

Enhancing Fraction Predicts Clinical Outcome following First-Line Chemotherapy in Patients with Epithelial Ovarian Carcinoma

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Abstract Purpose: To define a simple radiologic biomarker of prognosis in patients with advanced epithelial ovarian carcinoma on first-line chemotherapy.

Experimental Design: Twenty-seven patients receiving platinum-based chemotherapy with >2 cm residual disease [International Federation of Gynecology and Obstetrics (FIGO) stages IIIc or IV] after surgery were identified. The proportion of enhancing tumor tissue—the enhancing fraction—was calculated on pre-chemotherapy computed tomography scans at four Hounsfield unit (HU) thresholds and assessed for correlation with CA125 response, Response Evaluation Criteria in Solid Tumors (RECIST) radiologic response, and time to progression. Discriminative power was assessed by leave-one-out discriminant analysis.

Results: Pre-chemotherapy residual tumor volume did not correlate with clinical outcome. Pre-chemotherapy enhancing fraction at all thresholds significantly correlated with CA125 response ($P < 0.001$, $\rho = 0.553$ for 50 HU; $P < 0.001$, $\rho = 0.565$ for 60 HU; $P < 0.001$, $\rho = 0.553$ for 70 HU; $P = 0.001$, $\rho = 0.516$ for 80 HU). Significant correlations were also shown for radiologic response at all thresholds. Enhancing fraction predicted CA125 response with 81.9% to 86.4% specificity and Response Evaluation Criteria in Solid Tumors response with 74.9% to 76.8% specificity at 95% sensitivity (dependent on threshold). Enhancing fraction correlated with time to progression at the 60 HU ($P = 0.045$, $\rho = 0.336$) and 70 HU ($P = 0.042$; $\rho = 0.340$) thresholds.

Conclusion: Pre-chemotherapy enhancing fraction is a simple quantitative radiologic measure. Further evaluation in larger trials is required to confirm the potential of enhancing fraction as a predictive factor, particularly for patients who may benefit from the addition of antiangiogenic therapy.

Ovarian carcinoma is the sixth most common cancer and the seventh highest cause of cancer deaths in women worldwide (4.0% cases and 4.2% deaths). Around 204,000 new cases and 125,000 deaths are reported annually. Incidence rates are highest in North America and Europe (typically 9-14 per 100,000; ref. 1). Approximately 90% of ovarian cancers are

epithelial in origin, distinct from germ cell tumors, sex-cord stromal tumors, and metastases (2). Major prognostic factors following surgery are FIGO stage, residual disease bulk, and Karnofsky index (3). Around two thirds of patients with epithelial ovarian carcinoma present with advanced disease (FIGO stage III and IV) and have a poor prognosis following cytotoxic chemotherapy, with 5-year survival of ~12% to 18% (3, 4).⁵

Contrast-enhanced imaging techniques are commonly used to evaluate tumors (e.g., by accurately and noninvasively assessing tumor grade; refs. 5, 6). Furthermore, contrast-enhanced imaging has shown dose-related changes in tumor vascular variables following treatment with chemotherapeutic and antiangiogenic agents (7-9) that correlate with improved clinical outcome (10, 11). In these methods, the concentration of contrast agent within tumor tissue is estimated to provide measures that estimate microvascular perfusion, capillary endothelial permeability, and interstitial volume. Analysis can be complex and may require pharmacokinetic modeling, limiting the routine application of such techniques (12-16).

Alternative, simple image-based measures of the tumor vasculature that predict clinical outcome are, therefore, highly attractive. A phase I trial using dynamic contrast-enhanced

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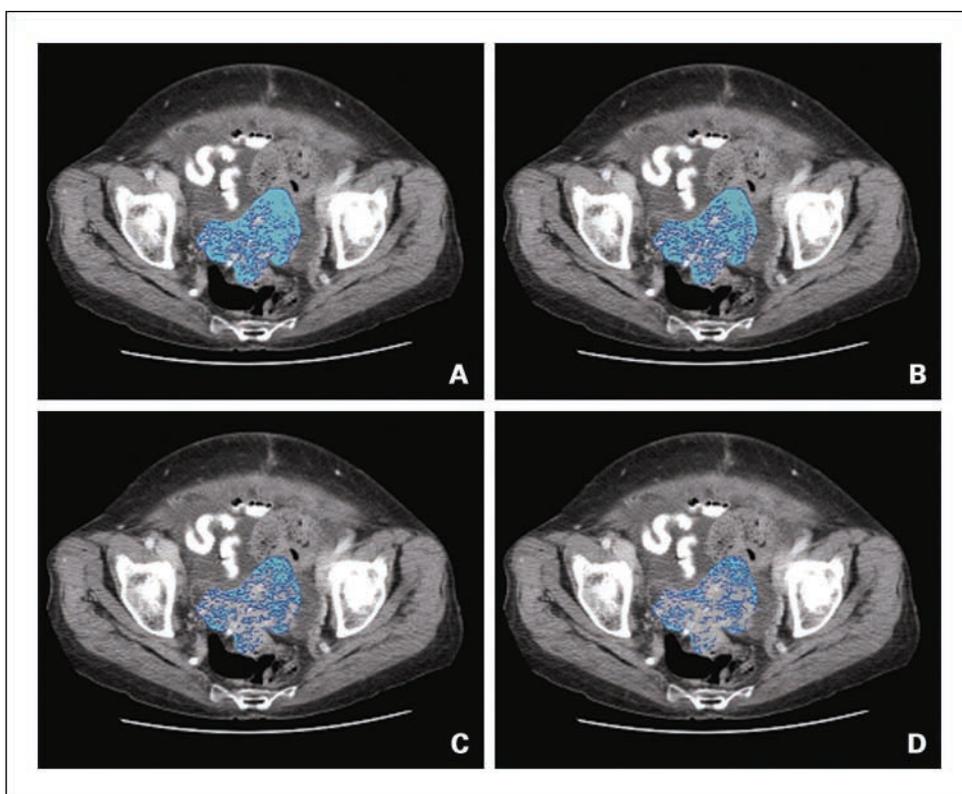
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⁵ <http://info.cancerresearch.uk.org/cancerstats/types/ovary/survival/>

Fig. 1. Enhancing fraction in a pelvic mass in a patient with advanced epithelial ovarian carcinoma, defined at thresholds of 50 HU (A), 60 HU (B), 70 HU (C), and 80 HU (D). The pixels consistent with cystic and calcified tissue were excluded from the whole tumor volume region of interest.



magnetic resonance imaging (MRI) has shown that the proportion of enhancing tissue within ovarian tumors—the enhancing fraction—may be a simple measure of overall perfused tissue within a tumor (17). Furthermore, rapid changes in enhancing fraction followed therapy with an antiangiogenic agent designed to reduce interstitial pressure. In another clinical trial, dynamic contrast-enhanced MRI measurements of enhancing fraction were shown to discriminate between stable and progressive disease in the absence of a clear treatment effect in patients with mixed solid tumors. Here, high enhancing fraction indicated poorer prognosis (18). These latter data suggest that enhancing fraction may be indicative of gross angiogenic state and growth potential within a tumor.

To further evaluate this hypothesis, we carried out a retrospective assessment of contrast-enhanced X-ray computed tomography (CT) data acquired during the standard management of patients with ovarian cancer. We measured the proportion of tumor tissue with Hounsfield units (HU) consistent with enhancement in postoperative patients with FIGO stage IIIC or IV epithelial ovarian carcinoma and hypothesized that tumor enhancement at pre-chemotherapy imaging could predict clinical outcome, thus identifying patients with poor prognosis who might benefit from an alternative therapeutic strategy, such as combination therapy with an angiogenesis inhibitor.

Materials and Methods

Patients treated by a single consultant at the Christie Cancer Centre (G.J.) were eligible for the study. All patients received first-line platinum-based cytotoxic chemotherapy according to standard protocols, following histopathologic confirmation of the diagnosis. Those with FIGO stage IIIC and IV epithelial ovarian cancer diagnosed

between June 2001 and September 2003 with >2 cm of residual disease within the abdomen or pelvis were identified. Inclusion criteria were CT scan between surgery and first cytotoxic chemotherapy administration; follow-up CT scan to assess radiologic response; and serial measurements of CA125 plasma concentrations. Patients with no documented history of previous CA125 secretion and those with predominantly cystic lesions were excluded. The study was approved by the local Research Ethics Committee.

Patients were imaged using a LightSpeed Plus CT scanner (GE Medical Systems) with typical clinical helical acquisition variables (tube voltage 120 kV, tube current 40 mA, 7.5-mm slice thickness). All images were acquired following i.v. injection of 200-mL Omnipaque-140 (GE Medical Systems, Amersham). Tumors >2 cm were selected; diffuse peritoneal lesions with indistinct margins were excluded. Image analysis was done using MRIcro.⁶ Regions of interest were manually drawn over all tumor-containing slices by two experienced radiologists (B.M.C. and D.G.). Areas of cyst and calcification within the tumors were considered present using thresholds set at <10 HU and >150 HU, respectively, and excluded from subsequent analysis. The residual (necrotic, noncalcified) tumor was defined as the whole tumor volume.

Because all data were acquired post-contrast as part of routine clinical imaging, we defined HU thresholds above which tissue was classified as enhancing; tissue below threshold was considered nonenhancing. Four separate HU thresholds of 50, 60, 70, and 80 HU were used to exclude the possibility that any findings would be a consequence of arbitrarily selected HU thresholds (Fig. 1).

Change in plasma CA125 levels, as defined by the Gynecologic Cancer Intergroup, was calculated after three cycles of chemotherapy (19). Response to treatment after six cycles of platinum-based chemotherapy was assessed by the CT-based Response Evaluation Criteria in Solid Tumors (RECIST) criteria (20). Both measures of response and their timing were done as consistent with routine clinical

⁶ <http://www.sph.sc.edu/comd/rorden/mricro>

practice. Patients were then grouped into those with stable disease or better (complete or partial response) versus those with disease progression, for both radiologic and CA125 criteria. Further classification of disease status was not included in the analysis to maintain the statistical power of this relatively small study. Time to progression (TTP) was calculated from start of treatment. Whole tumor volume and all four threshold measures of tumor-enhancing fraction were examined for evidence of correlation with each clinical outcome measure using Spearman's test for nonparametric data in SPSS 13.0. Potential difference in enhancement due to choice of single agent carboplatin versus combination therapy with paclitaxel was evaluated using an independent samples *t* test.

A leave-one-out linear discriminant analysis was done to evaluate the ability of pre-chemotherapy enhancing fraction to differentiate between the stable or better versus progressive disease and thus predict posttreatment outcome. Due to the relatively small number of patients, a leave-one-out scheme was used. For each possible pairing of response type and HU threshold, the following procedure was implemented: the first individual was considered a test subject and a linear classifier was trained on the remaining individuals' responses; the classifier was then used to predict the class for the left-out individual. This procedure was then repeated for each patient by leaving out the second, then the third, and so on. Classifier output was expressed as the probability of an individual belonging to the one class. Receiver operating characteristic (ROC) analyses were then done on these probabilities (21). The area under the ROC curve, a summary statistic of classifier performance, was computed using numerical integration. Differences between ROC curve areas were investigated to determine if some thresholds were better able to predict posttreatment outcome class (22).

Results

Twenty-seven women with a median age of 67 years (range, 43-86 years) were included. Karnofsky indices ranged from 40 to 90. Patient characteristics are shown in Table 1. A total of 36 tumors were assessed. Of these, nine tumors were in six patients with progressive disease by CA125 criteria.

Table 1. Patient demographics

Patient demographics	No. patients
Total	
FIGO stage IIIC	20
FIGO stage IV	7
Histopathology	
Serous	16
Endometrioid	4
Clear cell	2
Mixed serous/endometrioid	1
Not specified	4
No. disease sites	
One	18
Two	9
Previous surgery	
TAH/BSO/omentectomy	12
BSO/omentectomy	1
Oophrectomy alone	5
Omentectomy alone	3
None (biopsy proven)	6
Chemotherapy	
Single agent carboplatin	13
Carboplatin + paclitaxel	14

Abbreviations: TAH, abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

Table 2. Correlation of clinical outcome measures with enhancement, defined by the fraction of tumor tissue above each Hounsfield unit threshold

Threshold (HU)	Clinical outcome measure					
	CA125 response		Radiology response		TTP	
	<i>P</i>	ρ	<i>P</i>	ρ	<i>P</i>	ρ
≥50	<0.001	0.553	0.019	0.388	0.066	0.310
≥60	<0.001	0.565	0.015	0.402	0.045	0.336
≥70	<0.001	0.553	0.017	0.395	0.042	0.340
≥80	0.001	0.516	0.022	0.382	0.114	0.268

NOTE: Response measured by decrease in CA125 plasma concentration by Gynecologic Cancer Intergroup criteria and by the RECIST radiologic response criteria. TTP was recorded as number of days from commencement of first-line chemotherapy to diagnosis of recurrent disease.

No significant correlation was shown between whole tumor volume before chemotherapy and CA125 response ($P = 0.271$), radiologic response criteria ($P = 0.184$), or TTP ($P = 0.881$). There was no significant difference between enhancing fraction in those patients receiving combination carboplatin and paclitaxel versus those on single agent carboplatin ($P = 0.508$ for 50 HU threshold; $P = 0.737$ for 60 HU threshold; $P = 0.706$ for 70 HU threshold; $P = 0.691$ for 80 HU threshold).

Strong significant correlations were found between the fraction of post-contrast tumor tissue above 60 HU and 70 HU and CA125 response ($P < 0.001$ for both thresholds) and radiologic response ($P = 0.015$ for 60 HU threshold; $P = 0.017$ for 70 HU threshold). Significant correlation was also found between enhancing fraction and the TTP ($P = 0.045$ for 60 HU threshold; $P = 0.042$ for 70 HU threshold). Enhancing fraction defined by thresholds of greater than 50 HU and 80 HU correlated with CA125 and radiologic response but did not correlate with TTP. CA125 and RECIST measures of response were highly significantly correlated ($P < 0.001$; $\rho = 0.851$). Statistical measures are summarized in Table 2.

Figure 2 shows the distributions of tumor-enhancing fraction at each HU threshold for the stable disease or better versus progressive disease groups. Consistent differences were visible when disease status was defined using either CA125 or RECIST criteria. Figure 3 shows the relationship between TTP and enhancing fraction defined at the 60 HU level. There was a clear indication that patients with lower tumor-enhancing fraction tended to have longer TTP and that patients with stable disease or better (defined by CA125 response) had lower enhancing fractions.

Figure 4 shows the ROC curves for both CA125 and RECIST response for all enhancement thresholds. The area under the ROC curves ranged from 0.749 (80 HU threshold; radiologic response definition) to 0.864 (60 HU threshold; CA125 response). The SEs on the area were ~ 0.05 for the radiologic response definition and ~ 0.06 for the CA125 response; no statistically significant differences were found between the four HU thresholds for either definition of response. The areas under the ROC curve were greater when using the CA125 definition of response for all HU thresholds than when using the RECIST criteria.

Discussion

The majority of women with epithelial ovarian carcinoma present with incurable FIGO stage III or IV disease. Treatment with platinum-based chemotherapy is recommended following debulking surgery (23). Single agent carboplatin and carboplatin with paclitaxel are considered equivalent first-line therapies with regard to TTP and overall survival (24, 25). Most stage III and IV patients develop recurrent disease that eventually acquires chemoresistance. Despite the poor prognosis, significant variation in response to first-line chemotherapy is seen. At present, no simple marker predicts treatment response and/or progression-free survival. Development of such markers could enable early identification of patients who will respond poorly to conventional treatment and might benefit from combination therapy with an alternative agent such as an angiogenesis inhibitor.

The establishment of an effective vascular supply is an important prerequisite for tumor growth (26). Highly vascular

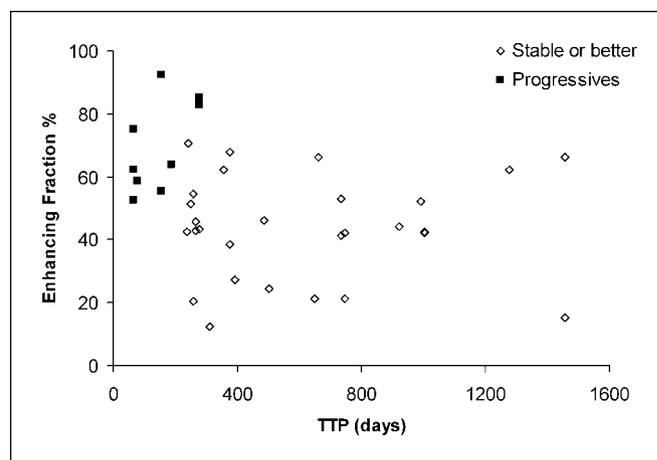


Fig. 3. Scatter plot showing the relationship between the enhancing fraction (defined as the fraction of whole tumor volume above 60 HU) and TTP. Lesions are grouped as stable or better versus progression (defined by CA125 response after chemotherapy).

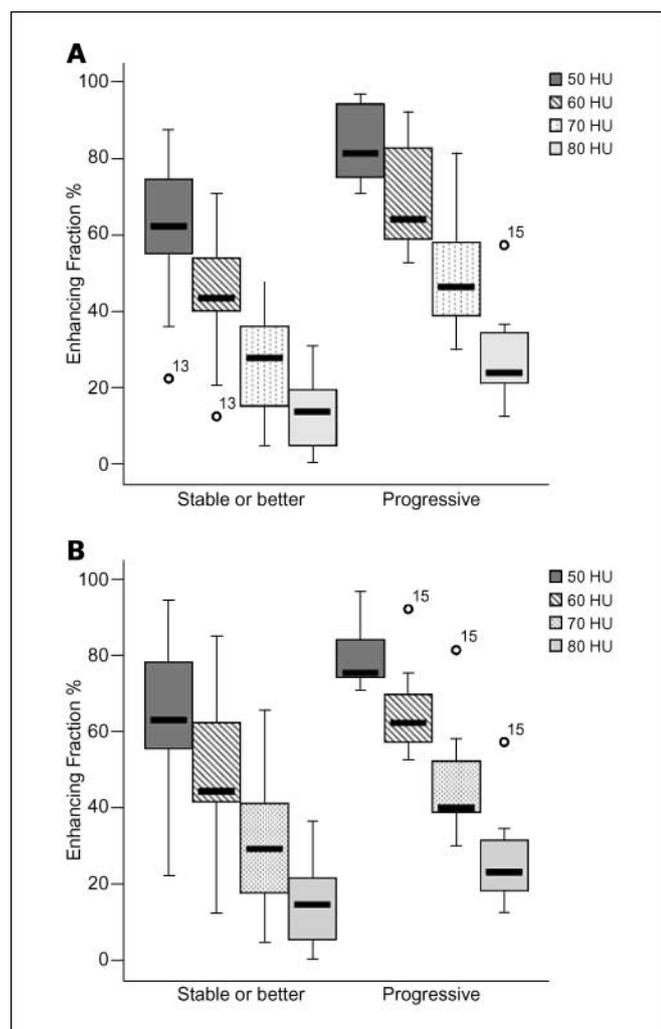


Fig. 2. Box plot showing the relationship between the enhancing fraction (expressed as a percentage of whole tumor volume) and response rate defined by CA125 level (A) and radiologic (RECIST) criteria (B). Data are presented for each Hounsfield unit definition of enhancing fraction. Patients with stable disease or better are grouped together and compared with those with progressive disease. Outliers are represented by small circles (O).

tumors have been shown to be more aggressive and associated with poor clinical outcome (27). Compounds that inhibit angiogenesis have been shown to improve clinical outcome in solid tumors (28–31). Imaging studies offer an attractive noninvasive method of evaluating tumor microvascular function in patients. Because the voxel sizes obtained in CT and MRI are at the millimeter scale, enhancement is a simple indicator of regional tumor perfusion.

A limited number of radiologic studies have reported a predictive relationship between enhancement and clinical outcome. Small enhancing tumor volume, defined on T_1 -weighted MRI, has been shown to predict prolonged survival in patients with recurrent high grade gliomas (32). Presence of hypervascular breast cancer liver metastases, assessed subjectively by relative enhancement on MRI, may serve as an independent predictor of disease progression (33). Change in relative perfusion in cervical cancer, measured by MRI signal intensity changes due to contrast agent, has predicted response to subsequent radiotherapy. In contrast with other results discussed above, this latter study indicated that patients with higher baseline tissue perfusion had a better clinical outcome (34). However, other cervical cancer studies have shown opposing results (35).

In our study, we tested the hypothesis that enhancing fraction might predict clinical outcome. Patients with similar volumes of residual disease and stage were grouped into those with stable disease or better versus those with disease progression—a strategy used in several contrast-enhanced imaging-based trials of angiogenesis inhibitors (7, 36). Retrospective data were used to define whole tumor volume and enhancing volume on single post-contrast CT scans because pre-contrast sequences are not routinely acquired during routine clinical imaging in our center; we therefore defined approximate “enhancing” fractions of tumor tissue according to post-contrast Hounsfield unit values.

Four different thresholds above 50 HU were chosen to define regions of interest heavily weighted toward enhancing tumor tissue because no well-established definition for tumor contrast enhancement in CT studies exists. The proportion of tissue classified as enhancing was significantly associated with and

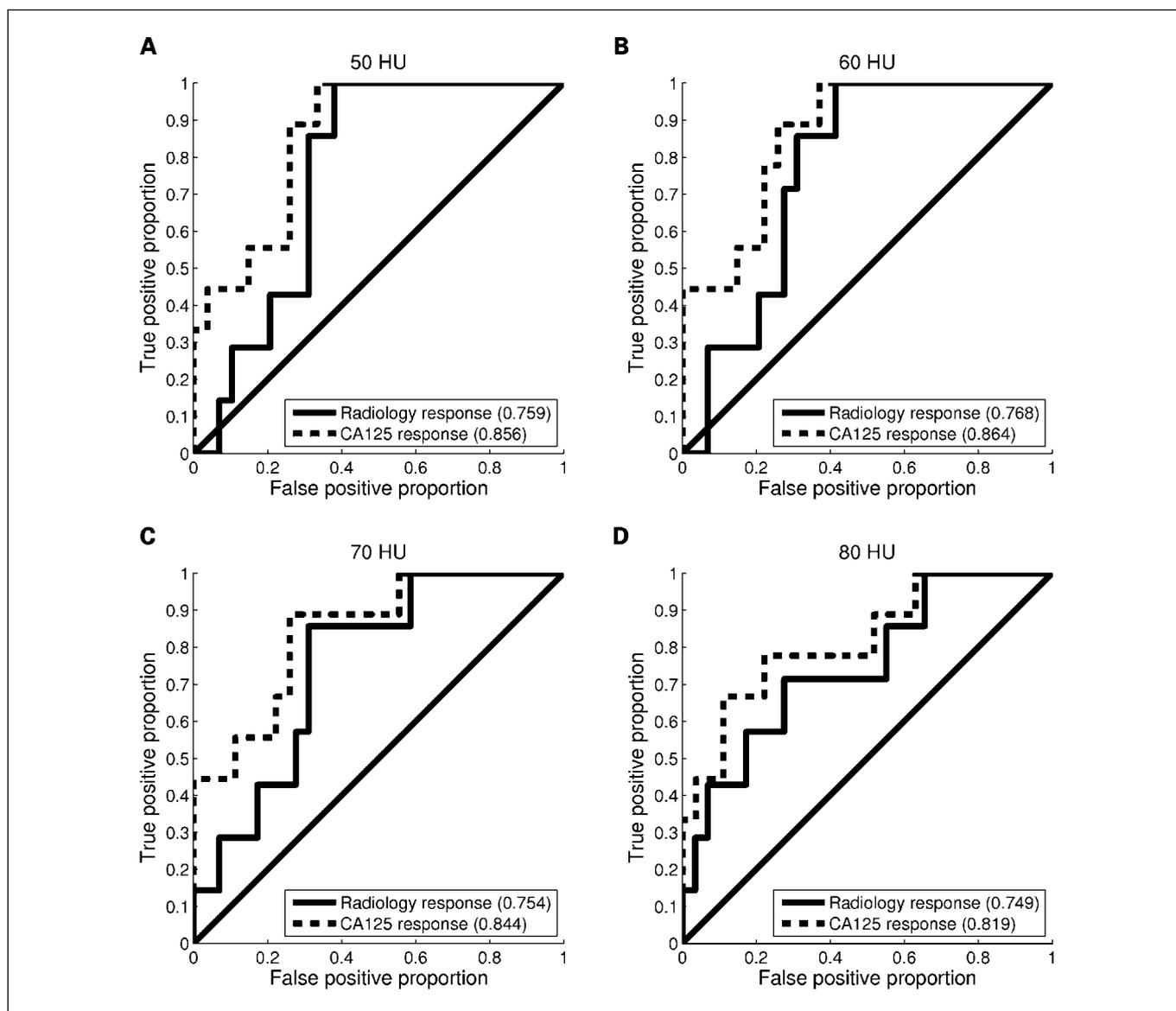


Fig. 4. ROC curves showing the ability of four different Hounsfield unit threshold definitions of enhancing fraction to predict radiology (solid lines) and CA125 response (dotted lines). Diagonal lines, performance of a random decision process. Numbers in brackets indicate area under the corresponding curve.

predicted both CA125 and radiologic response at each HU threshold. This reflects the fact that the higher threshold definitions are subsets of the lower threshold definitions and suggests that the results were independent of the precise definition of enhancement used. Furthermore, the proportion of tumor tissue above 60 HU and 70 HU correlated with TTP. These relationships were independent of the lesion size (in patients with at least 2 cm residual disease).

Enhancing fraction predicted CA125 response with 81.9% to 86.4% specificity and RECIST response with 74.9% to 76.8% specificity at 95% sensitivity (dependent on threshold). Some overlap was seen between those with progressive disease and those who did not progress for each HU threshold because enhancing fraction was not a perfect separator of clinical outcome. It is notable that the enhancing fraction predicted CA125 measures of response better than RECIST. Thus, enhancing fraction seems to predict systemic outcome,

despite being based on a measurement from an individual tumor.

The absence of pre-contrast CT images to define more objective estimates of enhancing tumor volume is both a strength and a weakness of this study. Direct measurement of tumor tissue attenuation using both pre- and post-contrast images may provide a more accurate measure of enhancement and improve predictive power. Such techniques introduce an additional image processing step and may require application of image registration software if significant patient movement occurs—a not inconsiderable complication (37, 38). Our method represents the simplest measure of enhancing fraction that can be extracted from clinical data and the relationship to clinical outcome seems to be robust to the exact choice of HU threshold used. We therefore anticipate that the method described may be an easily applicable tool for oncologists who require simple but powerful prognostic imaging

biomarkers of clinical outcome in patients with advanced ovarian cancer.

In conclusion, the results of this small retrospective study are highly significant. Our data suggest that the tumor-enhancing fraction pre-chemotherapy correlates with subsequent radiologic response, CA125 response, and TTP after completion of first-line chemotherapy. This is consistent with the hypothesis that more vascular tumors (high enhancing fraction) are more angiogenic, exhibit more aggressive tumor growth, and have poorer outcome. Our results concur with studies of gliomas and breast cancer liver metastases cited above. Enhancing fraction is a comparatively simple quantitative radiologic measure that can be calculated easily from conventional CT imaging done

during routine pretreatment evaluation, although more complicated methods of measuring contrast-enhancement could be used. Further prospective evaluation of enhancing fraction as a predictive biomarker of clinical outcome is required, and may assist identification of those patients who may benefit most from combination therapy with an angiogenesis inhibitor.

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