Can primary optimal cytoreduction be predicted in advanced epithelial ovarian cancer preoperatively?

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Abstract

Introduction: Prediction of optimal cytoreduction in patients with advanced epithelial ovarian cancer preoperatively.

Methods: Patients with advanced epithelial ovarian cancer who underwent surgery for the first time from Jan. to June 2008 at gynecologic oncology ward of TUMS (Tehran University of Medical Sciences) were eligible for this study. The possibility of predicting primary optimal cytoreduction considering multiple variables was evaluated. Variables were peritoneal carcinomatosis, serum CA125, ascites, pleural effusion, physical status and imaging findings.

Univariate comparisons of patients underwent suboptimal cytoreduction carried out using Fisher’s exact test for each of the potential predictors. The wilcoxon rank sum test was used to compare variables between patients with optimal versus suboptimal cytoreduction.

Results: 41 patients met study inclusion criteria. Statistically significant association was noted between peritoneal carcinomatosis and suboptimal cytoreduction. There were no statistically significant differences between physical status, pleural effusion, imaging findings, serum CA125 and ascites of individuals with optimal cytoreduction compared to those with suboptimal cytoreduction.

Conclusions: Because of small populations in our study the results are not reproducible in alternate populations. Only the patient who is most unlikely to undergo optimal cytoreduction should be offered neoadjuvant chemotherapy, unless her medical condition renders her unsuitable for primary surgery.

Introduction

Ovarian cancer is the leading cause of morbidity and mortality among the gynecologic cancers [1]. Epithelial ovarian cancers consist 90% of all ovarian cancers [2]. Stage 3 and 4 (as defined by the staging classification of the International Federation of Gynecology and Obstetrics) consist about 2/3 of cases of epithelial ovarian cancer in the time of diagnosis [1-3]. Advanced epithelial ovarian cancers are currently managed with laparotomy + hysterectomy + bilateral salpingooophorectomy + omentectomy + resection of tumoral mass as completely as possible and then platinum based chemotherapy.

Maximal diameter of residual tumor after surgery and before starting chemotherapy is an important determinant of prognosis, this has been shown by all studies about advanced epithelial ovarian cancer [4-6]. The definition of optimal surgery has been evolved and it is currently defined as residual tumor less than 1 cm [5]. Optimal surgery is associated with both a more favorable response to chemotherapy and prolonged survival [7]. The study of GOG has shown that only if the residual tumor is optimal (less than 1 cm) the survival will prolong [5]. The success rate of primary optimal cytoreduction for advanced epithelial ovarian cancers is highly variable, depending upon individual and institutional treatment philosophies and experiences. In centers with a particular interest and experience in cytoreductive
surgery, rates of optimal resection are reported in 60-90% of cases [8,9].

It is not possible to do primary optimal debulking for all patients, in these cases primary surgery not only does not have any benefit but also causes morbidity [10]. The 30-day mortality rate for women undergoing primary surgery for ovarian cancer ranged from 1-3% [11]. Moreover, not performing primary surgery in all cases results in omitting the chance of improved survival for some patients.

Primary debulking in patients with advanced epithelial ovarian cancer has been compared with chemotherapy and interval debulking in different studies. Equal survival has been reported in patients undergoing primary surgery compared to patients undergoing debulking surgery after taking chemotherapy by Onnes et al. [12]. They have reported that optimal debulking was achieved in 42% of patients who treated primarily with chemotherapy in comparison with 29% of patients who underwent primary surgery.

In 1999, Shwartz et al. demonstrated that women who underwent cytoreductive surgery after induction chemotherapy had statistically improved overall survival compared to women who did not undergo surgery [13]. One randomized prospective study demonstrated that women undergoing interval cytoreductive surgery had improved both overall and progression-free survival [11]. It is supposed that less invasive surgery is required for optimal cytoreduction after neoadjuvant chemotherapy. Ansquer et al. in their study have noticed that the morbidity of cytoreductive surgery after neoadjuvant chemotherapy is less than primary debulking [14]. It is noticeable that by performing primary cytoreductive surgery, surgical staging will be done, sensitivity to chemotherapy will increase, risk of mutation will reduce and general status of patient will improve. Considering these, nowadays primary surgery is the preferred management for patients with advanced epithelial ovarian cancer. In America 95% of patients with advanced epithelial ovarian cancer are treated with primary surgery [15].

Regarding that residual tumor is more than 1 cm in many patients underwent primary surgery, considering another method in this group of patients seems necessary. Although neoadjuvant chemotherapy and interval cytoreduction sounds to be good management but its indications have not yet determined.

A critical point in order to define indications of neoadjuvant chemotherapy for advanced ovarian cancer is determination of uniform selection criteria that can consistently identify patients with surgically unresectable disease without depriving others from potential advantage associated with an optimal primary resection. Several studies have been done for determining markers which can reliably predict optimal resectability [16-18]. CT-Scan findings [17], serum CA-125 [18], pleural effusion [19] and ascites [19,20] have been assessed in different studies in order to predict optimal debulking preoperatively but up to now the predictive performance of clinical parameters (e.g. ascites), serum CA125 values and imaging criteria have not demonstrated sufficient accuracy to achieve widespread applicability [13]. Thus further investigation concerning patient selection seems warranted. Therefore, we planned the prospective study for assessing the probability of predicting preoperatively optimal cytoreduction with considering combination of variants (abdominal and pelvic CT-scan or MRI findings - presurgical serum CA125 level- pleural effusion-ascites and physical status) in patients with advanced epithelial ovarian cancer who were admitted at gynecology oncology ward of the Tehran Vali-e-asr hospital and undergoing primary surgery from Jan. to June 2008.

Patients and Methods

Approval to conduct this study was obtained from research organization of gynecologic oncology department of Tehran University of Medical Sciences (TUMS). Patients with stage 3 and stage 4 epithelial ovarian cancer underwent primary surgery between Jan. to June 2008 at gynecologic oncology ward of Vali-e-Asr hospital of TUMS were eligible for entering the study.

The possibility of predicting primary optimal cytoreduction considering multiple variables was assessed in this group. Variables were peritoneal carcinomatosis, serum CA125 level, ascites, pleural effusion, physical status and imaging findings.

All surgeries were performed by gynecologic oncologists of TUMS. Optimal cytoreduction was defined as ≤ 1 cm residual disease. All imagings were reported by the professors of radiology of TUMS. Considered imaging parameters included: omental extention, liver involvement, peritoneal involvement and suprarenal adenopathy. Blood samples for measuring serum CA125 levels were taken at the morning.

Physical statuses of patients were defined according to physical status classification of the American society of anesthesiology. In addition we considered optimal and suboptimal cytoreduction. Residual tumor less than 1 cm after surgery was considered as optimal cytoreduction.

Univariate comparisons of the percentage of patients who underwent suboptimal cytoreduction carried out using Fisher’s exact test for each of the potential predictors. The wilcoxon rank sum test was used to compare variables between patients with optimal versus suboptimal cytoreduction.
Results
Forty one patients from patients who were admitted at Vali-e-Asr hospital of TUMS from Jan. to June 2008 met study inclusion criteria. Demographic and clinical data are described in table 1. Seventy-three percent of patients had FIGO (international federation of gynecology and obstetrics staging system) stage 3 disease while 17% of patients had FIGO stage 4 disease. Forty-one percent were optimally cytoreduced to ≤ 1 cm residual disease at the time of primary surgery.

Peritoneal carcinomatosis and suboptimal cytoreduction had statistically significant association. There were no statistically significant differences between physical status, pleural effusion, imaging findings, CA125 serum levels and ascites in patients with optimal cytoreduction compared to those who underwent suboptimal debulking.

Table 1 Clinical Data and Tumor Characteristic Study

| Characteristic                  | Patients |
|--------------------------------|----------|
|                                | No.      | %     |
| Clinical status                |          |       |
| 1                              | 27       | 65.9  |
| 2                              | 13       | 31.7  |
| Pleural effusion               |          |       |
| Positive                       | 7        | 17    |
| Negative                       | 34       | 82.9  |
| Bowel resection                |          |       |
| Positive                       | 1        | 2.4   |
| Negative                       | 39       | 96.6  |
| Intraperitoneal carcinomatosis  |          |       |
| Positive                       | 22       | 53.6  |
| Negative                       | 19       | 46.4  |
| Imaging findings               |          |       |
| Omental extension              |          |       |
| Positive                       | 6        | 14.6  |
| Negative                       | 34       | 85.4  |
| Liver involvement              |          |       |
| Positive                       | 5        | 12.1  |
| Negative                       | 36       | 87.9  |
| Peritoneal involvement         |          |       |
| Positive                       | 12       | 29.2  |
| Negative                       | 29       | 70.8  |
| Suprarenal adenopathy          |          |       |
| Positive                       | 0        | 0     |
| Negative                       | 41       | 100   |
| CA-125                         |          |       |
| ≤ 400                          | 11       | 27.5  |
| >400                           | 29       | 72.5  |
| Ascites                        |          |       |
| ≤ 1000                         | 22       | 53.6  |
| >1000                          | 19       | 46.4  |

Table 2 presents the percentage of patients who underwent suboptimal and optimal debulking for each of 9 considered variables. Optimal debulking was performed for 44.4% of patients with physical status 1 (according to classification of American society of anesthesiologist (A.S.A)) and 55.6% of these patients undergoing suboptimal debulking. Patients with A.S.A class 2 suboptimally debulked in 76.9% of cases and optimally debulked in 23.1%. About 85% of patients have pleural effusion were suboptimally debulked while only 14.3% of these patients were optimally debulked. Patients who did not have pleural effusion undergoing optimal cytoreduction in 41.2% and suboptimal cytoreduction in 58.8%. We had only one case of bowel resection which resulted in optimal debulking. Suboptimal debulking was performed in 84.2% of patients with peritoneal carcinomatosis, 50% with omental extension, 60% with liver involvement, 58.3% with peritoneal involvement, 63.3% with CA125 ≤ 400 and 59.5% with ascites ≤ 1000 in comparison with optimal cytoreduction undergoing in 15.8%, 50%, 40%, 41.7%, 36.4%, 45.5% of these groups of patients respectively.

Discussion
Our current study identifies intraperitoneal carcinomatosis as being the only statistically significant predictor of suboptimal cytoreduction. Table 2 demonstrates P value, positive predictive value and negative predictive value of each of the variables for predicting optimal and suboptimal debulking. There were no statistically significant relationship between considered variables and optimal or suboptimal cytoreduction except to intraperitoneal carcinomatosis.

There is no statistically significant difference between pleural effusions in individuals underwent optimal cytoreduction compared to those with suboptimal cytoreduction. It seems that low number of patients caused this result because the number of patients who were suboptimally cytoreduced is in confidence interval range of those who were optimally cytoreduced. The number of patients in our study is only 41. Considering small sample size of the study, proving these results demands larger randomized study. We used imaging findings as predictive predictors of suboptimal debulking according to previous studies which had mentioned these factors have predictive value.

To date, the predictive performance of clinical parameters, serum CA-125 threshold values, and radiographic imaging criteria have not demonstrated sufficient accuracy to achieve widespread applicability [13,21-24].

The most common criteria cited as justification for abandoning an up-front attempt at surgical cytoreduction are ascites volume greater than 1000 ml, peritoneal carcinomatosis, parenchymal liver disease, splenic metastasis or omental extension to the spleen, porta
hepatitis disease, and bulky disease involving the dia-
phragm[8] one of the earliest studies attempting to fore-
cast the surgical outcome of patients with advanced
stage ovarian cancer assessed the predictive value of
these criteria in a series of 42 patients[15].In this senti-
nel study, Nelson et al reported a positive predictive
value for a suboptimal surgical result of 67%.Not to be
overlooked, it is the fact that one out of every three
patients thought to have unresectable tumor would have
been left with optimal residual disease if offered primary
surgery. More recently, Axtell et al. [25] reported data
that highlight the difficulty in defining universally
applicable selection criteria that reliably predict surgical
outcome across institutions and surgeons.

One of the principle difficulties in development of any
reliable predictive model of surgical outcome for patients
with advanced ovarian cancer is the challenge of factors
in the significant impact of each institute surgeons’
philosophy, effort and ability to utilize advanced surgical
techniques to achieve maximal cytoreduction, in order to
omit this factor, in this study all surgeries were per-
mformed by gynecologic oncology professors of TUMS.

In summary, identification of risk factors for subopti-
mal cytoreduction in small populations such as ours is
not reproducible in alternate populations. Until prospec-
tive randomized trials have demonstrated that neoadju-
vant chemotherapy followed by interval cytoreduction is
equivalent in terms of survival outcomes to primary
optimal cytoreduction followed by chemotherapy,
extreme caution should be used when applying preo-
perative predictors to decide between primary surgical
exploration and neoadjuvant chemotherapy in the medi-
cally fit patient. Only the patient who is most unlikely
to undergo optimal cytoreduction should be offered
neoadjuvant chemotherapy, unless her medical condition
renders her unsuitable for primary surgery.

| Table 2 Univariate Analysis of Predictors of Suboptimal Cytoreduction |
|---------------------|---------------------|---------------------|---------------------|---------------------|
| Predictor            | Optimal Cytoreduction | Suboptimal Cytoreduction |
|                     | No. | percent | No. | percent | P |
| Clinical status      |     |         |     |         |   |
| 1                   | 12  | 44.4    | 15  | 55.6    | 1.91 |
| 2                   | 3   | 23.1    | 10  | 76.9    |   |
| Pleural effusion     |     |         |     |         |   |
| Positive             | 1   | 14.3    | 6   | 85.7    | .179 |
| Negative             | 14  | 41.2    | 20  | 58.8    |   |
| Peritoneal carcinomatosis |   |         |     |         |   |
| Positive             | 3   | 15.8    | 16  | 84.2    | .01 |
| Negative             | 12  | 54.5    | 10  | 45.5    |   |
| Omental extension    |     |         |     |         |   |
| Positive             | 3   | 50      | 3   | 50      | .460 |
| Negative             | 12  | 34.3    | 23  | 65.7    |   |
| Liver involvement    |     |         |     |         |   |
| Positive             | 2   | 40      | 3   | 60      | .866 |
| Negative             | 13  | 36.1    | 23  | 63.9    |   |
| Peritoneal involvement |    |         |     |         |   |
| Positive             | 5   | 41.7    | 7   | 58.3    | .664 |
| Negative             | 10  | 34.5    | 19  | 65.5    |   |
| Adenopathy           |     |         |     |         |   |
| Positive             | 0   | 0       | 0   | 0       |   |
| Negative             | 15  | 36.6    | 26  | 63.4    |   |
| CA-125               |     |         |     |         |   |
| ≤ 400                | 4   | 36.4    | 7   | 63.6    | .911 |
| >400                 | 10  | 34.5    | 19  | 65.5    |   |
| Ascitis              |     |         |     |         |   |
| ≤ 1000               | 10  | 45.5    | 12  | 54.5    | .205 |
| >1000                | 5   | 26.3    | 14  | 73.7    |   |
Authors’ contributions
AMM: supervised research project, carried out operations, supervised statistics.
MMM: participated in operation as first aid, collect data, drafted the manuscript, and acted as corresponding author and did the revisions. MMG: carried out operations, she was head of the department. FG: carried out operations. SA: participated in operation as first aid.

Competing interests
The authors declare that they have no competing interests.

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