Prediction of suboptimal cytoreduction of epithelial ovarian carcinoma by preoperative computed tomography

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Summary

In an aim to evaluate the diagnostic efficacy of preoperative abdominal-pelvic CT for the prediction of suboptimal cytoreduction of epithelial ovarian carcinoma (EOC) at primary surgery, CT scans of 48 patients who underwent primary surgery for EOC were retrospectively analyzed. The presence of at least one of the following CT findings: multiple implants > 1 cm in maximum diameter in the mesenteria of the small or large intestines, porta hepatis or intersegmental fissure or on the hepatic surface, diaphragmatic peritoneum, gastrohepatic or gastrosplenic ligaments or the extension of tumor infiltration > 2 cm on the omentum towards the spleen or stomach or the intestines encased by the tumor > 2 cm, diffuse peritoneal thickening or invasion of the lateral pelvic wall > 1 cm or multiple lymph nodes > 1 cm at the cardiophrenic and suprarenal levels were accepted as the critical markers for predicting suboptimal cytoreduction. Suboptimal surgery, defined as leaving a residual tumor mass > 1 cm, was determined in 18 (37.5%) patients. CT predicted suboptimal cytoreduction with 83.3% (15/18) sensitivity, 90% (27/30) specificity and 87.5% (42/48) accuracy. PPV and NPV values were 83.3% (15/18) and 90% (27/30), respectively. These results suggested that preoperative CT could successfully predict suboptimal surgery in patients with EOC.

Key words: Ovarian carcinoma; Cytoreduction; Computed tomography.

Introduction

Epithelial ovarian carcinoma (EOC) is the leading cause of death among gynecological malignancies. Although great advances have been achieved in the treatment of human cancer, the mortality rate of ovarian cancer has not improved significantly; 75% of patients are still diagnosed in advanced stages [1-3]. The current mode of treatment of advanced stage ovarian carcinoma includes optimal cytoreduction and surgical staging followed by combined chemotherapy of platinium and taxanes. It is well known that cytoreduction of the tumor is the key factor for an optimal response to chemotherapy and the maximal diameter of residual tumor prior to intiation of chemotherapy is an important determinant of prognosis [4, 5]. Although various sizes have been reported, it is believed that more favorable responses to chemotherapy and prolonged survival are achieved by reduction of the maximal tumor diameter to < 1 cm during surgery and this result is defined as optimal cytoreduction [6-10].

Optimal cytoreduction can not be achieved in all attempts due to disseminated tumor metastasis to life-threatening critical regions, and personal or institutional experiences [7]. Despite aggressive surgical efforts, it has been reported that optimal surgical outcome was not obtained in 10-67% of patients with advanced stage disease [11-13]. It is believed that surgical complications and delayed chemotherapy can result in decreased survival and quality of life in these patients. Neoadjuvant chemotherapy, given prior to aggressive surgery, has been shown to prevent serious surgical complications and increase the chance of optimal cytoreduction by eliminating, or at least decreasing, the size of the tumor in some critical areas of this subgroup of patients [14, 15]. However, the diagnosis of this subgroup of patients who will benefit from neoadjuvant chemotherapy, before any subobtimal surgical attemts, is anothor challenge. Although, numerous studies have evaluated the efficacy of pelvic-abdominal computed tomography (CT) imaging for the differential diagnosis of pelvic tumors and the extent and localization of metastasis, relatively little data exist regarding its use in predicting the outcome of primary cytoreductive surgery for advanced ovarian carcinoma [7, 8, 16-19].

This study was designed to evaluate the reliability of CT for predicting the optimal cytoreduction of EOC at primary surgery with the collaboration of the Departments of Gynecologic Oncology and Radiology.

Materials and Methods

This retrospective study was carried out collaboratively by the Departments of Radiology and Gynecologic Oncology after approval of the Ethics Board of the Medical Faculty. Forty-eight patients referred to the Gynecologic Oncology Clinic with the finding of a pelvic mass suspicious for ovarian cancer between November 2003 and September 2008 were included in the study. All of the patients were evaluated by abdominal and pelvic CT preoperatively and underwent surgery for staging and cytoreduction.

Preoperative CT scans were obtained with a helical unit (X Vision, Toshiba, Japan), with the imaging parameters of 7 mm collimation, 1:1 pitch, 120 kVp, and 150-300 mA. The imaging fields of all patients covered the total area between the dome of the diaphragm, including the base of the lungs superiorly and

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Table 1. — *Fifteen specific areas comprising the CT criteria used for prediction of optimal cytoreduction.*

Peritoneal sites	Nodal sites	Others
1. Hepatic surface	11. Suprarenal	13. Hepatic metastasis
2. Diaphragmatic peritoneum	12. Pericardiac	14. Pulmonary or pleural
3. Porta hepatis		15. Abdominal wall invasion
4. Intersegmental fissure		
5. Extension of infiltration on omentum towards spleen and stomach		
6. Gastrohepatic ligament		
7. Gastrosplenic ligament		
8. Diffuse peritoneal thickening		
9. Mesentery		
10. Intestines encased by tumor		

Table 2. — *Distribution of the patients with regard to histology, grade and stage.*

Parameters	Number of patients	%
Histological type		
Serous	37	77
Mucinous	3	6
Clear cell	2	4
Endometroid	5	10
Undifferentiated	1	2
Tumor Grade		
1	6	12
2	26	54
3	16	33
FIGO Stage		
I	11	23
II	2	7
III	30	62
IV	4	8

the pubic symphysis inferiorly. Oral (50 cc urografin 76% diluted in 1.5 l of water) and intravenous contrast agents (non-ionic contrast agent, either omnipaque 350, iomeron 350, ultravist 370, or xenetix 350, 100 ml) were used in all cases. Intravenous contrast medium was administered after a 70-sec delay via the right or left antecubital vein at a rate of 3 ml/sec using an automatic injector.

Preoperative CT images were evaluated by two radiologists who were blinded to the surgical outcome and the stage of disease. Imaging criteria were derived from the surgical and imaging literature [7, 8, 16-19] and supplemented by personal communication with a gynecologic oncologist. The CT findings accepted as the criteria for prediction of suboptimal cytoreduction are presented in Table 1. According to these criteria the CT findings of multiple implants > 1 cm in maximum diameter in the mesenteria of the small and large intestines, hepatic surface, diaphragmatic peritoneum, porta hepatis, intersegmental fissure, gastrohepatic ligament and gastrosplenic ligament, extension of the tumor infiltration on the omentum towards the spleen and the stomach, multiple intestinal segments encased by the tumor, diffuse peritoneal thickening more than 4 mm of thickness in at least two of the five peritoneal fields including the lateral colic gutter, lateral conal fascia, anterior abdominal wall, diaphragm and pelvic peritoneal surfaces, multiple tumor invasion of the lateral pelvic wall, and multiple lymph nodes > 1 cm at the cardiophrenic and suprarenal levels were all defined as markers for suboptimal surgery. In addition to these findings, tumor involvement of the hepatic parenchyma, tumor nodules in the lung or pleura and multiple tumor invasion of the abdominal wall were also defined as other markers (Figures 1a, 1b, 1c). Obtaining any one of these defined criteria by CT was accepted as a predictor of suboptimal surgical outcome.

All patients underwent explorative laparotomy within two weeks after CT scan, and surgical staging was performed including total abdominal hysterectomy, unilateral or bilateral oophorectomy, total or partial omentectomy or omental biopsy, paraaortic and pelvic lymph node dissection or sampling, multiple biopsies of suspicious nodules, peritoneal cytology by one of the two gynecologic oncology attending surgeons with maximum effort for excision of the total tumor mass or to decrease to a minimum diameter of < 1 cm. Excision of all visible tumors or the maximal diameter of a residual tumor mass < 1 cm in any critical site were accepted as optimal cytoreduction.

The results of CT findings and the outcome of surgery for each patient were compared, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the results of the CT findings for prediction of suboptimal surgery were calculated. Kappa analysis and Fisher's exact test were used to define the correlation between surgical outcome and CT findings.

Results

The median age of 48 patients was 54 years (range 24-78 years). Surgical staging revealed that 13 patients had early-stage disease (surgical stage I or II), while 35 had advanced stage disease (surgical stage III or IV). The histology, grade and surgical stage of the tumors are presented in Table 2. Suboptimal and optimal cytoreduction was achieved in 18 (37.5%) and 30 (62.5%) patients, respectively. When surgical stage and surgical outcome of the patients were compared, it was seen that optimal cytoreduction was achieved in all patients with early-stage disease, while 18 of the patients with advanced stage disease had suboptimal cytoreduction. The sites of residual tumor > 1 cm in patients with suboptimal cytoreductive surgery are shown in Table 3.

Based on the defined imaging criteria obtained by CT scan findings, it was presumed that 18 (37.5%) and 30 (62.5%) of the 48 patients would have optimal and suboptimal cytoreductive surgery, respectively. All 13

Table 3. — *Sites of residual tumor > 1 cm after suboptimal cytoreductive surgery.*

Sites of residual tumor	No. of patients
Hepatic surface	4
Diaphragmatic peritoneum	2
Porta hepatis	1
Intersegmental fissure	4
Omentum	4
Gastrohepatic ligament	3
Gastrosplenic ligament	4
Peritoneal surfaces	5
Mesentery of the small intestines	8
Lymph node at suprarenal level	4
Metastasis to the hepatic parenchyma	1
Pleural and pulmonary fields	2
Serosa of the intestines	2

Fig. 1a

Fig. 1b

Fig. 1c

Figure 1. — Contrast-enhanced CT findings: liver surface and diaphragmatic implants (arrows). (a); omental tumor extension to spleen and implants in the porta hepatis (arrows). (b); implants in the intersegmental fissure (arrow) (c).

patients with early-stage disease who had optimal cytoreduction were correctly predicted by CT criteria. However, all of the six incorrect predictions were observed in the patients with advanced stage disease, including three false-positive and three false-negative results. When compared to outcome of the surgery, it was found that defined imaging criteria of CT findings could predicte optimal cytoreduction with 83.3% (15/18) sensitivity, 90% (27/30) specificity and 87.5% (42/48) accuracy. PPV and NPV values were 83.3% (15/18) and 90% (27/30), respectively. Kappa analysis revealed that there were very high correlations between CT imaging criteria and outcome of the surgery in terms of predicting suboptimal cytoreduction ($\kappa = 0.726$, $Z = 4.925$, $p < 0.001$).

Each of the CT imaging criteria used for predicting suboptimal surgical outcome was tested according the surgical findings of the patients by Fisher's exact test and the results are given in Table 4. The mesenteric tumors observed by CT scan had a statistically significant association with the surgical findings ($p < 0.001$), while intersegmental fissures, gastrosplenic ligaments, diffuse peritoneal thickening, and lymph nodes at the suprarenal level were found to have moderately significant correlations ($p < 0.05$).

Table 4. — *Univariate analysis of CT criteria used for predicting suboptimal cytoreduction*.

CT criteria	No. of patients	*p*
Implant > 1 cm on the mesentery	9	0.001
Implant > 1 cm within the intersegmental fissure	4	0.019
Implant > 1 cm on the gastrosplenic ligament	4	0.019
Diffuse peritoneal thickening	6	0.019
Lymph node > 1 cm at the suprarenal level	4	0.019
Implant > 1 cm on the gastrohepatic ligament	3	0.054
Pulmonary-pleural nodule > 1 cm	2	0.054
Implant > 1 cm on the hepatic surface	5	0.069
Encasement of the intestines by the tumor and involvement of the serosa	2	0.148
Extension of the omentum towards the spleen-stomach	4	0.284
Implant > 1 cm within the porta hepatis	1	0.391
Hepatic metastasis	1	0.391
Invasion of the abdominal wall	1	0.391
Implant > 1 cm on the diaphragmatic peritoneum	3	0.552
Pericardiac lymph node > 1 cm	2	1

Discussion

Ovarian cancers present a great challenge to clinicians in terms of treatment, as most of them are diagnosed in advanced stage disease with a high mortality rate. Optimal cytoreduction during primary surgery, which evidently determines the success of adjuvant chemotherapy and survival, is the mainstay in the management of these patients [15]. Suboptimal cytoreduction can not only increase the mortality and morbidity of the patients due to surgery, but also delay the chemotherapy and decrease its effectivenes. Moreover, it was reported that chemotherapy given after suboptimal cytoreduction was no more effective than the chemotherapy given alone without any surgical attempt, as a neoadjuant agent for palliation [20]. Meantime, it has been emphasized that

Fig. 2

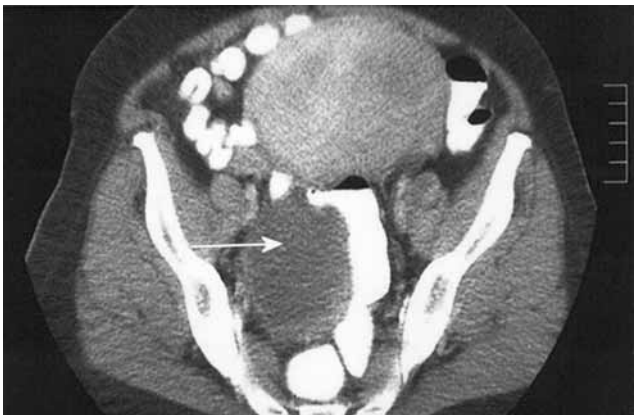

Fig. 3

Fig. 4

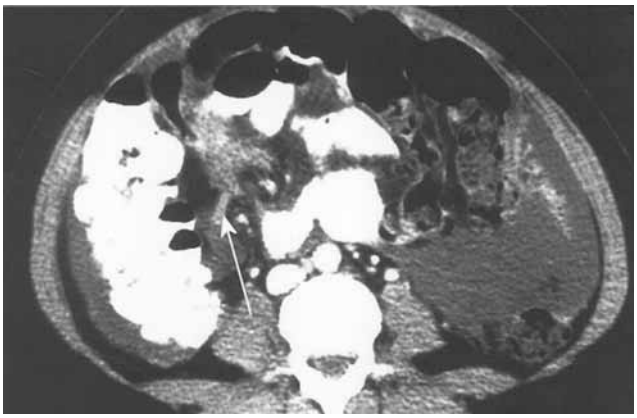

Figure 2. — Contrast-enhanced CT shows pelvic mass surrounding sigmoid colon (arrow). Optimal resection was not achieved due to involvement of the sigmoid colon serosa at surgery.

Figure 3. — Contrast-enhanced CT shows ovarian mass including massive calcification (arrow). Optimal resection was not achieved due to invasion of the lateral wall of the pelvis at surgery.

Figure 4. — Contrast-enhanced CT shows multiple implants within small bowel mesentery (arrow). At surgery mesenteric involvement could not be confirmed. Again examination demonstrated that the implants were inadequate for small bowel opacification.

success of a surgical effort for achieving optimal cytoreduction could increase when performed after neoadjuvant chemotherapy as an interval surgery [21, 22].

Several studies in the literature have attempted to define a preoperative imaging method which accurately predicted the surgical outcome of patients with advanced stage ovarian cancer and prevented suboptimal cytoreduction [8]. Nelson *et al*. first investigated the efficacy of preoperative CT for prediction of the surgical outcome of patients with epithelial ovarian cancer by using eight radiographic criteria of "inability to perform optimal cytoreduction" to < 2 cm residual disease in 1993 [17]. Meyer *et al*. employed a simple scoring system of five anatomic disease sites to predict surgical outcome and reported a diagnostic efficacy ranging from 58% to 100% in a retrospective study including 28 patients with ovarian carcinoma [16]. Bristow *et al*. reported that suboptimal surgery with residual tumor > 1 cm could be predicted with a sensitivity, specificity and accuracy of 100%, 85% and 92.7%, respectively, by using a very complex CT scoring system [8]. Byrom *et al*. proposed a simple method that could be used in clinical practice whereby residual disease < 0.5 cm was considered optimal cytoreduction and found a sensitivity and PPV of 88% and 85%, respectively [19]. However, most patients included in this study had benign or early-stage diseases. Other studies, using similar imaging methods also reported a diagnostic efficacy ranging from 52% to 99% for prediction of residual disease ranging from > 1 cm to > 2 cm [7, 18].

In this study, a simple method was defined by evaluating preoperative abdominal-pelvic CT images and observing multiple tumor nodules > 1 cm in the 15 critical areas including peritoneal and nodal areas, and hepatic, pulmonary and abdominal wall metastasis were used for prediction of suboptimal cytoreduction with residual tumor > 1 cm. Fifteen of the 18 patients who had suboptimal surgical cytoreduction were successfully predicted by CT with a sensitivity of 83.3%. There were three false-negative results in which complete resection was not possible at surgery while CT had predicted complete resectability. One of these patients had invasion of the lateral wall of the pelvis (Figure 2), another had residual tumor > 1 cm due to involvement of the sigmoid colon serosa (Figure 3), one had tumor deposits > 1 cm on the mesentery and involvement of the abdominal and pelvic parietal peritoneum thicker than 4 mm. Among the 30 patients who achieved optimal surgical cytoreduction, 27 were correctly predicted by CT with a specificity of 90%. The accuracy rate of the defined method was calculated to be 87.5%. There were three false-positive CT imaging results including one patient with omental infiltration to the spleen and mesenteric tumor nodules > 1 cm (Figure 4), two patients with tumor nodules > 1 cm on the diaphragmatic peritoneum and hepatic surface or pericardiac lymph node > 1 cm. Omental infiltration to the spleen was resected completely by total omentectomy and splenectomy, however, mesenteric tumor nodules could not be verified surgically. Two of the false-negative

results with mesenteric nodules were due to inadequate small bowel opacification, as these patients with Stage IV disease and terminal health status could not take oral contrast agent before the CT scan. For the other false-negative results with the peritoneum, hepatic surface or pericardiac nodal metastasis, pelvic and serosal involvement were believed to be due to the CT technique used in the study and could be eliminated by a thin-section CT scan.

Considering that all patients with early-stage disease achieved optimal cytoreduction, the potential of CT to predict suboptimal surgery has practical importance only in patients with advanced stage disease. Of the 35 patients with advanced-stage disease, 18 had suboptimal and 17 had optimal surgical cytoreduction. Although, all false-negative results were obtained in advanced stage disease, CT was able to predict the outcome correctly in 15 of the 18 patients with suboptimal and 14 of the 17 patients with optimal cytoreduction. Based on these data, sensitivity, specificity and accuracy rates were calculated as 83.3%, 82.3%, and 82.8% respectively. Kappa analysis revealed a very high level of agreement between the success of CT to predict surgical and prognostic outcomes in patients with advanced-stage disease (κ = 0.749, Z = 4.237, $p < 0.001$).

When the significance of the predictors of suboptimal disease were explored, omental and mesenteric diseases, diffuse peritoneal thickening, and diaphragmatic disease and large intestine mesenteric implants were defined as the most significant predictors of suboptimal disease [7, 19, 24]. This study also revealed that the mesenteric disease > 1 cm was the most significant parameter for predicting suboptimal surgery and when obtained preoperatively, the risk of suboptimal cytoreduction increased by 12-fold.

One of the main difficulties in improving any one of the acceptable models that predict surgical outcome in patients with advanced-stage ovarian cancer is the personal philosophy and diligence of the surgeon in achieving maximal cytoreduction and his/her ability to perform advanced surgical techniques [23]. The success rate of primary cytoreduction in advanced-stage ovarian cancer is considerably variable and depends on personal and institutional treatment philosophy and experience. The optimal cytoreduction ratio is in the range of 33% to 90% in centers with expertise in cytoreductive surgery [11, 12]. The rate of optimal cytoreduction in this series of patients (48.5%) was lower than that mentioned in the literature, as most of the patients with advanced disease were reluctant to have organ resection and colostomy or urinary diversion, and did not give informed consent for these procedures due to their cultural and religious beliefs [7, 24].

Conclusion

The results of this study suggest that CT could be used successfully for predicting suboptimal cytoreduction in primary ovarian cancer patients. However, preoperative CT criteria used for predicting surgical outcome might be rearranged for different institutions, as the result of surgical effort mostly depends on the surgical experience and philosophy of each institution and the desire of the patients of that society.

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