Use of the ultrasound surgical aspirator in ovarian cancer: a case-control study

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Summary

Background: This study was undertaken to evaluate the use of the ultrasound surgical aspirator in ovarian cancer and to determine if cytoreduction was improved with its use.

Methods: The study is a retrospective case control trial. Twenty-six consecutive ovarian cancer patients who had the ultrasound surgical aspirator used during their surgery were retrospectively compared to 25 consecutive ovarian cancer patients who did not have the ultrasound surgical aspirator used during their surgeries. The latter group had their surgeries immediately before the ultrasound surgical aspirator was introduced into the hospital. Both groups were similar in age, stage, histology type, grade, and median number of chemotherapy cycles.

Results: Patients that had the ultrasound surgical aspirator used had a 69% optimal cytoreduction rate compared to 16% in the control group (p = .001). This was statistically significant (p = 0.001). Survival time was equal in both groups.

Conclusions: Results of the study showed that use of the ultrasound surgical aspirator may permit more patients to be optimally cytoreduced.

Key words: Ultrasound surgical aspirator; Cytoreduction.

Introduction

The ultrasound surgical aspirator is a surgical adjuvant and is a new technology in the treatment of cancer. The ultrasound surgical aspirator creates vibrating waves near tissues, fragmenting those with a high water density more easily. Generating 23,000 cycles per second, the ultrasound surgical aspirator allows selected tissue to be broken apart and vacuumed into a container. With the ultrasound surgical aspirator, tumors can be removed without harming the underlying tissue. The ultrasound surgical aspirator has been used in gynecologic oncology for the treatment of radiation ulcers [1], vulvar intraepithelial neoplasia [2], and to assist in cytoreductive surgery in ovarian cancer [3]. Proponents of the ultrasound surgical aspirator claim it is important in the cytoreduction of ovarian cancer and can achieve optimal tumor resection with less morbidity [4]. This is important as studies have shown that after surgical debulking patients with minimal ovarian cancer remaining have prolonged survival [5-7]. Long-term results with the ultrasound surgical aspirator are not yet available to document the true efficacy of this technique.

The present retrospective study was undertaken to assess the efficacy of the ultrasound surgical aspirator in ovarian cancer surgery and to determine whether the ultrasound surgical aspirator improved cytoreduction in patients with advanced ovarian cancer.

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Methods and Materials

At the Johns Hopkins Hospital, 26 consecutive patients were identified who underwent primary cytoreductive surgery for ovarian cancer during the period from September 1988 to December 1991. The ultrasound surgical aspirator was used during the surgery of each of these patients. Another 25 consecutive patients with ovarian cancer who had primary debulking surgery in the period from January 1987 to September 1988 were identified as controls. The surgeries of the control patients occurred immediately before the ultrasound surgical aspirator was available in the gynecology unit at the hospital. Those patients for whom the ultrasound surgical aspirator was available but not used (n=36) were excluded. Thus a group of patients was formed who had only the ultrasound surgical aspirator used during their surgeries.

This is retrospective case-control study. Characteristics of each of these two groups were obtained by reviews of the hospital charts, operative reports, and pathology reports. Factors reviewed included stage, histopathology, grade, symptoms, type of surgery, initial tumor size, second-look surgery, operative time, blood loss, residual disease, and associated medical conditions. Follow-up was obtained from the tumor registry and physicians' charts.

Statistical Methods

Survival was the major statistical endpoint of this study. To estimate the event-time distribution, we used the method of Kaplan and Meier [8]. The log-rank statistic [9] was then used to compare the survival distributions of the two groups. Independent preoperative factors prognostic for survival were selected by using Cox's proportional-hazards regression model [10].

Table 1. — *Characteristics of study group.*

Characteristic	*USA used Frequency	*USA not used Frequency
Stage		
III	84.5%	88.0%
IV	15.4%	12.0%
Histology		
Serous	88.5%	92.0%
Mucinous	3.8%	0.0%
Endometrioid	7.7%	0.0%
Clear cell	0.0%	8.0%
Grade		
One	7.7%	4.0%
Two	19.2%	4.0%
Three	73.1%	92.0%
Presentation of Symptoms		
Single	57.7%	44.0%
Multiple	26.9%	44.0%
Unknown	15.4%	12.0%
Duration of symptoms		
Median months	1.0	1.5
Type of surgery		
Without bowel resection	76.9%	60.0%
With bowel resection	23.1%	40.0%
Cycles of chemotherapy		
Median	5	5
Range	4-17	4-18
Size of primary tumor		
< 5 cm	30.8%	36.0%
5-9 cm	38.5%	32.0%
10-14 cm	11.5%	20%
> 15 cm	19.2%	12.0%
Washings		
Positive	94.7%	86.7%
Negative	5.3%	13.3%
Primary residual disease		
Optimal	69.2%	16.0%
Suboptimal	31.8%	84.0%
Complications		
Complications	23.1%	20.0%
No complications	76.9%	80.0%
Blood loss		
Median	625 ml	775 ml
Range	250-2000 ml	150-1800 ml
Operative time		
Median	180 minutes	182.5 minutes
Range	115-255 minutes	150-270 minutes
Median survival		
Median age	63	63
Survival		
Died of disease	31.0%	76.0%
Alive	69.0%	24.0%

* Ultrasound surgical aspirator

For this overall survival endpoint, the hazard at time t is defined as the conditonal probability of dying in the next instant of time given that one has survived up to time t. The hazard is useful for comparative purposes because it is often convenient and correct to assume that hazards in different prognostic groups have a constant ratio across time. Covariates having some relative prognostic value (i.e., p, 0.15) were entered into a multivariate model and nonsignificant effects were removed in a stepwise fashion. Hazards are expressed relative to a baseline reference category for individual prognostic factors. All reported p values are two-sided.

Table 2. — *Analysis model: Cox proportional hazard survival analysis. Risk type: relative risk (multiplication).*

Factor	Coefficient	Standard error	p-value	Hazard ratio
Grade 3*	2.064	(1.02)	.043	7.876
Symptoms**	1.127	(0.437)	.010	3.087
Surgery***	.5885	(0.400)	.141	1.801
Residual disease	-.9189	(0.440)	.037	.3990
Second-look****	-.9511	(0.432)	.028	.3863
Optime	-.1267	(0.656)	.053	.9874
USA used	-.3257	(0.437)	.455	.7219

* Grade 3: Grade 3 vs Grades 1 & 2.
** Symptoms: Single vs multiple presenting symptoms.
*** Surgery: Tumor debulking including bowel resection vs no bowel resection.
**** Second-look: Second-look procedure performed vs not performed.

Table 3. — *Multivariate survival model.*

Factor	Hazard ratio	p-value	95% C.I.
Tumor grade			
1 or 2	1.000		
3	6.760	.065	(0.89; 51.34)
Symptoms reported			
Single	1.000		
Multiple	3.754	.005	(1.47; 9.55)
Second-look procedure			
No	1.000		
Yes	0.343	.027	(0.134; 0.887)

Table 4-A. — *Endpoint with power analysis.*

	Number of events	Estimated hazard ratio	Power
Survival	19	1.383	0.17

Table 4-B. — *Comparison of hazard ratio with statistical power.*

Hazard ratio	Number of events	Power
1.5	19	0.239
2.0	19	0.570
2.5	19	0.804

Results

Among the 51 patients, 90% (n=46) of their tumors were serous, 82% (n=42) were grade 3, and 86% (n=44) were Stage III. Twenty-six patients had the ultrasound surgical aspirator used during their initial surgery at primary cytoreduction. A complete summary of these and other relevant clinical characteristics of both groups is given in Table 1.

Patients in the two groups were similar in age and in preoperative tumor burden, stage, grade, and histologic type. In the group that had the ultrasound surgical aspirator used, 69% (18 out of 26 cases) were optimally cytoreduced, in contrast to only 16% (4 out of 25 cases) in the control group. This difference was statistically significant (p=0.001). Optimally cytoreduced is defined as nodules ≤ 1.5 cm of residual disease remaining.

The median survival for both the ultrasound surgical aspirator and the non-ultrasound surgical aspirator was approximately 700 days. Of the 26 patients who had the

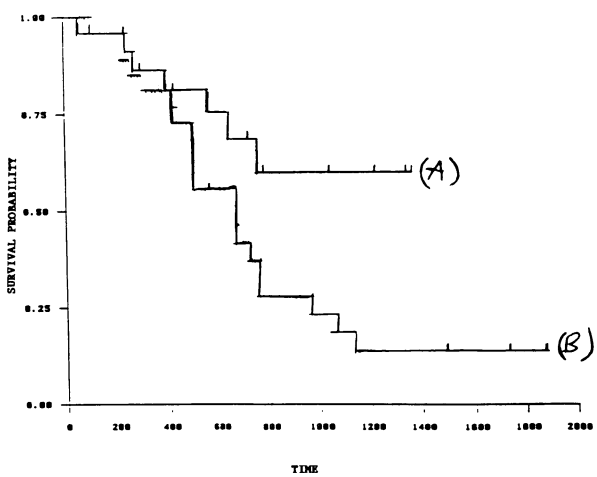

Figure 1. — Survival curve of ovarian cancer patients who had optimal cytoreduction status (A) and suboptimal cytoreduction status (B) at the end of surgery. Time in days.

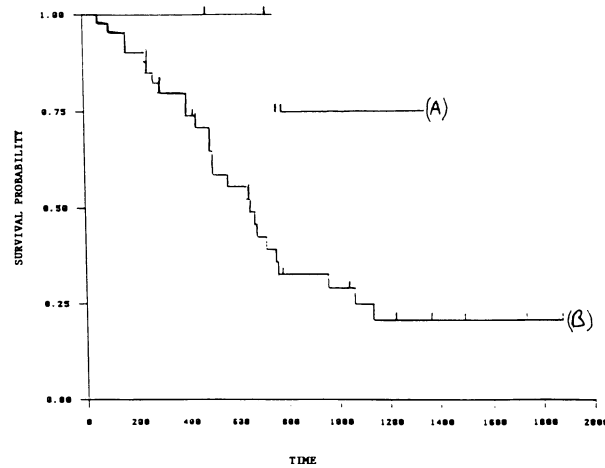

Figure 2. — Survival curve of ovarian cancer patients who had grade 1 or 2 tumors (A) and who had grade 3 tumors (B). Time in days.

ultrasound surgical aspirator used during their surgery, eight died of disease. Of the patients who did not have the ultrasound surgical aspirator used, 19 out of 25 died of disease. While Cox's proportional-hazards regression model indicated that the group that did not have the ultrasound surgical aspirator used during their surgery was at a slightly greater risk of dying than the group that did (hazard ratio = 1.4); this difference was not significant (p=0.46).

Factors significantly associated with improved survival in the entire group included low grade tumors (grade 1 or 2), presenting with single symptoms rather than multiple symptoms optimal cytoreduction (Figure 1), longer operative times and a second-look surgery. These univariate results are summarized in Table 2.

Multivariate regression results are given in Table 3. Only tumor grade and number of reported symptoms were independent variables. The category "Number of Reported Symptoms" is classified into patients complaining at the initial visit of one symptom or patients complaining of multiple symptoms. The second-look procedure also came up as an independent variable, but this is an artificial designation since the selection of these patients presents a good prognostic group. Adjusting for the number of reported symptoms and the second-look procedure, we found that patients with a tumor grade of 3 had a sevenfold greater risk of dying than patients with lower grade tumors (Figure 2).

Multiple symptoms reported when adjusted for tumor grade and the second-look procedure, also indicated a greater risk of death (hazard ratio = 3.8). It is unclear why multiple symptoms should be an independent risk factor. A reasonable explanation is that complaints of multiple symptoms would come from patients with a large burden of disease. Hence their survival would be compromised. The second-look procedure was associated with improved survival (hazard ration = 0.34) when adjusted for grade and symptoms. These results show that this group of ovarian cancer patients is similar to other reported patients.

Discussion

Survival rates among patients treated for advanced ovarian cancer have improved little over the past 20 years, even though the disease-free interval has been prolonged [11]. At the time of primary surgery it has been shown that optimal cytoreduction, i.e. less than 1.5 centimeter disease nodules, is an important prognostic factor. Thus, the goal of primary surgery is to achieve optimal tumor removal so that chemotherapy can effectively eliminate the remaining cells [12].

Given the importance of optimal cytoreduction, ovarian cancer surgery has evolved into a complex surgical effort. In the pelvis, end bloc resection of the pelvic contents is performed and, when necessary, an end to end rectal anastomosis. When indicated, there is tumor removal in the upper abdomen from the diaphragm, spleen, and bowel. Intestinal resections are performed to achieve an optimal status and to relieve obstruction. Large areas of peritoneum are removed because of ovarian cancer's propensity for involvement of this lining. The ultrasound surgical aspirator has an important role in these surgical efforts since it can remove ovarian cancer from the diaphragm, spleen, and bowel without resection of these organs.

This study suggests that use of the ultrasound surgical aspirator places more patients with advanced ovarian cancer into the optimal residual disease category after surgery. When the ultrasound surgical aspirator was used, 69% of patients were optimal in comparison to 16% when the ultrasound surgical aspirator was not used. Also, it placed more patients in the optimal category without an increase in operative time or blood loss. A potential selection bias of the study is the exclusion of the 36 patients that did not have the ultrasound surgical aspirator used during the same time period the ultrasound surgical aspirator was available. The exclusion was performed so as to obtain a pure ultrasound surgical aspirator group. The discretion of the surgeon is, therefore, not a bias.

Survival rates of the two groups, however, were not statistically different. The failure to find a difference can be explained by the power of our study. The number of events for an endpoint in the high risk group can provide a means of calculating the power of an analysis. Table 4 summarizes the approximate power this study had for detecting the estimated hazard ratio for non-ultrasound surgical aspirator treatment. Given the magnitude of the effect of ultrasound surgical aspirator treatment observed in this study, the power to detect this with 19 events (19 patients dying) was 17%. Our study, therefore, is not large enough to definitively comment on survival. With new drugs (Taxol and Topotecan) optimal status may become more important and the trend in this study should be the basis for large, randomized trials.

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