What is the appropriate use of CT in combination with tumor marker and medical examination findings in the follow-up of postoperative patients with ovarian cancer?

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Abstract

Background

The aim of this study was to establish the appropriate use of CT in combination with tumor marker and medical examination findings in the follow-up of postoperative patients with ovarian cancer based on the recurrence pattern in CT imaging and clinical findings.

Methods

The subjects were 194 consecutive patients with primary ovarian cancer treated at our hospital between 2014 and 2019. Recurrence patterns on chest and abdominopelvic CT images obtained for routine postoperative follow-up were evaluated retrospectively to optimize scan range. Medical records were reviewed to determine whether clinical signs and symptoms (patient-reported symptoms and transvaginal ultrasound findings) and tumor markers levels can be sufficiently reliable indicators of recurrence.

Results

A total of 890 CT examinations were performed for the 194 patients. Data from the 146 patients with no residual disease at the first CT after standard treatment were analyzed. Recurrence was detected by CT in 15 patients: abdominopelvic recurrence alone in 12 patients, and concurrent chest and abdominopelvic recurrence in 3 patients (2.1%). Abdominopelvic recurrence preceded chest recurrence in all cases. At the time of CT-based recurrence, 13 patients (87%) had medical examination findings and/or elevated tumor markers, while the remaining 2 patients had neither.

Conclusions

Regular medical examination and tumor markers were useful for detecting recurrence, but overlooked 13% of patients with recurrence. This indicates that routine abdominopelvic CT is essential for follow-up. However, routine chest CT may not be beneficial unless abdominopelvic recurrence is seen.

Background

Ovarian cancer ranked as the 8th most common cancer diagnosis and cause of cancer death in 2018, causing an estimated 184,000 to 295,000 deaths worldwide.[1] Ovarian cancer is treated by surgery to determine the histological type and pathological stage, followed by postoperative chemotherapy if necessary. Ovarian cancer responds well to initial treatment; however, even in stage I, about 10% of patients relapse within 5 years.[2]

Due to inadequate evidence regarding routine follow-up imaging studies for ovarian cancer patients, specific recommendations regarding scan range and timing have never been established, even in guidelines of the National Institutes of Health[3] (NIH) and the National Comprehensive Cancer Network[4] (NCCN). As computed tomography (CT) is often used as the standard imaging modality, radiation exposure must be minimized by optimizing the scan range and the timing of CT. If evaluation of the recurrence pattern of ovarian cancer indicated that chest metastases are only observed in certain patients, routine chest CT could be omitted for other patients, which would reduce total radiation exposure during post-treatment follow-up. The CT follow-up interval, and by extension the number of follow-up scans, could also be reduced if tumor marker levels and medical examination findings including patient symptoms and transvaginal ultrasound findings were reliable enough to predict recurrence, because CT could be considered solely for patients with concerning findings.

Therefore, the aim of our study was to establish the appropriate use of CT in combination with tumor marker and medical examination findings in the follow-up of postoperative patients with ovarian cancer based on the recurrence pattern in CT imaging and clinical findings.

Materials And Methods

Patients

This was a retrospective study of 233 consecutive patients with primary ovarian cancer who underwent initial surgery at our hospital between January 2014 and February 2019. Patients who never underwent CT examination (n = 14), patients with double primary cancer (n = 21), and patients whose follow-up was interrupted (n = 4) were excluded, leaving 194 patients included for analysis.

All patients who were candidates for optimal or complete surgery underwent staging laparotomy and debulking surgery. When primary debulking surgery was judged unfeasible, tumor stage was determined by laparoscopic biopsy, ascitic fluid cytology, and pleural fluid cytology based on CT findings, and interval debulking surgery was performed after neoadjuvant chemotherapy. The pathologic stage was determined by a gynecological pathologist at our hospital. Postoperative chemotherapy was performed depending on postoperative results. All patients were exclusively followed by gynecologists at our hospital, and were referred for chest and abdominopelvic CT scans as part of routine follow-up. Radiologic and clinical follow-up periods ranged between 4 and 68 months, with a median period of 27.5 months. Table 1 summarizes the stage at diagnosis, age, CT follow-up interval, and the histology of ovarian cancer. There were 102 patients with FIGO stage□, 14 with stage II, 55 with stage III, and 23 with stage IV. The histological types were serous carcinoma (n = 80), mucinous carcinoma (n = 26), endometrioid carcinoma (n = 29), clear cell carcinoma (n = 41) and other (n = 18). The average age at diagnosis was 54.3 years, and average CT follow-up interval was 8.0 ± 5.7 months.

Table 1
Histologic profile, FIGO stage, and follow-up duration in 194 patients

	FIGO Stage				Total
	I	II	III	IV	
Serous	25	5	34	16	80
Mucinous	24	0	2	0	26
Endometrioid	16	4	7	2	29
Clear cell	27	3	9	2	41
Other	10	2	3	3	18
Total	102	14	55	23	194
Average age (years)	51.8	53.6	60.7	52.3	54.3
CT follow-up interval (in months, mean ± SD)	10.3 ± 6.5	7.0 ± 2.2	5.3 ± 3.3	5.2 ± 2.4	8.0 ± 5.7

Data analysis

This was a retrospective study conducted with the approval of an ethics review board. Contrast-enhanced CT using non-ionic iodine-containing contrast agent administered intravenously was performed in addition to plain CT unless contraindicated. All axial CT images acquired from 0.5-mm collimation reconstituted with a slice thickness of 2 mm were initially interpreted by diagnostic radiologists, but were also re-interpreted by two radiologists (H.M. and G.N.; 4 and 16 years of experience as a radiologist, respectively) who were unaware of the patient's cancer antigen (CA)-125 and CA19-9 levels to assess for subtle recurrence. A consensus reading was performed when the findings were equivocal. Multiplanar images were reviewed whenever axial images were insufficient to confirm whether the lesion should be regarded as a recurrence. Then, findings of the chest and abdominopelvic CT from the first to the last scan for each patient were analyzed. Medical examination findings including symptoms (respiratory distress and abdominal distension), transvaginal ultrasound findings (ascites or pelvic tumor), and levels of tumor markers including CA-125 and CA19-9 were obtained from patients' medical records.

Criteria for CT features of recurrence or metastasis

Our criteria for CT features of recurrence or metastasis were as follows:

1. A lesion that grows over time irrespective of adjuvant chemotherapy
2. A lesion that decreases in volume after chemotherapy
3. Increasing unilateral pleural effusion, or cardiophrenic lymph nodes with a short axis ≥ 5 mm
4. Lymphadenopathy of other (not cardiophrenic) lymph nodes with a short axis ≥ 1 cm in diameter

Transient consolidation and interstitial changes in the lung fields were regarded as inflammatory changes.

Definition of tumor marker elevation

Tumor markers (CA-125 and CA19-9) were measured at each visit, within 2 weeks of a CT scan. Recurrence was defined as three consecutive increases in a tumor marker.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) for the presence of recurrence were calculated for tumor markers alone, transvaginal ultrasound alone, and the combination of the two. AUC was calculated by logistic regression analysis. JMP® Pro 15.1.0 was used to conduct all the statistical analyses.

Outcome measures

The following were evaluated for the group with no residual disease on the first CT after standard treatment, with or without chemotherapy:

1. Recurrence site category, which was classified as abdominopelvic cavity only, chest only, and both sites on CT according to surgical stage.
2. Presence of signs of recurrence at the latest examination (transvaginal ultrasound, tumor marker) when recurrence was noted on CT.
3. Diagnostic performance (sensitivity, specificity, PPV, NPV, and AUC) of tumor markers alone, transvaginal ultrasound alone, and the combination of the two for detection of recurrence.

Results

A total of 890 CT scans with a scan range from chest to pelvis were obtained for the overall group of 194 patients. The average number of CT scans was 4.59 per patient (range, 1–19 scans), and 111 patients (57.2%) had more than 4 scans. Among the total of 194 patients, 146 patients showed no residual disease on the first CT after standard treatment. A total of 539 CT examinations were performed for those 146 patients. Figure 1 shows the ovarian cancer treatment protocol and patient selection.

1. Recurrence site by surgical stage

The stage of the 146 patients was stage I for 102 patients, stage II for 14 patients, and stage III for 30 patients. Fifteen patients had recurrence (stage I: n = 6, 5.9%; stage II: n = 2, 14.3%; stage III: n = 7, 23.3%). Median time to recurrence was 16.1 months (9.9–51.0 months) overall, 16.1 months (12.2–35.8 months) for stage I, 14.4 months (11.3–17.5 months) for stage II, and 16.6 months for stage III. Twelve of these patients had abdominopelvic recurrence only (stage I: n = 4, 3.9%; stage II: n = 2, 14.3%; stage III: n = 6, 20.0%), and 3 had both chest and abdominopelvic recurrence (stage I: n = 2, 2.0%; stage II: n = 0; stage III: n = 1, 3.3%). In all these 3 patients, abdominopelvic recurrence preceded chest recurrence. No patient had

only chest recurrence. The forms of chest recurrence were pleural effusion (n = 1), cardiophrenic lymph node (CPLN) metastasis (n = 2), left supraclavicular lymph node (SLN) metastasis (n = 1), and parasternal lymph node (PSLN) metastasis (n = 1). The pleural effusion was proven to be malignant by cytology. Moreover, in all 3 patients, these findings were visible within the range of the abdominopelvic CT. These results are summarized in Tables 2and 3.

Table 2
Number of patients with recurrence on chest and abdominopelvic CT

FIGO stage	I	II	III	Total
Number	102	14	30	146
Recurrence (%)	6 (5.9)	2 (14.3)	7 (23.3)	15(10.3)
Chest only (%)	0	0	0	0
Abdominopelvic only (%)	4 (3.9)	2 (14.3)	6 (20.0)	12 (8.2)
Both chest and abdominopelvic (%)	2 (2.0)	0	1 (3.3)	3 (2.1)

2. Signs of recurrence at the latest examination

Six of the 15 patients with recurrence (40%) showed signs of recurrence including ascites (n = 4) and pelvic mass (n = 4) on transvaginal ultrasound or respiratory distress (n = 1) in their latest medical examinations when recurrence was detected on CT. Eleven of these 15 patients (73.3%) had elevated tumor markers, and 4 (26.7%) had both medical examination findings and elevated tumor markers. In other words, medical examination findings or tumor marker levels suggested recurrence in 13 patients (86.7%), but not in the remaining 2 patients (13.3%). Both of those patients were in stage Ic. In 3 of the 4 patients whose tumor markers were within the normal range at the initial diagnosis, tumor markers were not elevated at the time of recurrence (Patients No. 3, 6, and 7 in Table 3). In the remaining patient, only minimal elevation of CA125 (35.8 U/mL) was observed at the initial diagnosis (Patient No. 5 in Table 3). Tumor markers were elevated in 4 of the 8 patients in stage I/II (50%), but in all 7 patients in stage III (100%). These results are summarized in Table 3.

Table 3. Examination findings, tumor markers, and CT findings at the time of recurrence in 15 patients with recurrence.

Patient No.	FIGO Stage	Examination findings	Preoperative TM elevation	TM elevation		Preceding abdominal recurrence	Chest recurrence
				CA19-9	CA125		
1	Ic	Ascites, Mass Respiratory distress	No	No	Yes	Ascites, PD	Pleural effusion
2	Ic	Ascites	CA19-9 CA125	No	Yes	Ascites, PD, PAN	CPLN, SLN
3	Ia	Mass	No	No	No	PD	None
4	Ic	N/A	CA125	No	Yes	PD	None
5	Ic	N/A	CA125	No	No	PD	None
6	Ic	N/A	No	No	No	PLN, ILN	None
7	IIa	Mass	No	No	No	PD	None
8	IIc	N/A	CA125	No	Yes	PD	None
9	IIIc	N/A	CA125	Yes	No	PD	None
10	IIIb	Ascites	CA125	No	Yes	PD	None
11	IIIc	Ascites, Mass	CA125	No	Yes	PD	None
12	IIIa	N/A	CA19-9	No	Yes	PAN	None
13	IIIa	N/A	No	No	Yes	PAN	None
14	IIIc	N/A	CA125	No	Yes	PAN	None
15	IIIc	N/A	CA125	No	Yes	PD, PAN	CPLN, PSLN

TM: Tumor marker

Mass: Pelvic mass

PD: Peritoneal dissemination

PAN: Para-aortic lymph node

PLN: Pelvic lymph node

ILN: Inguinal lymph node

CPLN: Cardiophrenic lymph node

SLN: Supraclavicular lymph node

PSLN: Parasternal lymph node

N/A: No sign of recurrence

3. Diagnostic performance of tumor markers, transvaginal ultrasound, and the combination of the two for detection of recurrence

The sensitivity of tumor markers for detecting recurrence was 73.3% (11/15), specificity was 97.7% (128/131), PPV was 78.6% (11/14), NPV was 97% (128/132), and AUC was 0.86. The sensitivity of transvaginal ultrasound was 33.3% (5/15), specificity was 97.7% (128/131), PPV was 62.5% (5/8), NPV was 92.8% (128/138), and AUC was 0.69. The sensitivity of the combination of tumor markers and transvaginal ultrasound was 86.7% (13/15), specificity was 95.4% (125/131), PPV was 68.4% (13/19), NPV was 98.4% (125/127), and AUC was 0.91. These results are summarized in Table 4.

Table 4. Performance of tumor markers, transvaginal ultrasound, and the combination of the two in detection of recurrence.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Tumor markers only	73.3	97.7	78.6	97	0.86
Transvaginal ultrasound only	33.3	97.7	62.5	92.8	0.69
Both	86.7	95.4	68.4	98.4	0.91

PPV: Positive predictive value

NPV: Negative predictive value

AUC: Area under the curve

Discussion

In this study, we identified two important clinical features of postoperative ovarian cancer. The first is that chest metastasis was never detected alone, and was always preceded by abdominopelvic recurrence. Second, either medical examination findings or tumor marker levels suggested recurrence in 13 of the 15 patients with recurrence (87%), but not in the remaining 2 patients.

Regarding the first clinical feature, 2 of our 3 patients with chest metastases originally had stage I disease, but abdominopelvic recurrence preceded chest recurrence in all 3 of them. Hematogenic spread is a rare route of metastasis in ovarian cancer,[5] in contrast to lymphatic metastasis and metastasis to the adjacent organs, which are the most common routes.[6] In our study, one patient (Patient No. 1), had peritoneal dissemination (PD) and para-aortic lymph node (PAN) metastasis preceding CPLN and supraclavicular lymph nodes (SNL) metastasis, and another patient (Patient No. 15) also had PD and PAN metastasis preceding CPLN and PSLN metastasis. These facts imply that the cancer spread from abdominopelvic lymph nodes to thoracic lymph nodes through the lymphatic tract. This result indicates that routine chest CT can be eliminated, and it may be reasonable to add chest CT only after detection of abdominopelvic recurrence on abdominopelvic CT. Such a strategy could reduce radiation exposure and radiologists' reporting workload, and eliminate the additional medical costs for having radiologists create reports for unnecessary chest CT scans.[7]

There are two previous studies similar to our study. Sella et al. reported the rate of lung metastasis from ovarian cancer was 6% in 82 patients with stage III or IV disease.[8] The lower incidence of lung metastasis (2.1%) in our study can be explained by inclusion of patients with stage I and II disease, which is unlikely to metastasize to the lungs. In previous studies, pulmonary metastases tended to be preceded either by abdominopelvic disease[9, 10, 11] or a rise in tumor markers.[8] This result is consistent with our study. On the other hand, Dachman et al. observed chest metastases without abdominopelvic recurrence in six (2.7%) of 226 follow-up CT scans.[12] This is in conflict with our study, but we presume they were unable to detect the abdominopelvic disease in those six patients because their CT scan sensitivity (7–10 mm collimation) was too low to depict small implants. Thin slices and axial and multiplanar reconstructed images have been reported to be useful in detection of small implants.[13]

Regarding the second clinical feature, 13 of 15 patients with recurrence (87%) had signs of recurrence in their medical examination findings or tumor marker levels, which indicates that clinical examinations such as medical examination findings and tumor marker elevation are useful to identify signs of recurrence. However, the fact that the remaining 2 patients had none of those signs implies the need for routine abdominopelvic CT scan regardless of results of tumor marker levels and medical examination findings.

Although transvaginal ultrasound is a noninvasive examination that is easily performed and effective in detecting ascites and Douglas fossa dissemination,[14] it has some inherent limitations. It cannot always detect peritoneal dissemination due to its low sensitivity,[15] and cannot detect pelvic or para-aortic lymphadenopathy and inguinal lymphadenopathy because of its limited field of view. In our study, transvaginal ultrasound showed low sensitivity, specificity, and AUC for detection of recurrence of ovarian cancer (sensitivity: 33.3%, specificity: 97.7%, and AUC: 0.69).

In our study, only one patient among the 15 symptomatic patients with recurrence had respiratory distress. In previous studies, very few patients first presented with symptoms,[16] and very few recurrences

were detected by symptoms alone.[17] These results are consistent with our results and demonstrate that detection of recurrence by symptom monitoring may be difficult.

A multicenter European trial concluded that treating recurrences only based on detectable CA-125 levels in patients who are asymptomatic is not associated with increased survival and is associated with decreased quality of life,[18] but many other studies[19,20] have indicated that CA-125 is useful for the detection of ovarian cancer recurrence, although they used various thresholds. In our study, tumor markers (CA19-9 and CA-125) showed higher sensitivity, equal specificity, and higher AUC for detection of ovarian cancer recurrence (sensitivity: 73.3%, specificity: 97.7%, and AUC: 0.86) than transvaginal ultrasound. This was especially true for stage III tumors: all patients (7/7) in that stage had elevated tumor markers. In patients with stage III ovarian cancer, tumor marker levels might be reliable enough to predict recurrence, and even routine abdominopelvic CT might be omitted until tumor markers become elevated. However, our sample size is too small to draw a conclusion. When tumor markers and transvaginal ultrasound were combined, the sensitivity was 86.7%, the specificity 95.4%, and the AUC 0.91. These values are all better than transvaginal ultrasound alone and tumor markers alone, but they cannot completely predict recurrence. As a result, routine abdominal CT is unavoidable to detect recurrence during follow-up for ovarian cancer.

Our study has two limitations. First, most of the positive findings of recurrence and metastasis were based on our criteria, not pathological examination. However, in clinical practice, chemotherapy is started when CT findings indicate distant metastasis as biopsy to obtain a histological specimen of a recurrent lesion is invasive. Second, our study is a single-center retrospective study in Japan. The distribution of histological types of ovarian cancer within our patient group is similar to that in Asia, but serous carcinoma is the most common type in Europe and North America.[21] Most patients with ovarian cancer present with stage III disease per FIGO staging,[22] but in our study over half of patients presented with stage □ disease. This may be because pelvic examinations using transvaginal ultrasound even for screening have become routine and more cases of asymptomatic ovarian cancer were detected in an earlier stage.[23] Therefore larger scale multicenter studies are needed to support our findings.

Conclusions

Regular medical examination findings and tumor markers were useful for identifying recurrence in ovarian cancer patients after surgery, but still overlooked 13% of patients with recurrence. Therefore, routine abdominopelvic CT must be performed in postoperative follow-up regardless of tumor marker levels and medical examination findings. However, routine chest CT may not be beneficial unless abdominopelvic recurrence is seen.

Abbreviations

OC
ovarian cancer

NIH
National Institutes of Health
NCCN
National Comprehensive Cancer Network
CT
computed tomography
CA
cancer antigen
PPV
positive predictive value
NPV
negative predictive value
AUC
area under the curve
CPLN
cardiophrenic lymph node
SLN
supraclavicular lymph node
PSLN
parasternal lymph node
PD
peritoneal dissemination
PAN
para-aortic lymph node
SNL
supraclavicular lymph nodes.

Declarations

Ethics approval and consent to participate

This was a retrospective study conducted with the approval of the ethics committee of Osaka Medical Pharmaceutical University (No. 2020-104) and operated in compliance with the Helsinki Declaration. Informed consent was obtained by allowing patients to opt out of the study on the hospital website.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed 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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Not applicable.

Authors' contributions

H.M. and G.N. corrected clinical data and drafted the manuscript. S.F. and M.O. provided clinical information. S.T. and K.Y. helped with editing the manuscript. K.O. supervised and revised the final version of the manuscript.

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Figures

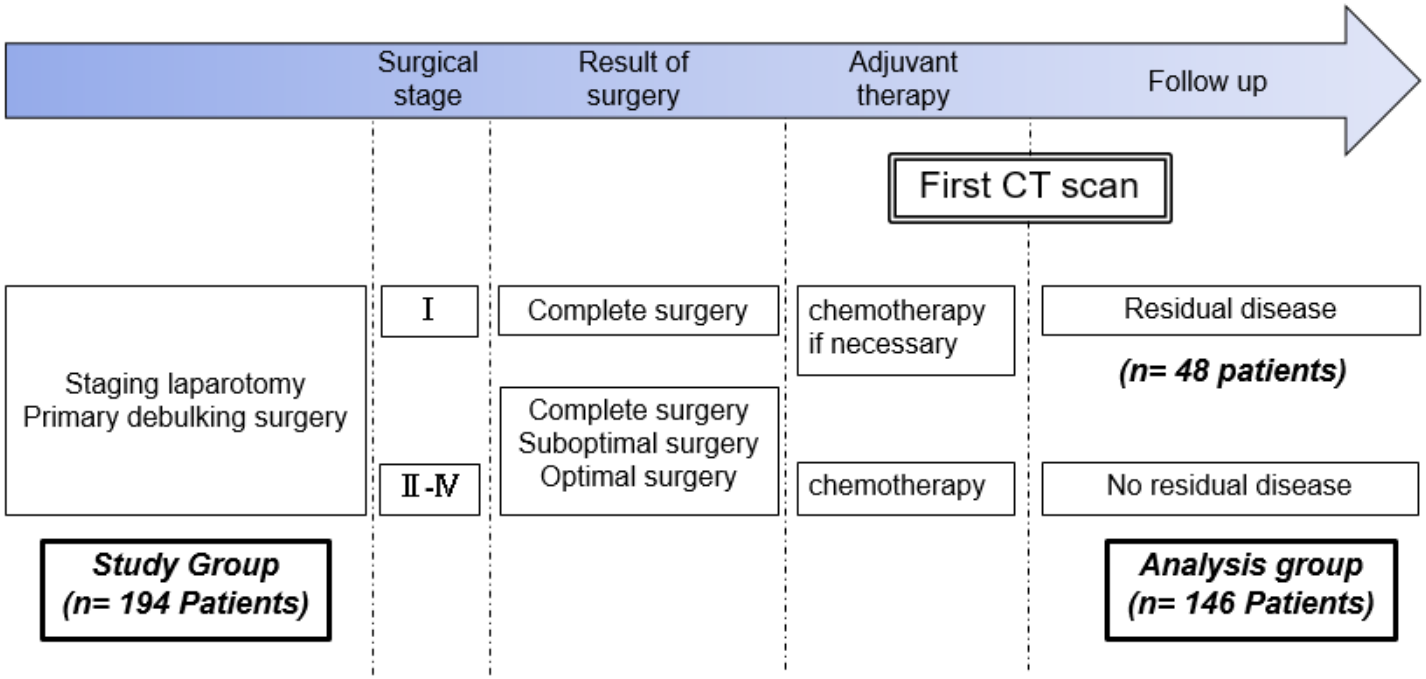

Figure 1

Flowchart showing ovarian cancer treatment process and the selection of patients