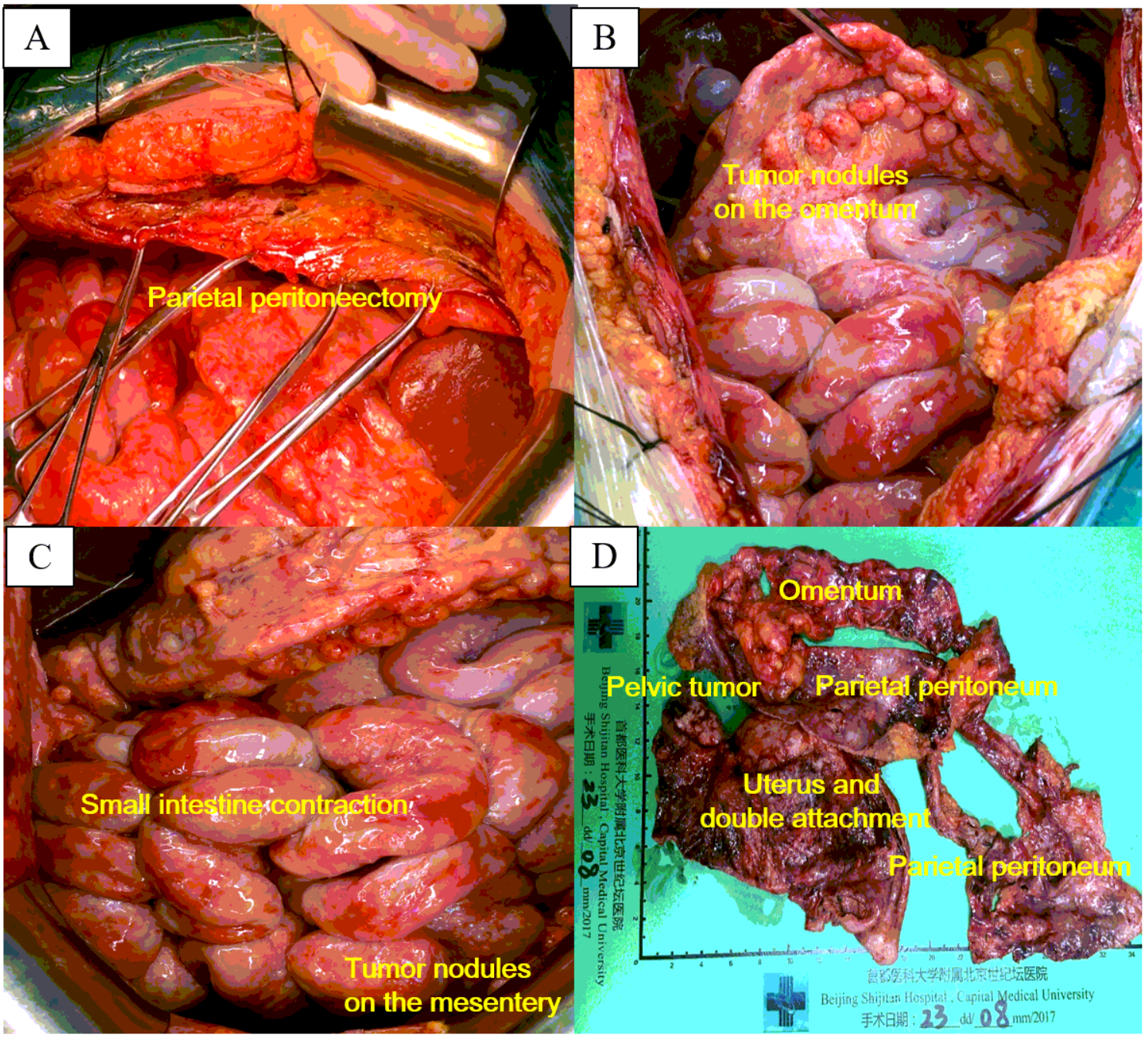

Figure 3

CRS intraoperative and postoperative specimens. A: Omentum contraction; B: Tumor nodules on the omentum; C: Small intestine contraction and tumor nodules on the mesentery; D: Postoperative specimens.

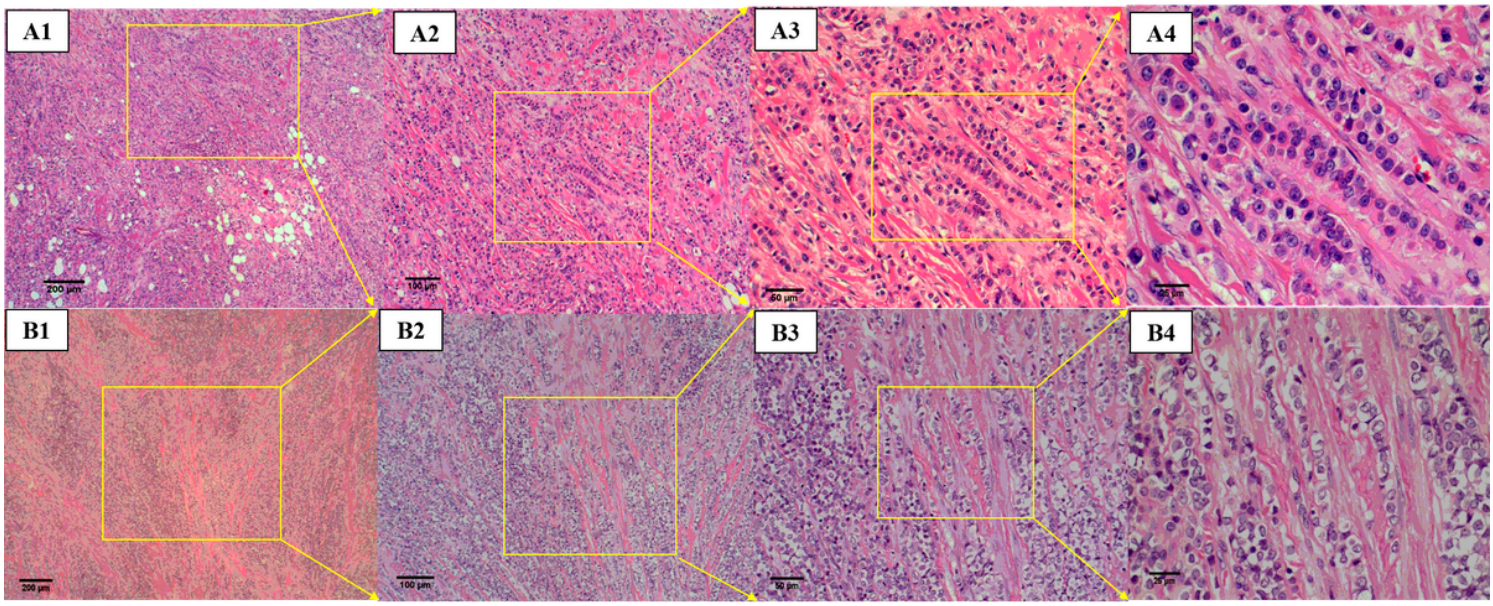

Figure 4

Pathological classification of primary (A1 - A4) and metastasis (B1 - B4) breast tumors (hematoxylin-eosin staining). A1: Invasive lobular carcinoma of the breast; A2: Tumor cells have poor adhesion and scattered in a single or single row of infiltrating interstitium; A3: Tumor cells infiltrate the stroma in a single row and forming a linear structure; A4: Tumor cells have smaller but the same size. Some cytoplasm contains eosinophilic globules and the nucleus is eccentric, round, small nucleolus and pathological mitosis are rare. B1: Invasive lobular carcinoma metastasises to the abdominal cavity and infiltrates into the peritoneal fibrous connectives; B2: Tumor cells have poor adhesion, diffuse, scattered in a single or single row of infiltrating interstitium; B3: Tumor cells infiltrate the stroma in a single row and forming a linear structure; B4: Tumor cells have the same size, nuclear round, small nucleoli are common and pathological mitosis is rare. The magnification of the pictures of the two-line from the left to right are ×50, ×100, ×200 and ×400, respectively.