

Evaluation of CA125, Physical and Radiological Findings in Follow-up of Ovarian Cancer Patients

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Abstract. *The majority of ovarian cancer patients will suffer from intraabdominal relapse within the first five years after surgery. Today various diagnostic tools, including ultrasound or CT, are available to detect an ovarian cancer recurrence. Radiological examinations at regular time-intervals may lead to the detection of tumor relapse, however these procedures have limited sensitivity and specificity. Moreover, imaging procedures are costly. CA125 is a tumor marker with high sensitivity in ovarian cancer patients. Tumor marker determination is a simple, reproducible technique, and may therefore be useful in routine follow-up in ovarian cancer patients, supplemented with additional imaging procedures. In a retrospective analysis of 58 patients with recurrent ovarian cancer, the sensitivity of clinical examination and tumor marker analysis was compared to radiological findings. Physical interview and physical examination were performed for all patients. CA125 levels were determined in 54 out of 58 patients at the time of diagnosis of recurrence. Forty-seven out of 58 patients received a vaginal ultrasound and 42 were examined by CT scan. In 45 out of 54 (83%) patients, CA125 was elevated at the time of recurrence. In 45 out of the 58 (78%) patients, a tumor was detected by physical examination. Forty-two out of the 58 patients had CT scans. Pathological findings were seen in 33 out of these patients (80%) Ultrasound revealed tumor recurrence in 33 out of 47 patients (70%). By a follow-up based on physical*

examination and CA125 determination, 53 out of 54 (98%) patients with recurrences could be identified. In patients with a pelvic recurrence, vaginal examination had the highest sensitivity in comparison to vaginal ultrasound and CT scan. Imaging techniques did not add clinically relevant information during follow-up and should therefore only be performed prior to surgical or therapeutical intervention.

Today ovarian cancer is one of the most frequent causes of cancer-related death in women (1). The majority of ovarian cancer patients is diagnosed at FIGO III stage with bulky disease in the abdominal cavity. Standard therapy in these patients is based on radical surgery to remove all visible tumor followed by adjuvant chemotherapy containing platinum and taxane regimens (1). However, despite these radical therapeutic strategies, the majority of ovarian cancer patients will suffer from intraabdominal relapse within a few years after surgery. Early detection of relapse may improve the outcome. Today various techniques are performed in clinical routine to detect an ovarian cancer recurrence. Radiological examinations at defined intervals may lead to the detection of tumor relapse, however the sensitivity and specificity of these procedures are not necessarily adequate. Furthermore, CT scans or ultrasound examinations at defined time-intervals are costly and no survival benefits have yet been demonstrated.

CA125 is a tumor-related antigen, which is elevated in the serum of most ovarian cancer patients (2, 3). The serum level of CA125 correlates with the tumor burden. An increase of CA125 levels indicates progression in ovarian cancer patients during clinical course. Since tumor marker determination is a simple, reproducible technique, routine follow-up in ovarian cancer patients by serial CA125 measurements may replace imaging techniques at

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Table I. Characteristics of patients.

Median age	58	Range (25-85)
FIGO	n	percent
I	10	(17.2)
II	5	(8.6)
III	33	(56.9)
IV	5	(8.6)
Unknown	5	(8.6)
Grading	n	percent
1	18	(31.0)
2	17	(29.0)
3	20	(34.5)
unknown	3	(5.2)
Histology	n	percent
Serous adenocarcinoma	32	(55.2)
Endometrioid adenocarcinoma	4	(6.9)
Clear cell adenocarcinoma	4	(6.9)
Mucinous adenocarcinoma	2	(3.4)
Other	16	(27.2)
Primary cytoreductive outcome	n	percent
R0	23	(39.7)
R1	16	(27.6)
R2	6	(10.3)
Unknown	13	(22.4)

regular time-intervals during follow-up. In a retrospective analysis of 58 patients with recurrent ovarian cancer, the sensitivity of tumor marker analysis and physical findings were compared to radiological findings.

Materials and Methods

In a retrospective analysis, the sensitivity of serial tumor marker measurement compared to physical and radiological findings were evaluated in 58 patients with recurrent ovarian cancer. The clinical characteristics are shown in Table I. Patients with early recurrences (within the first 12 months after surgery), as well as all patients with incomplete follow-up, were excluded. Follow-up examinations were performed at 3-month intervals for the first 2 years after surgery. Thereafter patients were seen at 6-month intervals in our outpatient department. At each follow-up visit physical and gynecological vaginal examination, serum tumor marker analysis for CA125 and vaginal ultrasound examination were performed. Abdominal ultrasound and CT scans were performed in patients considered to have a recurrence. Imaging techniques were also performed at regular intervals in patients who were enrolled in various clinical trials.

Results

The data of 58 patients with ovarian cancer recurrence were available. The majority of patients were at FIGO III stage at

Table II. Localization of tumor recurrence and CA125 status; more than one localization may apply.

Localization of recurrence	n	CA125	
		elevated	not elevated
Abdominal cavity, excluding pelvic recurrences	45	45	0
Pelvis	35	26	9
Lymph nodes supradiaphragmal	8	8	0
Lymph nodes infradiaphragmal	6	6	0
Lung	5	5	0
Other	1	1	0
Total number of patients	58 (100%)	45 (83%)	9 (17%)

Table III. Main symptoms reported by patients at the time of recurrence.

Symptoms	n	%
Well-being	23	40
Abdominal pain	13	22
Constipation	7	12
Enlarged lymph nodes	6	10
Ascites	4	7
Tiredness	4	7
Dyspnoea	1	2
Total	58	100

primary diagnosis (Table I). R0 resection could be achieved in 40% of the patients. Median disease-free survival was 19 months (95%-CI: 15-23). The majority of recurrences were pelvic recurrences followed by recurrences in other parts of the abdominal cavity (Table II). A physical interview and physical examination were performed for all patients. CA125 levels were determined in 54 out of the 58 patients at the time of diagnosis of recurrence. Forty-seven out of the 58 patients received a vaginal ultrasound and 42 were examined by CT scan.

Physical interview. At the time of diagnosis of the recurrence, 35 of the 58 (60%) patients complained about symptoms which were mainly abdominal pain (n=13, 22%) and constipation (n=7, 12%), followed by enlarged lymph nodes (n=6, 10%). A considerable number of patients (n=22, 40%) were free of symptoms and reported well-being (Table II).

Physical examination. The physical examination resulted in pathological findings in 45 of the 58 (78%) patients. The main physical findings were pelvic tumor masses (32

Table IV. Sensitivity and specificity of vaginal examination, ultrasound CT scan in ovarian cancer patients subdivided by occurrence of pelvic recurrence.

Diagnostic procedure	Pelvic recurrence n	Confirmed (%)	No pelvic recurrence n	Confirmed (%)
Vaginal examination	36	32 (89)	21	21 (100)
Vaginal ultrasound	30	24 (80)	17	17 (100)
CT scan	27	18 (67)	15	15 (100)

Table V. Frequencies of pathological findings (+ recurrences, - no recurrence) subdivided by diagnostic procedures in 54 patients.

Clinical interview n=54	Physical examination n=54	CA 125 n=54	Frequency (%)	Ultrasound n=44	CT scan n=39
-	-	-	1 (2)	n. p.	n. p.
-	-	+	6 (11)	1 / 6*	6 / 6*
+	-	+	5 (9)	0 / 4	1 / 4
-	+	-	5 (9)	5 / 5	2 / 3
+	+	-	3 (6)	2 / 2	0 / 1
-	+	+	10 (19)	5 / 7	5 / 6
+	+	+	24 (44)	18 / 20	17 / 19
32 (60%)	42 (77%)	45 (83%)	54 (100%)	31 (70%)	31 (79%)

* recurrence detected / number of patients who have received ultrasound and CT, respectively.

n.p.: not performed

patients), ascites (7 patients), enlarged lymph nodes (8 patients), or tumor infiltration of the rectum (2 patients). Recurrence was detected in 32 out of 36 (89%) patients with pelvic recurrence by vaginal gynecological examination (Table III).

CA125 determination. CA125 serum levels were available from 54 out of the 58 patients when recurrent disease was diagnosed. In 45 out of 54 (83%) patients, CA125 serum levels were elevated. CA125 started to increase about 5 months prior to the physical or radiological diagnosis of a recurrence. All nine patients with normal CA125 serum levels had a small local pelvic recurrence.

Ultrasound. In 47 out of 54 patients, vaginal and abdominal ultrasound was performed when recurrent disease was diagnosed. Thirty-three of the 47 patients (70%) had pathological findings. In 24 out of 30 (80%) patients with pelvic recurrence a tumor relapse was suggested by sonographic findings (Table IV). In the remaining 6 patients, the recurrence could not be detected by vaginal ultrasonography. Seventeen patients, with recurrence not involving the pelvis, had regular vaginal ultrasound results.

CT scan. Forty-two patients received CT scans of the pelvis and abdomen. Tumor recurrence was detected in 33 of these (80%) patients. CT scans confirmed recurrence in 18 out of 27 (66%) patients with a pelvic tumor (Table IV). All patients with no evidence of pelvic recurrence had regular CT findings.

Sensitivity of CA125, physical examination and radiological procedures. In 54 out of 58 patients clinical interview, vaginal examination and CA125 determination was performed at the time of diagnosis of recurrent disease. In the remaining 4 patients, the CA125 concentrations were not determined. However, the recurrence in these 4 patients was detected by physical examination and/or clinical interview (data not shown). Considering only the 54 patients in the final analysis, the combination of physical examination, gynecological examination and CA125 determination was able to identify 53 out of 54 (98%) patients with ovarian cancer recurrence without any imaging techniques (Table V). In one patient the recurrence was diagnosed during second-look surgery. Since there was no pathological finding in the preoperative staging, no imaging techniques were performed. CA125 had the highest sensitivity, followed by CT scan and physical examination.

Sensitivity of vaginal examination and imaging procedures in patients with pelvic recurrence. The diagnostic impact of imaging techniques, such as vaginal ultrasound and CT scans in comparison to physical examination were separately analyzed in patients with pelvic recurrence (n=36). The highest sensitivity was obtained by vaginal examination followed by vaginal ultrasound and CT scan. None of these procedures provided false-positive results.

Discussion

Although long-term survival of ovarian cancer patients appears to have improved over the last decade, still a major percentage of these patients suffers from tumor relapse (1). In patients with ovarian cancer recurrence curative treatment has not been achieved. Therefore maintaining a high quality of life is one of the major objectives.

Follow-up examinations in ovarian cancer patients are performed to determine tumor recurrence, the side-effects of therapy as well as to maintain the quality of life of the patient. Examination should be limited to procedures with only minor interference with the patient's daily life. They should also be highly reproducible in order to avoid inter-observer error. Scheduled follow-up examinations using imaging techniques such as vaginal ultrasound and CT scans at regular intervals may lead to the detection of a recurrence. However, it can be doubted, whether patients do benefit from the results of these imaging procedures. Therefore these procedures should not be included into standard follow-up examinations and be limited to patients in which a tumor recurrence is already suspected.

The determination of CA125 in serum is a simple, reproducible procedure with high sensitivity in ovarian cancer (4-6). The combination of physical and gynecological examination in combination with serial CA125 analysis in serum offers sufficient sensitivity for the detection of a recurrence and should therefore be regarded as the standard procedure for follow-up (7-9). Although serial CA125 analysis leads to early detection of a recurrence, diagnosis of recurrence should always be confirmed by other procedures prior to therapeutic intervention (10). In this situation additional examinations including vaginal ultrasound, CT and MRI scans may be useful in order to decide on surgical or chemotherapeutical intervention.

In patients with CA125 elevation without any hint of tumor recurrence in physical and/or gynecological examination, with regular findings in ultrasound, CT or MRI

scan, an operative laparoscopy or laparotomy prior to chemotherapeutic intervention may be considered, since a survival benefit in patients treated just because of CA125 increase without any other evidence of a tumor recurrence is not well established to date.

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