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ORIGINAL ARTICLE

A novel index for preoperative, non-invasive prediction of macro-radical primary surgery in patients with stage IIIC–IV ovarian cancer—a part of the Danish prospective pelvic mass study

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Abstract The purpose of this study was to develop a novel index for preoperative, non-invasive prediction of complete primary cytoreduction in patients with FIGO stage IIIC–IV epithelial ovarian cancer. Prospectively collected clinical data was registered in the Danish Gynecologic Cancer Database. Blood samples were collected within 14 days of surgery and stored by the Danish CancerBiobank. Serum human epididymis protein 4 (HE4), serum cancer antigen 125 (CA125), age, performance status, and presence/absence of ascites at ultrasonography were evaluated individually and combined to predict complete tumor removal. One hundred fifty patients with advanced epithelial ovarian cancer were treated with primary debulking surgery (PDS). Complete PDS was achieved in 41 cases (27 %). The receiver operating characteristic curves demonstrated an area under the curve of 0.785 for HE4, 0.678 for CA125, and 0.688 for age. The multivariate model (Cancer Ovarii Non-invasive Assessment of Treatment Strategy (CONATS) index), consisting of HE4, age, and performance status, demonstrated an AUC of 0.853. According to the Danish indicator level, macro-radical PDS should be achieved in 60 % of patients admitted to primary surgery (positive predictive value of 60 %), resulting in a negative predictive value of 87.5 %, sensitivity of 68.3 %, specificity of 83.5 %, and cutoff of 0.63 for the CONATS index. Non-invasive prediction of complete PDS is possible with the CONATS index. The CONATS index is meant as a supplement to the standard preoperative evaluation of each patient. Evaluation of the CONATS index combined with radiological and/or laparoscopic findings may improve the assessment of the optimal treatment strategy in patients with advanced epithelial ovarian cancer.

Keywords Ovarian cancer · HE4 · Primary debulking surgery · Neoadjuvant chemotherapy · Multidisciplinary team meetings · Non-invasive prediction model

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Introduction

Primary debulking surgery (PDS) followed by adjuvant platinum-taxane-based chemotherapy is the first choice of treatment of epithelial ovarian cancer (EOC). Macro-radical PDS is an important prognostic factor for women with EOC [1, 2]. However, patients treated with neoadjuvant chemotherapy (NACT) and interval debulking surgery have in some studies been found to have similar overall survival but reduced risk of complications compared to patients treated with PDS

[3–5]. Hence, NACT is an alternative, when primary macro-radical PDS is considered impossible.

However, planning of the optimal treatment strategy is a clinical challenge. No preoperative predicting tool of macro-radicality is available, neither exists any consensus about the assessment of optimal treatment strategy of patients with advanced (stage IIIC–IV) EOC. In Denmark, each patient is evaluated at a multidisciplinary team (MDT) conference with the presence of specialists in gynecology, radiology, oncology and, when needed, general surgery and pathology. An individual treatment strategy is planned based on a positron emission tomography/computed tomography (PET-CT) scan or magnetic resonance imaging (MRI) and the attending specialist's overall evaluation of the patient's health. Age and performance status (PS) are used to assess if a patient can tolerate the extensive surgery, which often is a necessity to obtain macro-radical surgery.

The serum markers cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are stable and clinically relevant markers [6]. Both markers are accepted for differentiating between benign ovarian tumors and EOC. Variable results have been demonstrated, when these markers are used for predicting surgical outcome [7–15]. Combined, the two markers seem to improve the accuracy of predicting macro-radical PDS [16, 17]. It should be noted that most studies evaluating CA125 as a predictor of surgical outcome defined successful PDS as residual tumor ≤1 cm.

Ascites is a simple surrogate measure for the volume and spread of EOC tissue and may be a predictive variable when assessing the probability of macro-radical PDS. Ascites has been evaluated preoperatively by PET-CT [18], CT [19–22], or ultrasonography in relatively small studies, compared to the number of variables included and/or evaluated intraoperatively (laparoscopy or laparotomy) [21, 23, 24]. However, no uniform volume cutoff has been defined in order to categorize patients as high or low risk of residual tumor after PDS.

The purpose of this study was to develop a preoperative, non-invasive method to select between two treatment strategies, PDS and adjuvant chemotherapy or NACT with the intention of interval debulking surgery.

In order to predict macro-radical PDS, we evaluated serum HE4 and CA125, age, Eastern Cooperative Oncology Group (ECOG) PS, and presence/absence of ascites at preoperative ultrasonography.

Material and methods

This study was a part of the Danish Pelvic Mass study, a prospective, ongoing study with use of archived specimens. Oral and written consent was given by each patient before enrollment. The Danish Ethical Committee has approved the study protocol (KF01-227/03 and KF01-143/04, H-3-2010-022).

Patients

From September 2004 to January 2010, a total of 164 patients with FIGO stages IIIC and IV EOC were consecutively included when admitted to the tertiary center, the Gynecologic Clinic, University Hospital of Copenhagen, Rigshospitalet, because of a pelvic mass potentially caused by EOC.

Exclusion criteria were treatment with NACT (n = 9) or palliative care (n = 4). Patients with preoperative known relapse of previous cancer or an active cancer other than EOC were not included. PS = 4 (n = 1) was also included, since these patients are not considered candidates for the extensive surgery.

Patients were examined according to the Danish Cancer Fast Track Guidelines, including gynecological examination, serum CA125 measurement, ultrasound examination, risk of malignancy index (RMI) calculation, PET-CT, and PS evaluation. This information combined with age, previous abdominal surgery and, if any, comorbidities including obesity was discussed at MDT, and a treatment strategy was planned. Macro-radical tumor removal was intended at PDS. All patients were operated by a specialist in gynecologic oncology. The patients included in this study were evaluated at a time, where largely all patients were offered PDS.

All diagnoses were confirmed by a pathologist specialized in gynecological pathology.

All patient data were registered continuously in the Danish Gynecologic Cancer Database (DGCD) by gynecologists, pathologists, and oncologists.

Blood samples

Blood samples were collected within 2 weeks of surgery and handled and stored according to strict Biobank guidelines by the Danish CancerBiobank [25]. Serum CA125 (U/ml) and HE4 (pmol/l) were quantitatively determined by a two-step chemiluminescent microparticle immunoassay (CMIA) by the Architect I2000sr System, Abbott Diagnostics.

Statistical analyses

HE4, CA125, age, ascites on ultrasound (presence/absence), and PS (0–3) were evaluated in order to predict residual tumor after PDS.

Univariate analyses were made using the chi-square test and Mann-Whitney U test. The Spearman rank correlation was used as a measure of association.

Multivariate analysis was performed using logistic regression modeling. Insignificant contribution ($p > 0.05$) to the model resulted in exclusion by backward reduction.

CA125 and HE4 were log base2 transformed; therefore, the OR is for a two-fold difference in a marker level. The Hosmer-Lemeshow test was used to assess the goodness of fit.

Receiver operating characteristic (ROC) curves were generated to assess the accuracy in prediction of complete PDS for log2(HE4), log2(CA125), age, and the multivariate index, called the Cancer Ovarii Non-invasive Assessment of Treatment Strategy (CONATS) Index.

The CONATS index was correlated to overall survival by Cox proportional hazards regression analysis. The hazard ratio is for a 20 % difference in the CONATS value. Overall survival was defined as time from surgery to death of any cause.

Internal validation of the CONATS index was performed using 100 bootstraps with backward selection.

A two-sided p value <0.05 was considered significant.

Statistical analyses were performed by SPSS Statistics (19.0 IBM Corporation), SAS (version 9.3, SAS Institute), and R package (version 4.2-0. http://CRAN. R-project. org/package=rms).

Results

Overall, 150 patients with advanced EOC were evaluated. All patients underwent PDS; macro-radical PDS was achieved in 41 patients (27 %), whereas 109 patients (73 %) had visible residual tumor.

Baseline data for surgical outcome according to histology and stage are outlined in Table 1. Baseline data for HE4, CA125, age, PS, and presence of ascites are outlined in Table 2.

HE4 and CA125 were significantly associated (correlation coefficient = 0.490, $p < 0.001$) as well as HE4 and age (correlation coefficient = 0.238, $p = 0.003$). No significant association was seen between CA125 and age ($p = 0.832$).

Age, HE4, CA125, presence/absence of ascites, and PS 0–3 were all highly significant ($p < 0.001$) in prediction of surgical outcome in the univariate analyses. ROC-AUC for age, HE4, and CA125 is shown in Table 2 and Fig. 1. The accuracy of the presence/absence of ascites on ultrasound as a predictor of surgical outcome was 67 %, as 28 patients without ascites were completely debulked, and 73 patients with ascites had residual tumor after PDS.

In the multivariate CONATS index, PS 2 and 3 were merged due to insignificant difference between the two groups ($p = 0.307$). Ascites ($p = 0.312$) and CA125 ($p = 0.166$) were excluded due to insignificant contribution to the model.

The equation of the CONATS index is

$$\text{CONATS} = -8.512 + 0.428 * \text{age}/10 + 0.648 * \log 2(\text{HE4}) + \text{PS}$$

Serum HE4 is in picomole per liter. PS is stated with the valuables 0 for PS = 0, 1.673 for PS = 1, and 1.904 for PS = 2–3.

The predicted probability (PP) is

$$\text{PP} = e^{(\text{CONATS})} / \left(1 + e^{(\text{CONATS})}\right)$$

The test is considered positive when PP is *below* a given cutoff—and the lower PP is, the higher is the chance of macro-radical PDS. A positive test should lead to recommendation of PDS.

The p value for the goodness of fit test was 0.568 indicating that the observed and expected event rates are similar; hence, the model formulation is adequate.

The CONATS index was highly correlated with overall survival ($p < 0.0001$, HR = 1.47 (95 % CI 1.26–1.72)).

OR, CI and p-values for the variables included in the CONATS index are shown in Table 3. ROC-AUC for the CONATS index is outlined in Fig. 1.

Table 4 presents different cutoff values for the CONATS index including the corresponding accuracies, sensitivities, specificities, positive predictive values, negative predictive values, false positives, and false negatives.

By dividing patients into three groups according to the cutoff levels presented in Tables 5, 46 patients (31 %) should be offered PDS (cutoff, PP ≤ 0.63), 46 patients (31 %) should be further investigated (cutoff, 0.63 < PP < 0.92), and 58 patients (38 %) should be admitted to NACT.

Of the 41 completely debulked patients, 29 (71 %) patients would correctly be offered PDS, 9 (22 %) further examined before deciding the optimal treatment strategy, and 3 (7 %) patients would incorrectly be admitted to NACT if the CONATS index had been used.

Of the 109 patients with residual tumor after PDS, 15 (14 %) would mistakenly be offered PDS, 47 (43 %) would need further examination, and 47 (43 %) would be correctly admitted to NACT.

Internal validation of the CONATS index using 100 bootstraps resulted in a concordance (AUC) of 0.839 confirming the chosen model. The step-down procedure resulted in the selection of HE4, PS, age, CA125, and ascites in 93, 90, 64, 48, and 29 % of the bootstraps, respectively.

Discussion

Macro-radical PDS is one of the most important prognostic factors for women with advanced EOC [1, 2]. However, even within the best onco-gynecological centers worldwide, the prevalence of complete PDS is varying and dependent on the local treatment strategies, patient selection strategies, and surgical skills. If macro-radical PDS is considered impossible, NACT followed by interval debulking surgery is considered a viable alternative due to a decreased risk of complications, but similar survival rates. Although several previous attempts have been made, no preoperative predicting tool of complete

Table 1 Histological subtype and FIGO stages

	Total (n = 150)	Complete tumor removal (n = 41)	Residual abdominal tumor (n = 109)
Histology			
Serous adenocarcinoma	137	35 (26 %)	102 (74 %)
Endometrioid adenocarcinoma	4	1 (25 %)	3 (75 %)
Mucinous adenocarcinoma	3	1 (33 %)	2 (67 %)
Clear cell adenocarcinoma	4	2 (50 %)	2 (50 %)
Carcinosarcoma	2	2 (100 %)	0
FIGO stage			
IIIC	118	33 (28 %)	85 (72 %)
IV	32	8 (25 %)	24 (75 %)

PDS is implemented at the MDT's, and no uniform assessment of optimal treatment strategy of patients with advanced EOC has been agreed upon.

During the last decade, the definition of optimal PDS has changed from residual tumor ≤1–2 cm in earlier studies to no visible residual tumor in more recent studies. Therefore, direct comparison of previously suggested methods to predict optimal tumor removal is challenging, and studies investigating prediction of complete cytoreduction were emphasized in the following discussion.

Non-invasive, preoperative assessment of resectability is preferable, and biomarkers and/or radiologic imaging are obvious choices for this purpose.

Traditionally, radiologic imaging has played a central role when deciding on an individual treatment strategy. Hence, gynecologic ultrasound and CT or PET-CT scans combined with the specialist's overall evaluation of the patient's health are still cornerstones in the preoperative prediction of surgical outcome. However, a recent systematic review of CT-based prediction models has concluded that no external validated studies with a good predictive performance of CT for residual disease exist [26].

In this study, we present the new non-invasive CONATS index for the prediction of complete PDS of EOC. All variables in the CONATS index are relatively cheap and easy to conduct at tertiary centers specialized in treatment of EOC.

In our study, as well as other studies, CA125 was inferior to HE4 in prediction of complete cytoreduction, and CA125 was excluded from the CONATS index due to an insignificant contribution to the model. The role of CA125 as a predictor

Table 2 Baseline data for variables in the CONATS index, including univariate analysis of differentiation between complete tumor removal and residual abdominal tumor

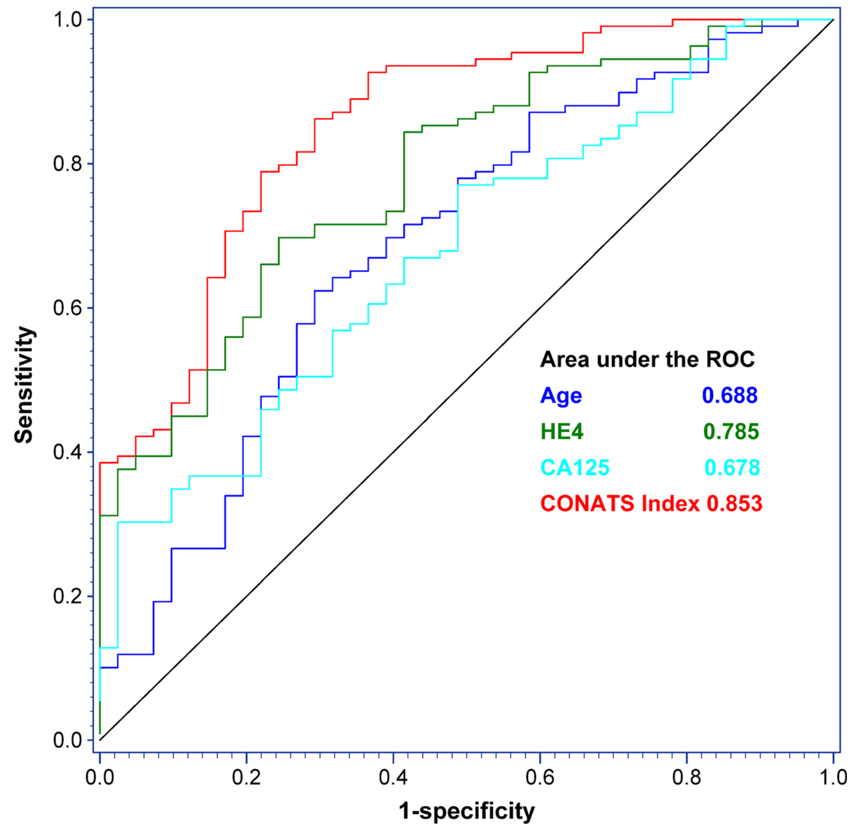
	Total (n = 150)	Complete tumor removal (n = 41)	Residual tumor (n = 109)	p value[a]	ROC-AUC
Continuous variables, median (range)					
Age, median (range)	65 (41–89)	58 (41–82)	69 (42–89)	<0.001	0.688
HE4, median (range)	889.7 (28.5–15,000.0)	282.0 (28.5–1934.3)	1328.3 (72.6–15,000.0)	<0.001	0.785
CA125, median (range)	967.5 (9.5–10,000.0)	395.5 (9.5–5578.6)	1140.0 (53.5–10,000.0)	0.001	0.678
Categorical variables, n (%)					
Performance status[b]				<0.001	–
0	62	30 (73 %)	32 (29 %)		
1	61	9 (22 %)	52 (48 %)		
2 and 3	21 + 6	1 + 1 (5 %)	20 + 5 (23 %)		
Presence of ascites[c]				<0.001	–
No	64	28 (68 %)	36 (33 %)		
Yes	86	13 (32 %)	73 (67 %)		

[a] Mann-Whitney U test was performed for continuous variables; chi-square test was performed for categorical variables

[b] The Eastern Cooperative Oncology Group (ECOG) Performance Status was used

[c] Presence of ascites at preoperative ultrasound examination performed at the tertiary center

Fig. 1 ROC-AUC of the CONATS index, age, CA125, and HE4



of complete tumor resection with PDS is still debated due to non-impressive results (AUCs between 0.64 and 0.68). In contrast, HE4 is more promising with reported AUCs between 0.63 and 0.86 [16, 17]. These results are concordant with the findings in the present study, where univariate analysis of HE4 demonstrated an AUC of 0.785, although direct comparison is difficult due to different study designs. Braicu et al. included stage II EOC and collected some of the blood samples intra-operatively instead of just preoperatively [17]. Angioli et al. excluded patients with PS ≥2, mucinous EOC, primary peritoneal cancer, or fallopian tube cancer [16]. In particular, the exclusion of mucinous EOC could improve the performance of HE4 and CA125, since both markers have been proven less useful in this histological subtype [27]. These authors also investigated the combination of HE4 (cutoff value 262 pmol/L) and ascites (>500 vs <500 ml evaluated by ultrasound) combined as predictors of macro-radical PDS. The study found a sensitivity of 100 % and specificity of 89.5 %. However, 21 out of 57 patients (37 %) were admitted directly to NACT [16]; hence, the authors were not able to conclude that macro-radical PDS was impossible among these cases. This, along with inclusion of stage II–IV EOC, may explain the exceptionally high rate of macro-radical PDS (94.7 %) among patients treated with PDS. In our study, all the participating patients were stage IIIC-IV EOC treated with PDS and patients with PS 2–3 were also included. Hence, the prevalence of macro-radical PDS was markedly lower (27 %) and the performance of the CONATS index may be affected by this (see Table 4). Patients with PS 0–3 are thoroughly evaluated at multidisciplinary team meetings in order to assess the possibility of successful primary surgery. More precaution in recommending primary surgery is necessary in patients with high PS. The CONATS index takes this into consideration; as the PS contributes more in the CONATS score when PS is high.

Table 5 demonstrates the performance of the CONATS index at suggested clinically relevant cutoffs. According to the Danish indicator level, macro-radical PDS should be

Table 3 Multivariate analysis

	Odds ratio	Confidence interval	*p* value
HE4	1.91	1.41–2.59	<0.001
Age[a]	1.53	1.03–2.29	0.036
Performance status[b]			
0	Ref	–	–
1	5.33	2.01–14.12	0.001
2 and 3	6.71	1.19–37.919	0.031

[a] For a 10-year difference

[b] The Eastern Cooperative Oncology Group (ECOG) Performance Status was used

Table 4 Performance of the CONATS index at different cutoffs in prediction of residual abdominal tumor after primary debulking surgery

Cutoff (PP)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	False positive (%)	False negative (%)
0.29	79.3	29.3	98.2	85.7	78.7	14.3	21.3
0.42	80.7	43.9	94.5	75.0	81.7	25.0	18.3
0.56	81.3	58.5	89.9	68.6	85.2	31.4	14.8
0.68	77.3	70.7	79.8	56.9	87.9	43.1	12.1
0.78	72.0	78.0	69.7	49.2	89.4	50.8	10.6
0.82	66.0	82.9	59.6	43.6	90.3	56.4	9.7
0.86	60.0	85.4	50.5	39.3	90.2	60.7	9.8

Prevalence of residual tumor = 73 %

achieved in 60 % of patients admitted to PDS (positive predictive value = 60 %). This may be achieved by using the CONATS index at the recommended lower cutoff (PP = 0.63). At this cutoff, 15 out of 109 patients with residual tumor would be offered PDS when in fact NACT would have been the better choice (specificity = 83.5 %).

By adding an additional cutoff (PP = 0.92), only three out of 41 patients would mistakenly not be recommended PDS (sensitivity = 90.2 %).

We recommend further clinical evaluation of the 56 (37 %) with PP values between the two cutoffs. An additive explorative examination may be laparoscopy.

Indeed, laparoscopy is suggested as a promising overall evaluator of resectability, but a Cochrane review from 2014, including seven studies evaluating stage IIB–IV OC, concludes that there were not sufficient data to firmly conclude if laparoscopy can evaluate the extensiveness of EOC [28]. Furthermore, laparoscopy including anesthetics is associated with an overall risk of complications of 1–5 %, depending on the type of surgery, surgical skills, and condition of the patient.

The present study has several strengths and limitations. All patient data were collected prospectively, and patients were treated at one tertiary center by trained gynecologic oncologists. Only patients whose physical condition did not allow excessive surgery or patients declining surgical treatment were offered NACT. Hence, the results are not biased by a large group of patients admitted to NACT. Furthermore, the HE4 measurements and calculations of the CONATS index were made after the patients were treated, thereby not influencing the clinician's choice of treatment.

However, due to centralization of the treatment, increased use of NACT, and a general development toward more aggressive surgery during the last decade, complete PDS is obtained in a larger proportion of patients operated today than in our patient material. Hence, the CONATS index should be validated in a recent cohort prior to implementation in the clinic. Based on our data, it was impossible to investigate whether the volume of ascites had any impact on the resectability.

In conclusion, this study demonstrates that non-invasive prediction of residual tumor of EOC at PDS is possible with the CONATS index. The CONATS index is meant as a supplement to the individual preoperative evaluation by experts. Evaluation of the CONATS index combined with radiological and/or laparoscopic findings may improve the ability to assess the optimal treatment

Table 5 Performance of the CONATS index at the suggested clinically relevant cutoffs

CONATS index cutoff	Recommended treatment	Patients total (150 patients) *n* = (%)	No residual tumor (41 patients) *n* = (%)	Residual tumor (109 patients) *n* = (%)	Sensitivity/ specificity %	Positive predictive value/ negative predictive value %
PP ≤ 0.63	PDS	44 (29 %)	29 (71 %)	15 (14 %)	68.3/83.5	60.9/87.5
0.63 < PP < 0.92	Further examination	56 (37 %)	9 (22 %)	47 (43 %)	–	–
PP ≥ 0.92	NACT	50 (33 %)	3 (7 %)	47 (43 %)	90.2/41.3	36.6/91.8

strategy of patients with advanced EOC. Prior to introduction of the CONATS index in the clinic, the index should be validated in different tertiary centers in cohorts treated by surgeons who strive to obtain ultraradical surgery at PDS.

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Compliance with ethical standards Oral and written consent was given by each patient before enrollment. The Danish Ethical Committee has approved the study protocol (KF01-227/03 and KF01-143/04, H-3-2010-022).

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Conflicts of interest None

References

1. Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol. 2003;90(2):390–6.
2. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des cancers de l'Ovaire (GINECO). Cancer. 2009;115(6):1234–44. doi:10.1002/cncr.24149.
3. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943–53. doi:10.1056/NEJMoa0908806.
4. Fago-Olsen CL, Ottesen B, Kehlet H, Antonsen SL, Christensen IJ, Markauskas A, et al. Does neoadjuvant chemotherapy impair long-term survival for ovarian cancer patients? A nationwide Danish study. Gynecol Oncol. 2014;132(2):292–8. doi:10.1016/j.ygyno.2013.11.035.
5. Fanfani F, Ferrandina G, Corrado G, Fagotti A, Zakut HV, Mancuso S, et al. Impact of interval debulking surgery on clinical outcome in primary unresectable FIGO stage IIIc ovarian cancer patients. Oncology. 2003;65(4):316–22.
6. Sandhu N, Karlsen MA, Hogdall C, Laursen IA, Christensen IJ, Hogdall EV. Stability of HE4 and CA125 in blood samples from patients diagnosed with ovarian cancer. Scand J Clin Lab Invest. 2014;74(6):477–84. doi:10.3109/00365513.2014.903430.
7. Saygili U, Guclu S, Uslu T, Erten O, Demir N, Onvural A. Can serum CA-125 levels predict the optimal primary cytoreduction in patients with advanced ovarian carcinoma? Gynecol Oncol. 2002;86(1):57–61.
8. Arits AH, Stoot JE, Botterweck AA, Roumen FJ, Voogd AC. Preoperative serum CA125 levels do not predict suboptimal cytoreductive surgery in epithelial ovarian cancer. Int J Gynecol Cancer. 2008;18(4):621–8. doi:10.1111/j.1525-1438.2007.01064.x.
9. Barlow TS, Przybylski M, Schilder JM, Moore DH, Look KY. The utility of presurgical CA125 to predict optimal tumor cytoreduction of epithelial ovarian cancer. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 2006;16(2):496–500. doi:10.1111/j.1525-1438.2006.00573.x.
10. Brockbank EC, Ind TE, Barton DP, Shepherd JH, Gore ME, A'Hern R, et al. Preoperative predictors of suboptimal primary surgical cytoreduction in women with clinical evidence of advanced primary epithelial ovarian cancer. Int J Gynecol Cancer. 2004;14(1):42–50.
11. Cooper BC, Sood AK, Davis CS, Ritchie JM, Sorosky JI, Anderson B, et al. Preoperative CA 125 levels: an independent prognostic factor for epithelial ovarian cancer. Obstet Gynecol. 2002;100(1):59–64.
12. Eltabbakh GH, Mount SL, Beatty B, Simmons-Arnold L, Cooper K, Morgan A. Factors associated with cytoreducibility among women with ovarian carcinoma. Gynecol Oncol. 2004;95(2):377–83. doi:10.1016/j.ygyno.2004.07.045.
13. Gemer O, Lurian M, Gdalevich M, Kapustian V, Piura E, Schneider D, et al. A multicenter study of CA 125 level as a predictor of non-optimal primary cytoreduction of advanced epithelial ovarian cancer. Eur J Surg Oncol. 2005;31(9):1006–10. doi:10.1016/j.ejso.2005.05.009.
14. Memarzadeh S, Lee SB, Berek JS, Farias-Eisner R. CA125 levels are a weak predictor of optimal cytoreductive surgery in patients with advanced epithelial ovarian cancer. Int J Gynecol Cancer. 2003;13(2):120–4.
15. Obeidat B, Latimer J, Crawford R. Can optimal primary cytoreduction be predicted in advanced stage epithelial ovarian cancer? Role of preoperative serum CA-125 level. Gynecol Obstet Investig. 2004;57(3):153–6. doi:10.1159/000076236.
16. Angioli R, Plotti F, Capriglione S, Aloisi A, Montera R, Luvero D, et al. Can the preoperative HE4 level predict optimal cytoreduction in patients with advanced ovarian carcinoma? Gynecol Oncol. 2013;128(3):579–83. doi:10.1016/j.ygyno.2012.11.040.
17. Braicu EI, Fotopoulou C, Van Gorp T, Richter R, Chekerov R, Hall C, et al. Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients: results from the OVCAD study. Gynecol Oncol. 2013;128(2):245–51. doi:10.1016/j.ygyno.2012.11.023.
18. Risum S, Hogdall C, Loft A, Berthelsen AK, Hogdall E, Nedergaard L, et al. Prediction of suboptimal primary cytoreduction in primary ovarian cancer with combined positron emission tomography/computed tomography—a prospective study. Gynecol Oncol. 2008;108(2):265–70. doi:10.1016/j.ygyno.2007.11.002.
19. Bristow RE, Duska LR, Lambrou NC, Fishman EK, O'Neill MJ, Trimble EL, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. Cancer. 2000;89(7):1532–40.
20. Ferrandina G, Sallustio G, Fagotti A, Vizzielli G, Paglia A, Cucci E, et al. Role of CT scan-based and clinical evaluation in the preoperative prediction of optimal cytoreduction in advanced ovarian cancer: a prospective trial. Br J Cancer. 2009;101(7):1066–73. doi:10.1038/sj.bjc.6605292.

21. Kim HJ, Choi CH, Lee YY, Kim TJ, Lee JW, Bae DS, et al. Surgical outcome prediction in patients with advanced ovarian cancer using computed tomography scans and intraoperative findings. Taiwan J Obstet Gynecol. 2014;53(3):343–7. doi:10.1016/j.tjog.2013.10.041.
22. MacKintosh ML, Rahim R, Rajashanker B, Swindell R, Kirmani BH, Hunt J, et al. CT scan does not predict optimal debulking in stage III-IV epithelial ovarian cancer: a multicentre validation study. J Obstet Gynaecol. 2014;34(5):424–8. doi:10.3109/01443615.2014.899330.
23. Salani R, Axtell A, Gerardi M, Holschneider C, Bristow RE. Limited utility of conventional criteria for predicting unresectable disease in patients with advanced stage epithelial ovarian cancer. Gynecol Oncol. 2008;108(2):271–5. doi:10.1016/j.ygyno.2007.11.004.
24. Angioli R, Palaia I, Zullo MA, Muzii L, Manci N, Calcagno M, et al. Diagnostic open laparoscopy in the management of advanced ovarian cancer. Gynecol Oncol. 2006;100(3):455–61. doi:10.1016/j.ygyno.2005.09.060.
25. Danish Cancer Biobank [database on the Internet]. 2012. www.cancerbiobank.dk. Accessed 22 Apr 2016.
26. Rutten MJ, van de Vrie R, Bruining A, Spijkerboer AM, Mol BW, Kenter GG, et al. Predicting surgical outcome in patients with International Federation of Gynecology and Obstetrics stage III or IV ovarian cancer using computed tomography: a systematic review of prediction models. Int J Gynecol Cancer. 2015;25(3):407–15. doi:10.1097/IGC.0000000000000368.
27. Karlsen NS, Karlsen MA, Hogdall CK, Hogdall E. HE4 tissue expression and serum HE4 levels in healthy individuals and patients with benign or malignant tumours—a systematic review. Cancer Epidemiol Biomark Prev. 2014. doi:10.1158/1055-9965.EPI-14-0447.
28. Rutten MJ, Leeflang MM, Kenter GG, Mol BW, Buist M. Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. Cochrane Database Syst Rev. 2014;2:CD009786. doi:10.1002/14651858.CD009786.pub2.