

The Utility of Computed Tomography Scans in Predicting Suboptimal Cytoreductive Surgery in Women with Advanced Ovarian Carcinoma

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BACKGROUND. Computed tomography (CT) scans of the abdomen and pelvis may predict which patients with ovarian carcinoma can undergo optimal cytoreduction at primary surgery. Previous studies have demonstrated that patients with ovarian carcinoma had optimal cytoreduction rates ranging from 50–60%. The authors sought to determine whether these findings applied to a surgical practice with a higher rate of optimal debulking. A predictive model using CT scanning and CA 125 values would allow the authors to determine which patients would be more appropriately treated with neoadjuvant chemotherapy.

METHODS. Preoperative CT scans for patients with Stage III/IV ovarian carcinoma (according to the staging system of the International Federation of Gynecology and Obstetrics) who were treated between 1996 and 2001 were evaluated retrospectively by 2 radiologists for 17 criteria evaluating the extent of disease. Clinical data were extracted from medical records. Residual tumors measuring ≥ 1 cm were considered suboptimal. Logistic regression was used to evaluate which criteria correlated with optimal cytoreduction.

RESULTS. Eighty-seven patients were identified retrospectively who met entry criteria and had preoperative CT scans of sufficient diagnostic quality. Sixty-two patients (71%) received optimal cytoreductive surgery and 45 (52%) required aggressive surgical procedures. In a multivariate model, only diffuse peritoneal thickening (DPT) independently predicted suboptimal surgical resection ($P = 0.016$). However, a model using both DPT and ascites on most CT scans had a positive predictive value of 68% and a sensitivity of 52% for predicting suboptimal cytoreduction.

CONCLUSIONS. The presence of DPT and large-volume ascites was associated with a very low rate of optimal cytoreduction (32%) in a surgical practice. These patients may be more appropriately treated with neoadjuvant chemotherapy followed by surgical cytoreduction. *Cancer* 2004;101:346–52.

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The American Cancer Society estimated that 25,400 new cases of ovarian carcinoma were diagnosed in 2003. Ovarian carcinoma is the leading cause of gynecologic mortality in the U.S. and was responsible for an estimated 14,300 deaths in 2003.¹ At the time of diagnosis, approximately two-thirds of women will have advanced-stage ovarian carcinoma (i.e., Stage III/IV disease) as defined by the staging classification of the International Federation of Gynecology and Obstetrics. Optimal surgical cytoreduction of tumor bulk to < 1 cm and platinum-based chemotherapy are the cornerstones of treat-

ment. Numerous studies have shown that the maximum dimension of residual tumors remaining after the completion of cytoreductive surgery is an important prognostic indicator.²⁻⁵

Despite aggressive surgical approaches to the treatment of patients with ovarian carcinoma, extensive tumor bulk or the presence of tumor in specific locations may prohibit optimal resection at primary surgery. The success rate of achieving optimal cytoreductive surgery varies among reporting institutions, generally ranging from 35–50%.⁶ A recent metaanalysis by Bristow et al.² reviewed 53 studies comprising 6885 patients with Stage III/IV ovarian carcinoma (81 patient cohorts). In that study, the authors sought to determine the relative effect of percent maximal cytoreductive surgery on survival. In the studies reviewed, the mean percentage of maximal cytoreductive surgery was 41.9%. However, in the centers without surgeons specially trained in gynecologic oncology, optimal debulking rates were often < 25%. Although the survival benefit of optimal surgery has been well established, patients who undergo suboptimal debulking are exposed to significant surgical morbidity without receiving the survival benefit of surgery. The 30-day mortality rate for women undergoing primary surgery for ovarian carcinoma ranged from 1–3%.⁷⁻¹⁰ In addition, major morbidity as reported by these studies includes cardiac failure, wound dehiscence, hemorrhage requiring reoperation, and prolonged ileus. Considering that patients who undergo suboptimal debulking derive minimal benefit from surgical debulking, it would appear prudent to identify these patients preoperatively to offer them an alternate approach to the current standard of care.

To address this problem, several studies have investigated the use of neoadjuvant chemotherapy and have suggested that this treatment modality may reduce morbidity and mortality while retaining the survival benefits of primary surgery. Debulking after the receipt of neoadjuvant chemotherapy appears to be associated with less operative morbidity and improved rates of optimal cytoreduction.^{6,11-15} Chambers et al.¹¹ in 1990 and Schwartz et al.¹³ in 1994 compared the outcomes of patients with clinical evidence of advanced-stage ovarian carcinoma treated with neoadjuvant chemotherapy with patients with suboptimally debulked Stage IIIC and Stage IV ovarian carcinoma who were later treated with chemotherapy. They found that the overall survival was the same for both groups of patients but that the patients who received neoadjuvant treatment better tolerated chemotherapy. In addition, in 1999, Schwartz et al.¹⁴ demonstrated that women who underwent cytoreductive surgery after induction chemotherapy had statis-

tically improved overall survival compared with women who did not undergo surgery. These data suggest a need to prospectively identify patients who are most likely to undergo suboptimal surgery and who may be more appropriately treated with neoadjuvant therapy.

Computed tomography (CT) scans have been used extensively as a diagnostic and surveillance tool in patients with ovarian carcinoma. Several investigators have attempted to identify preoperative radiologic criteria that would predict suboptimal debulking.¹⁶⁻¹⁸ Factors that were found to be correlated with suboptimal cytoreduction have included omental extension to the spleen and the presence of suprarenal lymphadenopathy. These factors were associated with relatively high positive predictive values (PPV) and negative predictive values (NPV). However, these investigations were limited by small study populations and were biased by the prevalent low rate of optimal debulking in the study populations (50%). The relevance of the findings to a more aggressive surgical practice is unclear.

The goal of the current study was to determine whether CT scans and CA 125 levels are useful in predicting suboptimal cytoreduction at institutions with a higher optimal debulking rate. These CT criteria must be reproducible and readily identifiable to be useful in a clinical setting.

MATERIALS AND METHODS

A search of our medical records identified 321 patients who underwent primary cytoreductive procedures for ovarian carcinoma between 1996 and 2001. Including CT scans performed at outside institutions prior to referral, 95 patients had a preoperative CT scan available for review. Scans without oral and intravenous contrast or those of poor quality were excluded. Therefore, the study cohort was comprised of 87 patients with Stage III/IV ovarian carcinoma and a preoperative CT scan of acceptable quality.

Hard copy CT scans were evaluated by 2 radiologists using 17 criteria to determine the extent of disease. The examiners were blind as to whether these patients received optimal cytoreduction. Although the default slice thickness on the CT scanners at the study institution is 5 mm, several outside scans had a maximal slice thickness of 10 mm. Criteria examined included diffuse peritoneal thickening (DPT), ascites on at least two-thirds of CT scan sections, bowel encasement with tumor, extension of omental tumor into the spleen or pancreas, diaphragm or lung involvement > 1 cm, omental caking, porta hepatis or gallbladder fossae tumors > 1 cm, hepatic surface implants > 1 cm, presence of disease near the root of the mesen-

tery, large bowel mesentery tumors > 2 cm, small bowel mesentery tumors > 2 cm, suprarenal lymphadenopathy > 1 cm, peritoneal implants > 2 cm, inguinal canal disease or pelvic lymphadenopathy > 2 cm, infrarenal paraaortic lymph nodes > 2 cm, invasive pelvic sidewall disease, and the presence of hydroureter.

Demographic data, preoperative CA 125 levels, surgical procedures, extent of cytoreduction, site of residual disease > 1 cm, operating time, estimated blood loss, number of blood units transfused, complications, and deaths within 30 days of surgery were retrospectively extracted from medical records. Removal of all tumors $\geq$ 1 cm was considered an optimal cytoreduction.

Logistic regression and multivariate analysis using maximal likelihood ratios were used to evaluate the predictors that correlated with optimal surgical resection using JMP statistical software (SAS Institute, Cary, NC). All *P* values correspond with two-sided hypothesis tests and were calculated using the log likelihood ratio test for univariate and multivariate analyses. The current study was approved by the institutional review board of the Mayo Foundation. In accordance with the Minnesota Statute for Use of Medical Information in Research, only patients who consented to the use of their medical records were included in the current analysis.

RESULTS

Demographic and clinical data are shown in Table 1. Procedures were performed by one of eight gynecologic oncologists at the Mayo Clinic (Rochester, MN). Sixty-seven patients (77%) presented with FIGO Stage III ovarian carcinoma and 20 patients (23%) presented with Stage IV disease. Grade 3 lesions were found in 93% of patients. Only six patients (7%) had Grade 1 or 2 carcinomas. Greater than 65% of tumors were of serous differentiation. Optimal cytoreduction was achieved in 62 patients (71%) 25 of whom (29%) had no macroscopic residual disease. In 25 patients (29%), lesions > 1 cm remained at the conclusion of the surgery. Of the patients who did not undergo optimal debulking, 20 (80%) had residual tumor > 1 cm at > 1 site and 10 patients (40%) had residual disease at > 2 sites. The median operating time was 3.5 hours (range, 1.2–7.4 hours). Table 2 shows the procedures performed. They varied according to the extent of disease. Forty-five patients (52%) received radical surgical procedures including radical hysterectomy; resections of the bowel, diaphragm, liver, or spleen; and inguinal lymphadenectomy.

Considering the advanced stage of ovarian carcinoma in these patients and that radical procedures

TABLE 1
Patient Characteristics

Characteristics	No. of patients (%)
Age (yrs)	68 (35–87 yrs) ^a
< 50	9 (10)
50–59	13 (15)
60–69	30 (34)
70–79	29 (33)
$\geq$ 80	6 (7)
Tumor grade	
1	3 (4)
2	3 (4)
3	81 (93)
FIGO stage	
III	67 (77)
IV	20 (23)
Histologic subtype	
Serous	58 (67)
Endometrioid	9 (10)
Mucinous	4 (5)
Undifferentiated	4 (5)
Mixed	4 (5)
Clear cell	3 (4)
Other	5 (6)
Preoperative CA 125 level	388 (8–16,600) ^a
Estimated blood loss	600 (200–2200 mL) ^a
Surgery time	3.7 (1.2–7.4 hrs) ^a
Optimal cytoreduction	62 (71)
Suboptimal cytoreduction	26 (29)

^a Median values and ranges.

FIGO: International Federation of Obstetrics and Gynecology

TABLE 2
Radical Procedures Performed to Achieve Optimal Cytoreduction^a

Procedures	No. of patients (%) ^a
Radical hysterectomy	12 (14)
Large bowel resection	28 (32)
Small bowel resection	5 (6)
Colostomy	7 (8)
Splenectomy	9 (10)
Diaphragmatic stripping/resection	9 (10)
Liver resection	2 (2)
Inguinal lymphadenectomy	1 (1)

^a Percentages are not additive as multiple procedures were performed on some patients.

were performed in > 50% of the cohort, complications were uncommon and consistent with previous investigations.^{9,19} The median estimated blood loss was 600 mL (95% confidence interval [95% CI], 587–854 mL) and the mean number of transfusions was 2.1 U (95% CI, 1.5–2.7 U). No transfusions were given to 45% of the cohort. Among the 77 patients with complete follow-up information, there were 4 deaths occurring in the first 30 days (5.2%), 3 pulmonary embolisms (3.8%), 5 wound infections (6.5%), and 1 myocardial

TABLE 3
Univariate Analysis of CT Predictors for Optimal Cytoreduction

Predictors	No. of patients	P values
DPT	28	0.0001
Ascites on most cuts	33	0.0029
Bowel encasement	32	0.0066
Omental extension (to spleen or pancreas)	31	0.0149
Diaphragm or lung tumors > 1 cm	37	0.0159
Omental caking	58	0.1320
Porta hepatis or gallbladder fossae tumors > 1 cm	16	0.3800
Liver implant > 1 cm	22	0.4175
Presence of disease near root of mesentery	5	0.5427
Large bowel mesentery tumors > 2 cm	23	0.5917
Small bowel mesentery tumors > 2 cm	11	0.7223
Suprarenal lymph nodes > 1 cm	17	0.7680
Peritoneal implants > 2 cm	34	0.8102
Inguinal canal disease or pelvic lymph nodes > 2 cm	10	1.000
Infrarenal paraaortic lymph nodes > 2 cm	16	1.000
Invasive pelvic sidewall disease	15	1.000
Presence of hydroureter	4	1.000

CT: computed tomographic scan; DPT: diffuse peritoneal thickening.

infarction (1.3%). The four deaths included one patient who died of progressive respiratory failure secondary to a myasthenia-like paraneoplastic syndrome. Two patients died of respiratory failure associated with a pulmonary embolism and with aspiration. The fourth patient developed systemic inflammatory response syndrome after reoperation for an anastomotic leak. Other complications included one patient who underwent reoperation for intraabdominal bleeding and the one aforementioned patient who required surgical repair of an anastomotic leak (1 of 31 bowel resections, leak rate 3.1%).

The median preoperative CA 125 level was 388 units/mL (range, 8–16,660 units/mL) for the 74 patients for whom data was available (85%). A CA 125 level > 35 units/mL was present in 94.6% of patients. Contrary to other published reports, we were unable to demonstrate a correlation between preoperative CA 125 values and the success of cytoreduction ($P = 0.66$). More specifically, in 35 patients, the preoperative CA 125 level was > 500 units/mL. Optimal cytoreduction was achieved in 71% of these patients, a figure that is not significantly different from the rate of 69% in patients with a CA 125 level < 500 units/mL. Although most patients had preoperative CA 125 levels available, the small potential for selection bias should be considered.

The 17 factors evaluated by CT scans were subjected to univariate analysis to determine their ability to predict optimal cytoreduction (Table 3). DPT, diaphragm or lung base involvement, bowel encasement, ascites on two-thirds or more of the CT scans, and omental extension into adjacent structures were

found to be statistically significant. However, when these factors were evaluated in a multivariate model, only DPT was found to be an independent predictor of the success of cytoreduction ($P = 0.016$). Ascites on the majority of CT scans and bowel encasement were found to be of borderline significance ($P = 0.08$). Omental extension and diaphragm involvement were not found to be significant predictors ($P = 0.35$ and $P = 0.70$, respectively).

Because DPT appeared to be statistically significant in a multivariate model to determine which patients could undergo optimal cytoreduction, we conducted a prospective study to investigate the reproducibility of making this determination. For our purposes, DPT was defined as ≥ 4 mm involving at least 2 of the following 5 areas: lateral colic gutters, lateral conal fascia, anterior abdominal wall, diaphragm, and pelvic peritoneal reflections.

To determine the interobserver variability associated with DPT, CT scans were chosen randomly from DPT-positive and DPT-negative groups. The CT scans for 43 patients (20 previously read as demonstrating DPT) were reread by 2 radiologists. There was agreement for 93% of the cases (95% CI, 81–98%).

We then created models using all the possible combinations of the five statistically significant predictors identified by univariate analysis. Table 4 shows the most useful models. DPT alone had a PPV of 57% and a NPV of 85%. Therefore, if DPT was present, 57% of patients received a suboptimal cytoreduction versus 29% of the entire cohort. Although DPT alone was found to have a good NPV and sensitivity, the PPV value was poor. The addition of ascites on at least two-thirds of the CT scans to DPT increased the PPV and specificity, but appeared to have a minimal effect on sensitivity and NPV. Further addition of diaphragm or lung base involvement to the model markedly increased the PPV and specificity, but at the expense of NPV and sensitivity, such that only 14 of 26 suboptimally debulked patients would be detected by this model. The combination of DPT and ascites on at least two-thirds of CT scans would appear to be the most simple and, therefore, most clinically useful model to predict suboptimal cytoreduction. It offers a good compromise between PPV and sensitivity. Other models using various combinations of omental extension or bowel encasement with DPT, large-volume ascites, and diaphragm or lung base involvement had much lower PPV and sensitivity values.

DISCUSSION

Other investigators have suggested that preoperative prediction of optimal debulking using CT scans is possible.^{16–18} Alternatively, some authors attest that

TABLE 4
The Most Useful Models to Predict Suboptimal Cytoreduction

Characteristics	No. of patients	PPV	NPV	Sens	Spec	OR (95% CI)	P
DPT	28	57	85	64	81	7.4 (2.7–21.7)	0.0001
DPT and ascites most cuts	19	68	82	52	90	10.1 (3.3–34.2)	< 0.0001
DPT, ascites, diaphragm	14	79	81	44	95	15.5 (4.2–75.4)	0.0001

PPV: positive predictive value; NPV: negative predictive value; Sens: sensitivity; Spec: specificity; OR: odds ratio; 95% CI: 95% confidence interval; DPT: diffuse peritoneal thickening.

magnetic resonance imaging may be more useful than CT scans in the detection of peritoneal spread of ovarian carcinoma.^{20–22} Nelson et al.¹⁸ retrospectively identified 34 patients with Stage III/IV disease who had undergone CT imaging scans before cytoreduction. Removing the patients with early-stage lesions from the analysis, 62% of patients received optimal cytoreduction, but this was defined as resection of all tumors < 2 cm. Nelson et al. were able to predict suboptimal cytoreduction using the following criteria: attachment of the omentum to the spleen and tumors > 2 cm in the mesentery, liver, diaphragm, gallbladder fossa, suprarenal paraaortic lymph nodes, pericardiac lymph nodes, and the lungs. Using these criteria, the PPV was 66.7% and the NPV was 93.8%. They concluded that CT scanning is a valuable tool for predicting optimal cytoreduction.

Pooling data from Johns Hopkins and Massachusetts General Hospital, Bristow et al.¹⁶ analyzed preoperative CT scans from 41 women with advanced ovarian carcinoma and created a model to predict those patients who were likely to undergo an optimal cytoreduction. Useful predictors included peritoneal thickening, peritoneal implants > 2 cm, bowel mesentery tumors > 2 cm, suprarenal lymph nodes > 1 cm, omental extension to the spleen, pelvic sidewall involvement, and hydroureter. Using predictive index scores ≥ 4 , the authors were able to achieve a PPV of 87.5% and an NPV of 100%. In that series, 49% of patients underwent resection for all tumors > 1 cm. The authors concluded that their scoring system might have clinical utility in predicting which patients would undergo an optimal cytoreduction. However, this model is complex and difficult to apply to clinical practice.

In contrast to other series, only 1 of the 17 predictors evaluated, DPT, was found to be a statistically significant independent predictor of suboptimal cytoreduction. This is most likely a reflection of the interdependence among the surgical-pathologic variables present in patients with advanced ovarian carcinoma. Although the term “diffuse peritoneal thickening” may appear to be a rather subjective term, it was defined strictly enough for the current study to be

very reproducible (93%). We would suggest that others use this empirically derived definition in subsequent studies to validate this finding, because it appears to be reproducible by reviewing radiologists. It should be remembered that two techniques of CT scans were used in the current study. However, we believe that factors such as DPT and large-volume ascites would be correctly identified by using 5-mm or 10-mm sectioning techniques. It would appear that the addition of ascites on two-thirds or more of the CT scans to DPT is a simple model with clinical utility in our surgical practice. If both DPT and large-volume ascites were present, the optimal cytoreduction rate was only 32% versus 71% for the entire cohort. In contrast, if both predictors were absent, the optimal cytoreduction rate was 82%. The presence of these 2 factors could predict 52% of suboptimal surgeries. Furthermore, of all patients who underwent optimal cytoreduction, only 10% had both predictors present. The association of large-volume ascites and DPT with poor cytoreduction rates would appear to be logical, and likely indicates the presence of diffuse miliary disease that is very difficult to resect. In the current study, 52% of patients underwent radical procedures (Table 2). It is not possible to determine the applicability of this model in a less aggressive surgical practice. We should also point out that these findings are apt to be irrelevant when a gynecologic oncologist is not available for intraoperative care. Unfortunately, this remains a common occurrence in the U.S. In addition, given the retrospective design of the current study and the finding that less than half of patients received CT scans preoperatively, there undoubtedly exists some bias, reiterating the need for these studies to be confirmed prospectively.

Others have found an association between preoperative CA 125 levels and success at optimal surgical resection. Chi et al.²³ analyzed 100 consecutive patients with Stage III ovarian carcinoma and used a receiver operating characteristic curve to identify a cutoff CA 125 level with the most predictive power. Although their overall optimal cytoreduction level was 45%, 73% of patients with a CA 125 level < 500 underwent optimal cytoreduction. In contrast, only 22% of

those with a CA 125 level > 500 underwent optimal cytoreduction. Stratification of patients according to CA 125 levels allowed Chi et al. to retrospectively identify 78% of those patients who underwent suboptimal debulking. Other authors have verified these findings.^{24,25} In contrast, Memarzadeh et al.²⁶ published an investigation of 99 patients with advanced ovarian carcinoma. With a relatively high overall optimal resection rate of 73%, they found that the preoperative CA 125 level was a poor predictor of optimal resection. They concluded that the CA 125 level should be viewed in context with other features before surgery and that the CA 125 level did not necessarily predict which patients would have poor outcomes after cytoreduction. In the current study, we did not find the CA 125 level to be a useful predictor of suboptimal debulking. Optimal cytoreduction rates were found to be no different between patients with a CA 125 level < 500 and those with a CA 125 level > 500.

In comparing the available data from the current study with those from others, the current study findings emphasize that resectability is a relative term. Likewise, cogent prognosticators of suboptimal cytoreduction are likely to vary between groups of physicians with differing surgical techniques and philosophies. Studies demonstrating the value of specific predictability criteria need to be interpreted with extreme caution because the reproducibility of findings is likely to be dependent on a similar practice pattern and anticipated optimal debulking rates. In the current study, a model using only 2 of 17 predictors was a useful indicator of suboptimal cytoreduction, in contrast to other investigations using up to 8 predictors. It is important for all gynecologic oncologists to objectively determine their optimal cytoreduction rates and decide if CT scans would be useful in their own surgical practices. In our practice, patients with DPT and large-volume ascites appear to have rates of optimal cytoreduction that are substantially below our average rate. These patients may be alternatively treated with neoadjuvant chemotherapy followed by surgical debulking. This is a complex issue and the outcome depends on the patient's underlying medical conditions, surgical risks, feelings regarding surgery, and the expertise of the operating surgeon. Ultimately, some individualization based on these data may translate into better outcomes and reduced morbidity for patients with ovarian carcinoma.

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