Case Report

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Hyperthermic intrathoracic chemotherapy with cisplatin for ovarian cancer with pleural metastasis

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Intrathoracic metastasis of ovarian cancer has poor prognosis regardless of treatment modality. Recent development of surgical techniques and the new concept of direct infusion of chemotherapeutic agents with hyperthermia could help with the treatment of disseminated diseases in ovarian cancer. Using video-assisted thoracoscopic surgery and intracavitary chemotherapy with hyperthermia, we tried hyperthermic intrathoracic chemotherapy for a case of stage IV high-grade serous ovarian cancer with pleural metastasis. There was no high-grade complication related to the procedure. The patient is alive without disease at 32 months after initial treatment.

Keywords: Drug therapy; Fever; Neoplasm metastasis; Ovarian neoplasms

Introduction

Ovarian cancer is the leading cause of death among the gynecological cancers and difficult to cure. Nearly 70% to 80% of patients are diagnosed at an advanced stage with peritoneal carcinomatosis or distant metastasis. In patients with complete cytoreduction after surgery, the recurrence rate is >50% [1]. The main treatment for ovarian cancer consists of cytoreductive surgery and platinum-based chemotherapy. The important goals of surgery are staging of disease extent and removing as much of the tumor as possible, which are closely related to responsiveness to chemotherapy and survival rate. Chemotherapy is closely related to the results of surgery and plays a role in reducing tumor volume and eliminating microscopic lesions. To increase survival, many new surgical techniques and antineoplastic agents have been developed and studied. Gynecological oncologists have extended the indications for surgery as a result of multidisciplinary surgical procedures and new surgical devices. The use of high-resolution scans or advanced laparoscopic instruments means that oncologists can better predict which patients are likely to have a resectable tumor, which allows timely surgery or chemotherapy [2]. The development of new antineoplastic agents and the new concept of targeted therapy play a role in increasing survival of ovarian cancer patients. Regardless of these efforts to overcome the low survival rate, intrathoracic or pleural metastasis, with or without pleural effusion, is difficult to treat with current standard treatment. Cytoreductive surgery can be assessed using video-assisted thoracoscopic surgery and this procedure can help in determining the best treatment option for these patients [3]. Video-assisted thoracoscopic surgery is also supposed to enable the accurate pathological diagnosis and intrathoracic resection of pleural and cardiophrenic lymph node metastasis in patients with ovarian cancer with acceptable morbidity [4].

Several reports suggest a survival benefit after optimal cytoreduction for intrathoracic metastasis of ovarian cancer [5]. Recently, in addition to cytoreductive surgery and intraperito-

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neal chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) has been introduced to improve drug delivery to the tumor. HIPEC is considered to be a promising new strategy. We applied this concept to the treatment of intrathoracic metastatic lesions in ovarian cancer. Here, we report a case of stage IV high-grade serous ovarian cancer treated with hyperthermic intrathoracic chemotherapy (HITHOC) with cisplatin.

Case report

A 46-year-old premenopausal woman was admitted to our hospital with a 2-month history of abdominal fullness and aggravating abdominal pain. She had no specific medical and surgical history. Ultrasound revealed a lobulated, heterogeneous pelvic mass measuring 13×10×12 cm^3. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (CT) and chest CT suggested ovarian cancer with pleural metastasis. ^{18}F-FDG positron emission tomography/CT showed an 11-cm mass in the pelvic cavity with high attenuation and hypermetabolism, and a 6-cm mass in the cul de sac. There were many hypermetabolic nodular lesions in the abdominal cavity and tiny fissural nodules in the right lung on chest CT, which suggested intrathoracic metastasis (Fig. 1).

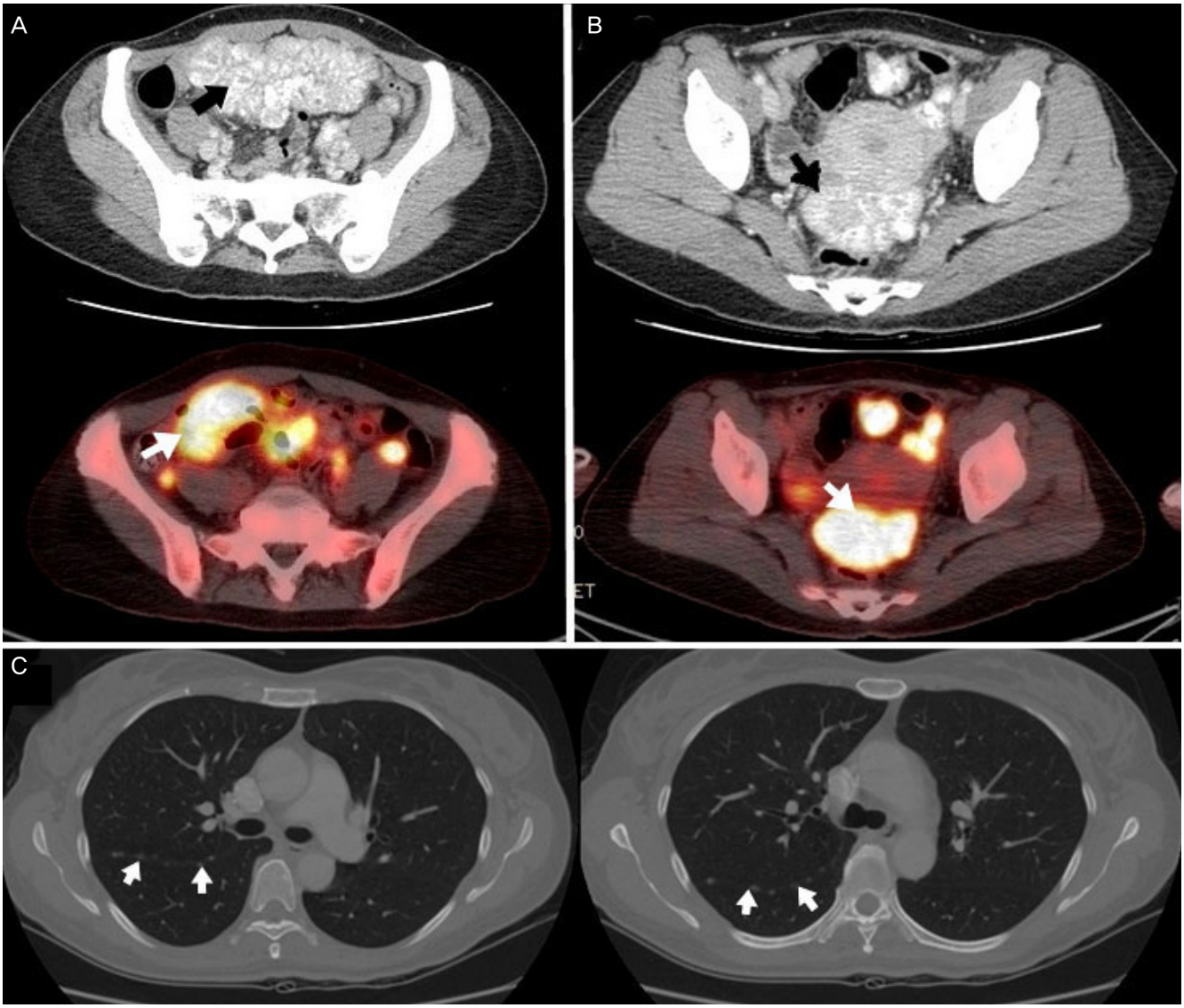

Fig. 1. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) suggested ovarian cancer. ^{18}F-FDG PET/CT showed an (A) 11-cm mass in the pelvic cavity with high attenuation and hypermetabolism (arrow) and (B) a 6-cm mass in the cul de sac (arrow). (C) Chest CT showed tiny fissural nodules (arrow) in the right side lung, which suggested intrathoracic metastasis.

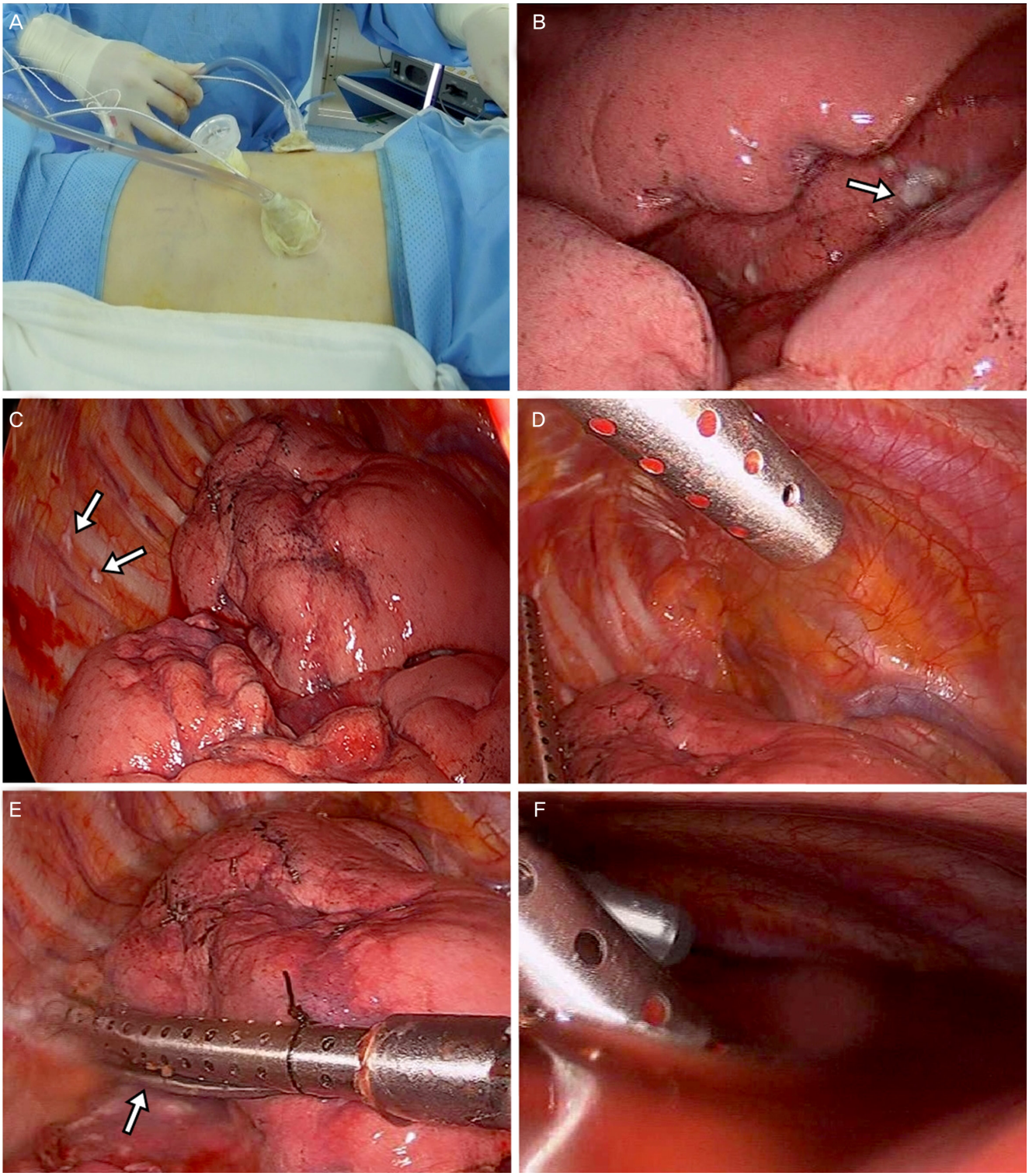

Fig. 2. Video-assisted thoracoscopic surgery and hyperthermic intrathoracic chemotherapy. (A) Three thoracostomies for thoracoscopy and inflow and outflow catheters. (B) Exploration to measure tumor extent (arrow, metastatic lesion). (C) After electrofulguration and wedge resection (arrows, metastatic lesion). (D) Insertion of lower inflow and upper outflow catheters. (E) Infusion of chemotherapeutic agent (arrow, attached temperature sensor). (F) Right chest cavity filled with infusion

There were no lung parenchymal lesion and no pleural effusion which usually develop in pleural metastasis. The size of fissural nodules was less than 1 cm. All imaging modality showed no evidence of metastatic lesions in lymphatic chains. The serum CA 125 concentration was 209 IU/mL (upper limit, 35 U/mL). Other tumor markers, such as carcinoembryonic antigen and CA 19-9, were within the normal range.

Exploratory laparotomy was performed based on suspicion of ovarian cancer. The right ovary was replaced with a mass measuring 13×11×12 cm^3 and scanty ascites. Total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, lower anterior resection of the colon, partial bladder cystectomy, and appendectomy were performed. There was no visible residual tumor in the peritoneal cavity. Lymphadenectomy was performed not in the primary but in the interval surgery after three cycles of chemotherapy. Primary debulking surgery was suboptimal due to residual tumor in the intrathoracic cavity. Pathological examination revealed high-grade serous adenocarcinoma, which was thought to originate from the ovary.

After the operation, the patient was started on carboplatin (area under the curve, 5.0)/paclitaxel (175 mg/m^2) combination chemotherapy for three cycles every 3 weeks. Bevacizumab (15 mg/kg) was concurrently administered with chemotherapy every 3 weeks starting from the second cycle. After three cycles of chemotherapy, CT was performed to determine the treatment response of the abdominal and chest lesions. Follow-up CT after three cycles of chemotherapy showed no lesions in the abdominal cavity but no changes in the intrathoracic lesions. Exploratory laparotomy was performed for inspection of the abdominal cavity. There was no visible lesion in the peritoneal cavity. Several biopsies were performed at sites at which there were tumors at the initial operation, along with washing cytology and lymphadenectomy. The pathological examination revealed no evidence of remnant malignant lesions.

After the fourth cycle of chemotherapy, video-assisted thoracoscopic surgery were performed for intrathoracic cytoreductive surgery and HITHOC. The patient was placed in a lateral position and three posterolateral thoracostomies were used for thoracoscopy and inflow and outflow of perfusion. After pleural exploration to measure tumor extent and confirm that resection seemed feasible, the lesions on the parietal and visceral pleura were fulgurated using electrocautery, and wedge resection of the right lower lobe reduced the tumor volume. The pathologic report confirmed that the intrathoracic lesions were metastatic ovarian cancer. After surgical cytoreduction for the pleural lesions, the size of residual lesions in the intrathoracic cavity was less than 5 mm. Perfusion catheters were inserted into the thoracic cavity through two thoracostomies (Belmont Hyperthermia Pump, Billerica, MA, USA). The other thoracostomy was used for thoracoscopy to monitor perfusion. Temperature sensors were put into the thoracostomies with the inflow and outflow catheters. The priming volume (3 L Ringer's lactate solution) was pumped into the pleural cavity until an intrathoracic temperature of 42°C was achieved. Afterward, cisplatin (120 mg/m^2) was added, and the perfusion was continued for 90 minutes at a rate of 800 to 1,000 mL/min (Fig. 2). At the end of the chemotherapy perfusion, the circulation kit with the perfusion catheters was removed. A standard thoracic drain was inserted with mild suction. The patient stayed in the intensive care unit for 1 day. There was no high-grade toxicity (grade 3 or 4) related to HITHOC. After HITHOC, an additional eight cycles of chemotherapy were completed. Bevacizumab was concurrently administered until cycle six.

Follow-up CT after completion of chemotherapy showed no lesions in the intraabdominal and intrathoracic cavity. The serum CA 125 concentration decreased to normal level. The patient is alive without disease at 24 months after initial treatment and 14 months after the end of treatment.

Discussion

Surgical treatment for intrathoracic metastasis is challenging in ovarian cancer due to poor prognosis, unfamiliarity with thoracic surgery, and postoperative complications. The development of surgical instruments and techniques, and new treatment concepts such as targeted therapy or hyperthermia, may give gynecological oncologists the opportunity to perform active and invasive treatment. The targeted antineoplastic agent, bevacizumab, has been reported to give survival benefits in advanced or metastatic ovarian cancer when is used in combination with intravenous paclitaxel plus carboplatin [6]. Following publication of the landmark study, Gynecologic Oncologic Group protocol 172, in 2006, there was an important clinical announcement suggesting that intraperitoneal chemotherapy should become the standard of care for patients with newly diagnosed stage 3 optimally cyto-

reduced, epithelial ovarian cancer. However, toxicity, catheter complications, and dose schedule prevented the clinical use of intraperitoneal chemotherapy.

New alternatives such as HIPEC have been proposed to improve treatment outcomes and reduce treatment-related morbidity in advanced ovarian cancer patients. It has been shown that HIPEC improves survival in patients with ovarian cancer, however, another study has shown no survival advantage for HIPEC [7,8]. In a phase II study, Lim et al. [9] reported the feasibility and acceptable morbidity of HIPEC after cytoreductive surgery in ovarian cancer. Deraco et al. [10] reported favorable outcome and morbidity after cytoreductive surgery and HIPEC for treatment of recurrent epithelial ovarian cancer. The rate of grade 3 to 5 postoperative adverse events with severe morbidity was 26.3% and the rate of procedure-related mortality was 5.3%.

The morbidity and mortality for HIPEC of ovarian cancer are lower than those for treatment of primary and gastrointestinal peritoneal carcinomatosis and similar to those for cytoreductive surgery alone for surgical treatment of peritoneal recurrence of ovarian cancer [11]. Although direct comparison is not possible because of the different types of disease and treatment, the safety of HIPEC is not worse than that of intraperitoneal chemotherapy. However, it is difficult to assess the pure morbidity and mortality of HIPEC, separately from cytoreduction because HIPEC should be performed after cytoreductive surgery.

A multimodal approach consisting of cytoreductive surgery and HITHOC has been developed for the treatment of disseminated intrathoracic lesions in primary thoracic diseases. Surgery alone cannot achieve microscopically complete resection. Residual tumor cells remain in the pleural cavity, enhancing local tumor recurrence. Therefore, cytoreductive surgery combined with adjuvant therapies, including intracavitary chemotherapy, deserve consideration to eliminate cancer cells when the treatment endpoint is to increase survival in ovarian cancer. To our knowledge, there were no well-designed large clinical studies for the HITHOC. Small number of phase I or II studies has been conducted.

This combined treatment strategy has been considered to show acceptable morbidity and mortality for the treatment in primary thoracic diseases [12,13]. Even though there are no large studies for the efficacy of HITHOC small individual studies suggest that this treatment modality might provide better local tumor control and survival benefit [14,15].

On the basis of its acceptable safety, HITHOC can be used with intrathoracic surgery for curative or palliative treatment of ovarian cancer with intrathoracic metastasis. Only a few studies of HITHOC with intrathoracic surgery for treatment of ovarian cancer with intrathoracic metastasis have been reported; therefore, careful consideration is needed to select appropriate candidates for this innovative surgical strategy. Preoperative performance status, age, extent of combined intrathoracic cytoreductive surgery, and curative or palliative endpoints should be considered. In conclusion, in carefully selected patients, HITHOC can be considered for treatment of ovarian cancer with intrathoracic metastasis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Cascales-Campos P, Gil J, Feliciangeli E, Parrilla P. HIPEC in ovarian cancer: treatment of a new era or is it the end of the pipeline? Gynecol Oncol 2015;139:363-8.
2. Petrillo M, Vizzielli G, Fanfani F, Gallotta V, Cosentino F, Chiantera V, et al. Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: proof of a concept. Gynecol Oncol 2015;139:5-9.
3. Diaz JP, Abu-Rustum NR, Sonoda Y, Downey RJ, Park BJ, Flores RM, et al. Video-assisted thoracic surgery (VATS) evaluation of pleural effusions in patients with newly diagnosed advanced ovarian carcinoma can influence the primary management choice for these patients. Gynecol Oncol 2010;116:483-8.
4. Lim MC, Lee HS, Jung DC, Choi JY, Seo SS, Park SY. Pathological diagnosis and cytoreduction of cardiophrenic lymph node and pleural metastasis in ovarian cancer patients using video-assisted thoracic surgery. Ann Surg Oncol 2009;16:1990-6.
5. Akahira JI, Yoshikawa H, Shimizu Y, Tsunematsu R, Hirakawa T, Kuramoto H, et al. Prognostic factors of stage IV epithelial ovarian cancer: a multicenter retrospective study. Gynecol Oncol 2001;81:398-403.

6. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.
7. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol 2015;22:1570-5.
8. Chiva LM, Gonzalez-Martin A. A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer. Gynecol Oncol 2015;136:130-5.
9. Lim MC, Kang S, Choi J, Song YJ, Park S, Seo SS, et al. Hyperthermic intraperitoneal chemotherapy after extensive cytoreductive surgery in patients with primary advanced epithelial ovarian cancer: interim analysis of a phase II study. Ann Surg Oncol 2009;16:993-1000.
10. Deraco M, Virzi S, Iusco DR, Puccio F, Macri A, Famulari C, et al. Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study. BJOG 2012;119:800-9.
11. Bakrin N, Cotte E, Golfier F, Gilly FN, Freyer G, Helm W, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. Ann Surg Oncol 2012;19:4052-8.
12. de Bree E, van Ruth S, Baas P, Rutgers EJ, van Zandwijk N, Witkamp AJ, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. Chest 2002;121:480-7.
13. Ried M, Potzger T, Braune N, Neu R, Zausig Y, Schalke B, et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. Eur J Cardiothorac Surg 2013;43:801-7.
14. Yellin A, Simansky DA, Paley M, Refaely Y. Hyperthermic pleural perfusion with cisplatin: early clinical experience. Cancer 2001;92:2197-203.
15. Chua TC, Yan TD, Yap ZL, Horton MD, Fermanis GG, Morris DL. Thoracic cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy for pseudomyxoma peritonei. J Surg Oncol 2009;99:292-5.