RESEARCH ARTICLE

Detection of Recurrence in a Surveillance Program for Epithelial Ovarian Cancer

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Abstract

Ovarian cancer patients need a surveillance program for the detection of tumor progression after completion of treatment. The methods generally consist of history taking, physical examination, tumor marker monitoring and imaging. However, the details of recurrence detection with each method are not well defined. To clarify this issue, ovarian cancer patients who achieved complete or partial responses and developed tumor progression at the follow up time between January 2004 and December 2010 in University Hospital Chiang Mai, Thailand, were reviewed. Clinical data, CA 125 level and imaging results at the tumor progression time were recorded and analyzed. There were 144 ovarian cancer patients meeting the inclusion criteria with the mean age of 51 years and 62.5% of them were in an advanced stage. Complete response was achieved in 89 patients (61.8%) after primary treatment. The median progression free survival and overall survival were 15.5 months and 37.5 months, respectively. Abnormal symptoms presented in 49.3% of the studied patients and 59.7% developed physical examination abnormalities. In addition, CA 125 was elevated in 89.6% while in 74.3% of tumor progression was identified by CT-scan. Short treatment time period and a high level of CA 125 were significant independent prognostic factors in these patients. In conclusion, careful history taking, physical examination and monitoring of CA 125 levels are important methods for tumor progression detection in a surveillance program for epithelial ovarian cancer patients.

Keywords: Surveillance program - epithelial ovarian cancer - recurrence - detection - Thailand

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Introduction

Epithelial ovarian cancer is the seventh ranking common female cancer in the world and is the third most common cancer in gynecology with the age-standardized incidence rate equal to 6.98 per 100,000 persons per year (http://globocan.iarc.fr). Furthermore, this disease reveals a high recurrence rate especially in the advanced stage. Previous study noted that over 80% of advanced ovarian cancer revealed a recurrence episode (Foley et al.,2013). The surveillance program after treatment of epithelial ovarian cancer has developed many guidelines including those from The European Society of Medical Oncology (ESMO) (Aebi et al., 2008). These guidelines recommend history taking, physical examination including pelvic examination and checking serum CA 125 every three months for the initial two years, every four months during the third year and every six months thereafter. Another famous guideline recommendation is from National Comprehensive Cancer Network (NCCN) (NCCN Version 2.2011) that suggests a similar manner for surveillance with minimal differences in interval times for follow up. The NCCN guideline follows up patients every two to four months in the first two years, three to six months in the next three to five years and then annually thereafter. Both guidelines recommend imaging only when the clinical picture indicated progression of the disease or rising of the CA 125.

In our center, the surveillance program includes history taking, physical and pelvic examination, CA 125 or other tumor marker that rise initially before treatment every three months in the first year, four months in the second year and six months in the third to fifth year then subsequently yearly. In patients who could not undergo a pelvic examination, the pelvic ultrasonography was done instead. However, suitable methods for a surveillance program with the purpose of early detection of the recurrence or the disease progression and prolonged survival were unclear. Chan et al. (2008) revealed the limited role of regular physical examination in the detection of the recurrence of ovarian cancer. Besides this, a Dutch multicenter study found no support evidence of clinical benefit in terms of prolonged survival in routine follow up of ovarian cancer patients (Geurts et al., 2011). Nevertheless, studies regarding the detail of method detection of the tumor progression in the surveillance programs are still limited. Therefore, we conducted this retrospective study to explore this issue and also to

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identify the significant prognostic factors that related to the survival outcome in patients with recurrence.

Materials and Methods

After protocol approval by the local ethics committee, the medical records of epithelial ovarian cancer between January 2004 and December 2010 were reviewed. Only patients with clinically complete or partial response according to WHO criteria (Tirkes et al.,2013) and revealed recurrence or disease progression during the follow up time were included.

The patients who had more than one primary site of cancer were excluded. The follow up schedule in our center was every three months in the first year, every four months in the second year, and every six months in the third to fifth year, then annually. At each visit, all of the patients were examined by gynecologic oncology staffs or senior fellows. The blood test for tumor marker was checked every visit. The imaging was done when the clinical picture indicated or a rising tumor marker was found.

The basic clinical data, the symptoms and the findings of physical and pelvic examination and the progression status were recorded. The tumor marker results at the recurrence or progression time and the earlier results were also noted. The method of imaging and the outcomes were recorded. The criteria of progression utilized WHO criteria. The progression free survival (PFS) was defined as the time between the month of initial treatment and the month of detecting the tumor progression or last contact while the overall survival (OS) was defined as the same starting time of PFS to the month of patient death or last contact.

Statistical analysis of the data was carried out using the SPSS for Window program (Version 17.0, Chicago, IL, USA). Descriptive data of all studied patients were presented as means with range and discrete data were reported as number and percentages. The overall survival was estimated by the Kaplan-Meier method. Multivariate analysis was analyzed by Cox proportional hazards model. Statistical significance was specified when a P- value was less than 0.05.

Results

There were 144 patients who met the inclusion criteria in the study period. Approximately half of the patients were in stage III. The most common histology was serous cystadenocarcinoma followed by endometrioid carcinoma and clear cell carcinoma. Over 80% of the studied patients had a moderate to poorly differentiated tumor grade. Most of the studied patients received carboplatin plus paclitaxel as first line treatment and about 60% of the patients achieved complete response. The median progression free survival was 15 months whereas the overall survival was 37.5 months. Over 70% of the patients died.

For the results of surveillance program, about half of the studied patients had developed symptoms at the time of tumor progression. The most common symptom was abdominal distension that occurred in a quarter of all studied patients followed by abdominal pain. Only 3% of the studied patients palpated a pelvic mass by themselves. The physical examination revealed abnormities in 60% of all tumor progression patients. The vaginal stump mass was the most frequent positive sign of these patients that occurred in a half of the patients with an abnormal physical examination. The second most common abnormal physical examination was an abdominal mass that occurred about 10%. Two patients developed abnormal neurologic examinations. The first one complained with dizziness and weakness of both legs. The CT-brain showed cerebellum invasion. The other one presented with blurred vision and diplopia. The CT-brain indicated multiple dural metastases. This case also had pulmonary metastasis detected by chest X-ray.

Regarding tumor marker, all except one patient were evaluated using CA 125 during the follow up period and which was determined to be rising in over 90%. Of four patients in whom the level of CA 125 was missing, three patients were followed up by another hospital with no data in our medical record whereas the remaining was tested with CA 19-9 which was rising at the progression time. CT-scan was the most frequent imaging for the detection of tumor progression. However, 23 patients did not undergo any imaging. The progression in these patients was detected by positive physical examination with abnormal rise of CA 125 in 17 cases and the remaining six patients were diagnosed as recurrence with marked increase of CA 125 level. Four of these six patients died of their disease after treatment in the recurrence phase. The median level of CA 125 at the progression time of all studied patients was 114 mIU/L with a range of 9 to 4,555 mIU/L. Almost patients with partial response revealed only positive imaging at the progression time. The median interval time between normal levels of CA 125 to the rising level of all studied patients was four months (1-34 months).

Referring to the surveillance program that include history taking, physical examination, CA 125 level and imaging, 26% of the patients were positive in all four items while 22% of them were positive only CA 125 level and imaging. It is notable that the symptoms and/or physical

Table 1. Multivariate Analysis to Predict Overall Survival

Factors	No. (%)	RR	(95%CI)	p value
Stage				
I-II	54 (37.5)	1		0.079
III-IV	90 (62.5)	1.521	(0.953-2.429)	
Level of CA 125				
Normal	11 (7.6)	1		0.021
Rising	129 (89.6)	3.355	(1.199-9.390)	
Treatment free interval (months)				
>7	108 (75.0)	1		<0.001
≤6	36 (25.0)	4.896	(2.855-8.396)	
Outcome of initial treatment				
Complete response	89 (61.8)	1		0.609
Partial response	55 (38.2)	0.88	(0.540-1.435)	
Symptom at tumor progression				
No	73 (50.7)	1		0.217
Yes	71 (49.3)	1.313	(0.852-2.025)	
Physical examination				
Normal	73 (50.7)	1		0.326
Abnormal	71 (49.3)	1.248	(0.802-1.942)	

*RR, relative risk; CI, confidence interval

examination were abnormal in 66 patients (45.8%) who developed tumor progression or recurrence. Furthermore, the frequency of symptoms and positive physical examination at recurrence in patients who achieved complete response were 53.9% and 58.4% that was not significantly different from the frequency of symptoms and abnormal physical examination in the patients who achieved partial response at tumor progression that were detected as 41.8% and 58.4% with a P-value at 0.158 and 0.687, respectively.

In Table 1, the independent factor that affected the overall survival of the patients who developed recurrence/ progression in the study was a rising CA 125 and a short treatment free interval (less than or equal to six months).

Discussion

The procedure surveillance program of the ovarian cancer patients in many institutes includes monitoring the symptoms, the physical examination, serum CA 125 assay and the imaging (Salani et al.,2011).

In the present study, the symptoms of the patients who revealed progression of disease was nearly 50% which was similar to the previous report from Chan et al. (2008). They studied 80 ovarian cancer patients who achieved complete response after initial treatment and developed recurrence thereafter with 52.5% of them revealing abnormal symptoms. The most common symptom was abdominal pain that occurred about 20% followed by abdominal distension that occurred in only six percent which differed from our report that found abdominal distention as high as 25%. The inconsistent data might be from the type of patients studied. In the present study, the patients who achieved partial response were included in the study while only complete response patients were included in Chan's study. However, the differences in the present symptoms in both groups of patients who achieved complete or partial response in the present study were not significant.

An abnormal physical examination in the present study occurred in nearly 60% of the studied patients. This finding corresponded to the previous studies that revealed a positive physical examination in 34-51% (Chan et al., 2008; Menczer et al.,2006). However, the abnormal physical examination usually was found with other positive findings in the detection of tumor recurrence. Only 3.8-4.6% of the recurrence ovarian cancer patients in the previous reports were found solely to have an abnormal physical examination (Chan et al.,2008; Menczer et al., 2006). In the present study, only one patient demonstrated an abnormal physical examination alone. Thus, the other procedures for detection recurrence are necessary along with the physical examination.

The vaginal stump mass was the most frequent abnormal finding in our study that was discovered in one-third of the patients studied. This finding was similar to earlier studies (Fehm et al.,2005;Chan et al.,2008; Menczer et al.,2006.) . Fehm et al (Fehm et al.2005) suggested that vaginal examination revealed the highest sensitivity for detecting pelvic recurrence when compared to vaginal ultrasound and CT scan. Therefore, physical examination especially per vaginal evaluation is very necessary in the surveillance program.

CA 125 is the favored tumor marker for follow up in the ovarian cancer patients for most institutes. Ninety percent of the patients in the present study revealed a rising level with tumor progression. However, 121 patients (84%) showed the other positive findings in detected tumor progression. The median leading time before CA 125 raised was four months. This finding resembled the earlier review that showed the median lead time of CA 125 rising in a range of three to five months (Geurts et al.,2011) . In addition, there was a randomized study that found that the value of prompt treatment of asymptomatic patients with abnormal rising CA 125 levels was not beneficial in term of increased survival when compared to starting treatment when clinically indicated(Rustin et al.,2010). In the present study, six patients were diagnosed as recurrence with the abnormal rising of CA 125 alone. Of these patients, four patients died of disease thereafter. This event might be explained from the false negative of imaging to identify the tumor progression.

The imaging especially CT- scan is quite often employed when there are suspicious symptoms or signs or rising of CA 125. However, the sensitivity of this method varies between literature reviews from 40-93% (Salani et al.,2011). The important limitation is the detection of peritoneal lesions that are dependent on site, size and the presence of ascites (Salani et al.,2011). In the present study, over 70% of patients revealed suspicious lesions from CT-scans. Pelvic ultrasonography was infrequently used to detect tumor recurrence in our study despite the most common lesion being in the pelvis due to the more favorable use of the CT-scan. However, the pelvic ultrasonography was used to detect tumor recurrence in seven percent of our patients. MRI was rarely used in our study due to its high cost and long queue even it showed a high sensitivity for pelvic lesions, bowel and mesentery involvement (Miller and Rustin, 2010).

Regarding the predictive factor for survival in this present study, only treatment free interval and the high level of CA 125 were significant factors. Gadducci et al (Gadducci et al.,2009) also found that time to recurrence was an independent factor for survival while the symptoms at recurrence had no significant impact. Another prognostic factor in the present study was the rising level of CA 125 that corresponded to Levy et al. They suggested that the serum CA 125 level of more than 35 U/ml revealed a poor outcome (Levy et al.,2013).

The strength of our study was the large number of studied patients in a single institute that used a uniform surveillance program. We included the patients who achieved partial response because of limitation data for these kinds of patients. Most previous studies revealed only patients who had a complete clinical response. The data of the detection of tumor progression for these patients should be of benefit for administration of further treatment after discussion with these patients. On the other hand, the limitation of our study was its retrospective nature. Some information was missing. However, the results of our study confirmed that the majority of tumor progression patients were detected by both the suspicious

symptoms and an abnormal physical examination. The attending physician should be concerned with history taking and careful physical examinations for all of the follow up patients.

In conclusion, the surveillance program which included all four methods revealed value in the detection of recurrence or progression status of the patients who attended the follow up. The careful history taking and physical examination was the major method for determine tumor progression. CA 125 should be used for monitoring in each visit because over 90% of the tumor progression patients revealed abnormal levels of this tumor marker. The short treatment time interval and the high level of CA 125 were the independent prognostic factors that affecting survival outcome for ovarian cancer.

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