Early identification of recurrence in ovarian cancer: a comparison between the ovarian cancer metastasis index and CA-125 levels

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Ovarian cancer (OC), is the second most common gynecologic malignancy. A clinical observational study was performed to investigate whether indicators that assess the risk of metastasis can identify recurrence earlier in OC patients. By successfully recruiting 41 patients with OC who underwent chemotherapy, we compared cancer antigen-125 (CA-125) and the ovarian cancer metastasis index (OCMI), which was previously developed by us in the clinic for this purpose. Our results showed that patients and their families generally took a sensible attitude toward disease progression and were willing to accept a new way to gain knowledge about the disease. Herein, the new way was the possibility of monitoring recurrence by introducing the OCMI into the clinic. Fifteen patients experienced recurrence during chemotherapy, implying treatment failure. For 53% of these patients, an abnormally high OCMI suggested a strong tendency toward metastasis at least one chemotherapy cycle prior to the pathological examination confirming recurrence. In comparison, the early recognition rate of recurrence using CA-125 levels was merely 13%. Furthermore, we found that the mean values of the OCMI no longer declined after the fourth chemotherapy cycle, implying that excessive chemotherapy brings no benefit to OC patients. In conclusion, our findings provide a novel and feasible approach to monitor the effectiveness of chemotherapy in the treatment of OC by assessing the potential risk of metastasis.

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ABSTRACT

Ovarian cancer (OC), is the second most common gynecologic malignancy. A clinical observational study was performed to investigate whether indicators that assess the risk of metastasis can identify recurrence earlier in OC patients. By successfully recruiting 41 patients with OC who underwent chemotherapy, we compared cancer antigen-125 (CA-125) and the ovarian cancer metastasis index (OCMI), which was previously developed by us in the clinic for this purpose. Our results showed that patients and their families generally took a sensible attitude toward disease progression and were willing to accept a new way to gain knowledge about the disease. Herein, the new way was the possibility of monitoring recurrence by introducing the OCMI into the clinic. Fifteen patients experienced recurrence during chemotherapy, implying treatment failure. For 53% of these patients, an abnormally high OCMI suggested a strong tendency toward metastasis at least one chemotherapy cycle prior to the pathological examination confirming recurrence. In comparison, the early recognition rate of recurrence using CA-125 levels was merely 13%. Furthermore, we found that the mean values of the OCMI no longer declined after the fourth chemotherapy cycle, implying that excessive chemotherapy brings no benefit to OC patients. In conclusion, our findings provide a novel and feasible approach to monitor the effectiveness of chemotherapy in the treatment of OC by assessing the potential risk of metastasis.

INTRODUCTION

Large scale epidemiological studies have shown that ovarian cancer (OC) is the second most common gynecologic malignancy, after breast cancer (Brawley, 2015; Torre et al., 2015; Siegel et al., 2017). Worldwide, the number of newly diagnosed OC cases was close to 220,000 in 2008, but this number increased to about 240,000 in 2012 (Jemal et al., 2011; Ferlay et al., 2015). It is expected that this number will increase further due to population aging. Despite having a lower incidence rate than breast cancer, OC causes the largest number of gynecological cancer-associated deaths (more than 100,000 deaths per year). One important reason is that it is difficult to detect early stage OC in a timely fashion due to the lack of effective biomarkers for early screening (Menon et al., 2014). The relatively low incidence of OC inevitably increases the relative cost of early screening procedures and the potential risk of erroneous identification (Henderson et al., 2018). This raises the threshold for the screening of rational biomarkers.

Undoubtedly, the discovery of clinically available biomarkers for early screening will greatly reduce the mortality rate of OC. Before this discovery becomes a reality, an easier and more feasible strategy is to provide more valuable treatment management for patients who have been diagnosed with OC. Surgery plus chemotherapy is the present mainstream OC therapeutic strategy. As about 70% of OC cases are diagnosed at advanced stages (Jayson et al., 2014), multi-cycle chemotherapy is unavoidable. Therefore, a big challenge is how to avoid treatment failure due to drug resistance, which is common. In the clinic, about half of OC patients face this unfortunate outcome, undergo recurrence, and eventually succumb to the disease (Marcus et al., 2014; Au et al., 2015). One solution is to develop prognostic biomarkers that can detect recurrence as early as possible. A successful early warning provides doctors an invaluable opportunity to redesign the treatment plan. Up to now, only two biomarkers for early detection of OC

61   recurrence have been approved by the US Food and Drug Administration: cancer antigen-125 (CA-125)

62   and human epididymis protein 4 (HE4). However, the effectiveness of any individual biomarker or a

63   combination of the two has been shown to be very limited (Van Gorp et al., 2011).

64   According to the official definition of the International Federation of Gynecology and Obstetrics, OC

65   can be divided into four stages, stage I to stage IV (Prat and FIGO Committee on Gynecologic Oncology,

66   2014). Stage I indicates no tumor cell migration event has occurred. However, the next three stages indicate

67   an increasing range of tumor cell dissemination from the ovaries to other organs. Multi-organ metastasis

68   often indicates a more serious disease status and lower chance of survival (Bast et al., 2009). Based on the

69   inner logic of this definition, we developed a novel indicator, the ovarian cancer metastasis index (OCMI),

70   which integrates CA-125 levels with six routine clinical examination indicators by a neural network cascade

71   (NNC)-multiple linear regression hybrid model (Qu et al., 2018). NNC is an artificial neural network

72   (ANN) with a serial data input architecture, in which multiple small ANN units that handle single input

73   parameter are connected in tandem to complete the overall prediction task (Li et al., 2015; Hou et al., 2016;

74   Cui et al., 2018). Our work suggested that the OCMI could successfully identify the existence and extent

75   of multi-organ metastasis for a given patient with OC.

76   Metastasis suggests the existence of active cancer cells. This may further imply resistance to

77   chemotherapeutic agents and the possibility of recurrence. Based on this reasonable hypothesis, we

78   performed this clinical study, in which 41 patients with OC were recruited. In this study, we investigated

79   the potential logical relationship between abnormal OCMI values and the recurrence event that is going to

80   happen during the next period of multi-cycle chemotherapy. Such an effort was aimed to establish an

81   association between metastasis and recurrence in OC and develop a novel biomarker for early prediction of

82   recurrence.

83

MATERIALS AND METHODS

Ethical statement

This work was a clinical observational study that was approved by the Ethics Committee of the Second

Affiliated Hospital of Harbin Medical University (Approval number: KY2017-217) and carried out in

accordance with the Declaration of Helsinki. Each participant recruited in this study was informed of the

project, signed a written consent form, and completed a short questionnaire (File S1). The purpose of the

questionnaire survey was to identify patients' or family members' attitude about early prediction of

recurrence. The family members and the patients were considered to have the same decision-making ability.

In the entire study, no biological samples were collected from any patient.

Inclusion and exclusion criteria

All the patients enrolled in this study were diagnosed with epithelial ovarian cancer and underwent multi-

cycle chemotherapy. Patients were excluded from the study if they were diagnosed with another malignant

tumor or endometriosis.

Patient information collection

For each patient, the information in her medical record was use to confirm recurrence and to calculate the

OCMI, following the method established previously (Qu et al., 2018). The information included the

patient's age, pharmacotherapeutic regimen, number of metastatic organs confirmed during surgery,

ascites, laterality, imageologically-diagnosed or pathologically-confirmed recurrence, and four blood test

indicators (CA-125, lymphocyte percentage, prealbumin, and blood platelet count) that were measured at

103   the time of diagnosis, before surgery, and before each cycle of chemotherapy.

104   **Calculation of the OCMI**

105   OCMI values were calculated for each patient when the four blood test indicators mentioned above were

106   available, typically at the time of diagnosis, before surgery, and before any cycle of chemotherapy. An

107   established neural network cascade (NNC)-multiple linear regression (MLR) hybrid model (Qu et al., 2018)

108   was directly used for this calculation. The hybrid model contained an NNC and an MLR formula. The NNC,

109   an artificial neural network model of a serial data input architecture (Li et al., 2015; Hou et al., 2016; Cui

110   et al., 2018), was previously built using a training dataset containing 534 patients with OC (Qu et al., 2018).

111   Briefly, the four blood test indicators were normalized into a 0 to 1 digital number before further use, as

112   previously described (Zhu and Kan, 2014). After that, the normalized values of the four blood test indicators

113   were inputted into the NNC, and the NNC output was calculated using STATISTICA Neural Networks

114   (SNN, Release 4.0E; Statsoft, Tulsa, OK, USA). Finally, the NNC output, ascites, and laterality were

115   inputted into the MLR formula to calculate the OCMI value. If no ascites was found, the variable was

116   valued at 0; otherwise, it was valued at 1. For the laterality variable, a value of 0 represented unilateral OC

117   and a value of 1 indicated bilateral OC.

118   **Determination and validation of metastasis discrimination thresholds**

119   The training dataset containing 534 patients with OC (Qu et al., 2018) was used to determine thresholds for

120   CA-125 levels, the NNC, and the OCMI for discriminating whether metastasis occurs in a patient with OC

121   (Table S1). MedCalc version 15.8 (MedCalc, Mariakerke, Belgium) was used, and receiver operating

122   characteristic (ROC) curve analysis was performed to obtain the optimal thresholds of CA-125 levels, the

123   NNC, and the OCMI. In addition to the area under the ROC curve (AUROC), the sensitivity, specificity,

124   accuracy, and Youden index were calculated at the optimal cut-off point. The Youden index was the sum

125   of the sensitivity and the specificity minus 1, as defined previously (Youden, 1950). Additionally, an

126   independent validation set of 267 patients with OC (Qu et al., 2018) was used to validate the prediction

127   accuracies of metastasis identification using the optimal thresholds of CA-125 levels, the NNC, and the

128   OCMI (Table S2).

129   **Statistical analyses**

130   All data are expressed as mean ± standard deviation. Spearman's correlation test and Chi square test were

131   performed using Graphpad Prism version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA). MedCalc

132   version 15.8 was applied to perform ROC curve pairwise comparison based on the methodology of DeLong

133   et al. (DeLong et al., 1988). Differences were only considered to be significant at $p < 0.001$.

134

135   **RESULTS**

136   **The questionnaire showed good acceptability of the OCMI from the patient aspect**

137   In our previous study (Qu et al., 2018), metastasis was defined that metastasis in any one of the 15 organs

138   (bladder, diaphragm, greater omentum, internal genital organ, large intestine, liver, lymph node, mesentery,

139   paracolic sulci, peritoneum, rectouterine fossa, small intestine, spleen, stomach, and ureter) was

140   intraoperatively examined for a patient. And multi-organ metastasis means that more than one organs were

141   found to have cancer metastasis in the intraoperative examination. Based on the good ability of the OCMI

142   for identifying multi-organ metastasis in OC patients (Qu et al., 2018), we hoped to introduce the OCMI

143   into clinical practice. This work is an exploratory study for this purpose. A questionnaire was designed and

144   applied to investigate whether patients and patients' families can accept the OCMI-based early identification

145 of recurrence (Supplemental File 1). A total of 22 patients and 28 patients' families were invited to

146 participate in the questionnaire (Figure 1A). The response rate was 82%. Only 6 patients and 3 patients'

147 families refused to fill out the questionnaire. Finally, the necessary medical record information of 41

148 patients was collected to calculate the OCMI (Supplemental Table 1).

149 Although 16 patients and 25 patients' families agreed to participate in the study, more than two-thirds of

150 the participants expressed doubts about the OCMI (Figure 1B). However, most of the responders expressed

151 the desire to receive the OCMI test results in the shortest possible time (Figure 1C). Six patients chose to

152 face the result alone, but the majority of patients chose to consult with their families, regardless of the result

153 (Figure 1D). Finally, all the participants agreed to adopt the OCMI for disease management during

154 hospitalization and after discharge.

155 **The OCMI has a stronger metastasis risk recognition ability than CA-125 levels**

156 A published dataset of 534 patients with OC (Qu et al., 2018) was used to set the metastasis discrimination

157 thresholds of the OCMI and CA-125 levels (Supplemental Table 2). Our previous study had shown a greater

158 advantage of the OCMI in identifying multi-organ metastasis than the NNC or CA-125 levels (Qu et al.,

159 2018). When using the optimal cut-off points, the OCMI had a higher accuracy in multi-organ metastasis

160 risk recognition than CA-125 levels (Table 1). In the present study, ROC curve comparison analysis was

161 performed to investigate the comparative advantage of the OCMI in identifying potential metastasis risk

162 (Figure 2). The OCMI successfully identified metastasis better than the NNC or CA-125 levels ($p < 0.001$).

163 The AUROC for the OCMI was 0.856, but that for CA-125 levels was 0.752. When using the optimal cut-

164 off point, the prediction accuracy of the OCMI was 77.2%, which was superior to that of CA-125 levels

165 (74.0%; Table 2).

166 **The OCMI achieves early identification of recurrence better than CA-125 levels**

167 For each patient, blood test indicators (CA-125, lymphocyte percentage, prealbumin, and blood platelet

168 count) were recorded before each cycle of chemotherapy, and the OCMI was calculated using the method

169 previously described (Qu et al., 2018). An obvious decline in the CA-125 levels was observed from the

170 beginning of chemotherapy to the fifth chemotherapy cycle. However, after that time, the CA-125 levels

171 no longer decreased (Figure 3A). A similar trend was observed with the OCMI (Figure 3B). During our

172 observation period, 15 patients experienced recurrence (Supplemental Table 1). It should be noted that 60%

173 of the recurrence events happened at the seventh chemotherapy cycle, whereas no recurrence was observed

174 from the beginning of chemotherapy to the fifth chemotherapy cycle. By using multi-organ metastasis

175 discrimination thresholds (CA-125 = 376 U/mL and OCMI = 0.558), 2 patients had early identification of

176 recurrence by CA-125 levels, but 6 had early identification using the OCMI. Following the metastasis

177 discrimination thresholds (CA-125 = 313 U/mL and OCMI = 0.504), 2 patients who underwent recurrence

178 were identified early by CA-125 levels, but 8 were identified early by the OCMI (Figure 3C). On the

179 contrary, among the 26 non-recrudescent patients, only 3 had OCMI values higher than 0.504 from the

180 beginning of chemotherapy to the fifth chemotherapy cycle. Comparatively, 4 non-recrudescent patients

181 had CA-125 levels higher than 313 U/mL during the same period.

182

183 **DISCUSSION**

184 Due to the lack of effective early monitoring tools for OC recurrence, we can only take remedial measures

185 after patients develop recurrence (Davidson and Tropé, 2014; Au et al., 2015; Nezhat et al., 2015; Bowtell

186 et al., 2015). In this exploratory work, we attempted to establish a link between metastasis and recurrence

187   using a quantitative index that was developed to assess the degree of metastasis in OC patients (Qu et al.,

188   2018). The OCMI is an integrated index generated from six conventional clinical examination indicators.

189   One advantage of not developing a separate and new clinical test is that it can be immediately brought into

190   clinical practice. According to the definition of the index, a greater OCMI indicates a wider range of

191   metastasis or a higher metastasis risk. In the present study, we further confirmed that the OCMI could

192   identify recurrence early by identifying patients at high risk of metastasis. It has been generally accepted

193   that metastasis is the main indicator of the pathological development of OC (Bast et al., 2009; Prat and

194   FIGO Committee on Gynecologic Oncology, 2014). This is also the logical basis for this study. Several

195   limitations of this study should be taken into consideration. One limitation is that the sample size of this

196   single center study is small, and therefore, the conclusions made here need to be re-validated in a larger

197   multicenter study in the future. Another limitation is that the early recognition rate of recurrence by the

198   OCMI is still not satisfactory, and further improvement of the OCMI is needed in the future. One feasible

199   direction is to integrate more useful indicators into the calculation of the OCMI.

200   Suffering from a malignant tumor causes patients to experience a greater depth of loneliness, but does

201   not generally cause them to be overly pessimistic (Çıracı et al., 2016; Thieme et al., 2017). Consistently,

202   our findings suggest that the vast majority of OC patients and their families could face the disease rationally

203   when a new possibility appeared. They chose to accept it tentatively instead of rejecting it. Active

204   participation of the vast majority of OC patients and their families implies an embodiment of optimism

205   rather than passive acceptance due to excessive pessimism. Although our method was not able to provide

206   a completely new and promising treatment, patients still wanted to know their OCMI test results as early

207   as possible. This tendency indicates that good treatment and deep understanding of the disease are equally

208   important to OC patients. Undoubtedly, valuable information can help them make decisions that are more

209   in line with their interests. Throughout the study, we were always aware of patients' desire for valuable

210   information about their disease condition.

211   On the one hand, the lack of necessary disease assessment information often leads doctors to tentatively

212   implement overtreatment; on the other hand, patients' psychological acceptance is often underestimated by

213   doctors and therefore it is difficult for patients to get information that is necessary for disease self-

214   assessment. This constitutes a vicious cycle. Overtreatment will undoubtedly maximize patients' harm and

215   minimize the benefit of clinical treatment for cancer (Loeb et al., 2014; Mukhtar et al., 2015). When a

216   malignant disease, such as OC, has a high probability of treatment failure, disease assessment information

217   is more meaningful for patients. This helps them have more opportunities to rationally design their

218   remaining time and make it more valuable.

219   In our study, we considered two threshold standards for the OCMI. A high threshold (OCMI = 0.558)

220   was produced from a previous ROC curve analysis for identifying multi-organ metastasis. Our result

221   indicates that only 40% of the patients with recurrence could be identified in advance of five chemotherapy

222   cycles. By using the MedCalc software, a lower threshold (OCMI = 0.504) was generated in this study from

223   a ROC curve analysis for identifying metastasis, rather than multi-organ metastasis. Our finding indicates

224   that application of the lower threshold of OCMI led to a higher recognition rate of patients with recurrence.

225   Eight of the 15 patients with recurrence were identified in advance of at least one chemotherapy cycle.

226   Meanwhile, only 3 of the 26 patients without recurrence were suggested to have a high risk of relapse.

227   Comparatively, use of CA-125 alone, a specific biomarker of OC, failed to identify patients with recurrence

228   before the recurrence was confirmed by clinicopathological examination. The early recognition rate of

229   recurrence was 13% using CA-125 levels as a biomarker. Furthermore, our findings also suggest that

230   increasing the number of chemotherapy cycles did not further reduce the risk of cancer metastasis in OC

231   patients. Clinical observations demonstrated that patients could only show a limited response to over-

232   chemotherapy (Bowtell et al., 2015) and over-chemotherapy led to a greater possibility of recurrence

233   (Agarwal and Kaye, 2003). Our findings further suggest that over-chemotherapy does not provide more

234   benefits in blocking cancer metastasis than moderate chemotherapy does.

235   In conclusion, we provide a new and useful tool for the early identification of relapse during

236   chemotherapy administration in OC patients. Our findings suggest that model refining of only a few of

237   routine clinical indicators can bring a new possibility of early prediction of cancer recurrence. More

238   importantly, this method means a valuable opportunity to replace the failed chemotherapy regimen before

239   recurrence really occurs. We believe that introducing the OCMI into clinical practice represents a feasible

240   and low-cost strategy and the OCMI can fill in the information shortage of clinical disease management of

241   OC, which is caused by low efficiency of CA-125.

242

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316

317   **FIGURE LEGENDS**

318   **Figure 1. Results of the questionnaire. A.** Distribution of questionnaire respondents. **B.** Respondents'

319   attitudes toward the OCMI. **C.** The time-cost of the OCMI result. **D.** Persons that were informed of the

320   OCMI result. OCMI: ovarian cancer metastasis index.

321   **Figure 2. AUROC comparison results.** NNC: neural network cascade; OCMI: ovarian cancer metastasis

322   index, AUROC: area under the receiver operating characteristic curve.

323   **Figure 3. Comparison between CA-125 levels and the OCMI in the early identification of recurrence.**

324   Variation tendencies of CA-125 levels (**A**) and the OCMI (**B**). **C.** Scatter plots of CA-125 values and OCMI

325   values in recurrent patients (five chemotherapy cycles before recurrence). The left dotted line represents

326   the CA-125 metastasis threshold (CA-125 = 313 U/mL) and the right dotted line indicates the metastasis

327   threshold using the OCMI (OCMI = 0.504). OCMI: ovarian cancer metastasis index, CA-125: cancer

328   antigen-125.

329

330   **Table 1. Receiver operating characteristic curve analysis results for identifying multi-organ**

331   **metastasis.**

332   **Table 2. Receiver operating characteristic curve analysis results for identifying metastasis.**

333

334 **Supplementary data**

335 **Supplementary File 1. Questionnaire on using the OCMI to identify the recurrence risk in ovarian**

336 **cancer.**

337 **Supplementary Table 1. Information of patients included in the study.**

338 **Supplementary Table 2. The dataset of ovarian cancer metastasis.**

Receiver operating characteristic curve analysis results for identifying multi-organ metastasis.

1   **Table 1. Receiver operating characteristic curve analysis results of identifying multi-organ**

2   **metastasis.**

Index	Threshold	Sensitivity (%)	Specificity (%)	Youden index J	Accuracy (%)
CA-125	376	80.6	52.3	0.329	66.5
NNC	0.565	71.3	69.9	0.412	70.6
OCMI	0.558	84.0	68.8	0.528	76.4

Receiver operating characteristic curve analysis results for identifying metastasis.

1 **Table 2. Receiver operating characteristic curve analysis results of identifying metastasis.**

Index	Threshold	Sensitivity (%)	Specificity (%)	Youden index J	Accuracy (%)
CA-125	313	75.8	65.6	0.414	74.0
NNC	0.458	78.3	65.6	0.439	75.8
OCMI	0.504	75.6	85.4	0.607	77.2

Figure 1

Results of the questionnaire.

A. Distribution of questionnaire respondents. **B.** Respondents' attitudes toward the OCMI. **C.** The time-cost of the OCMI result. **D.** Persons that were informed of the OCMI result. OCMI: ovarian cancer metastasis index.
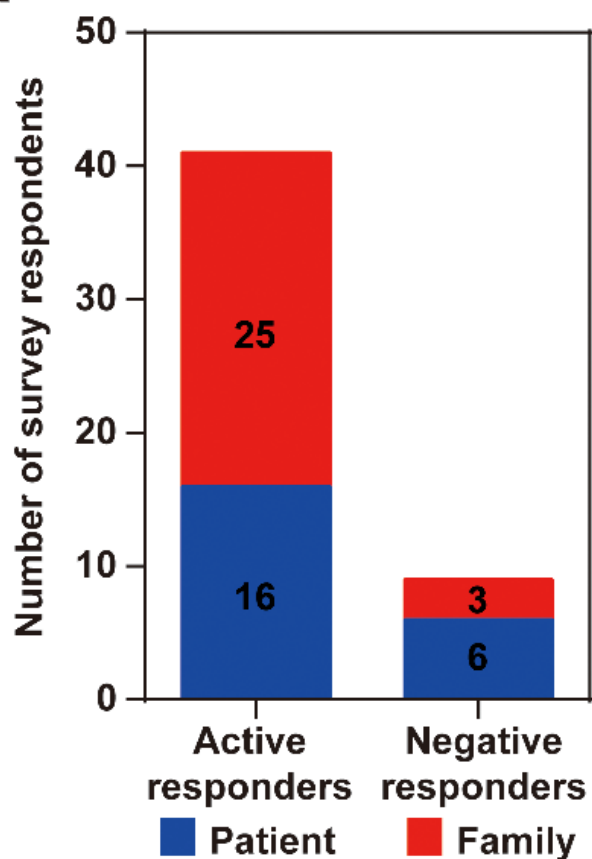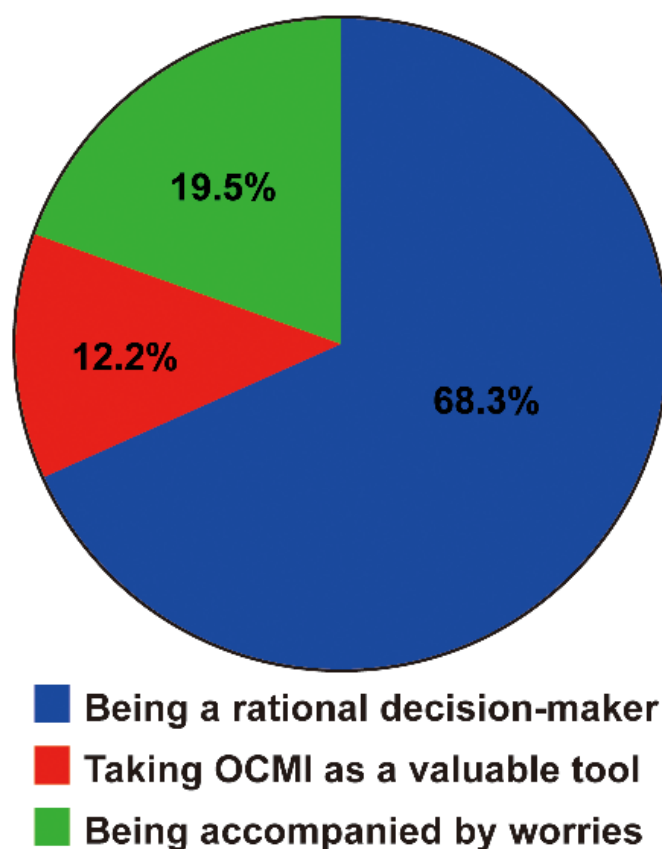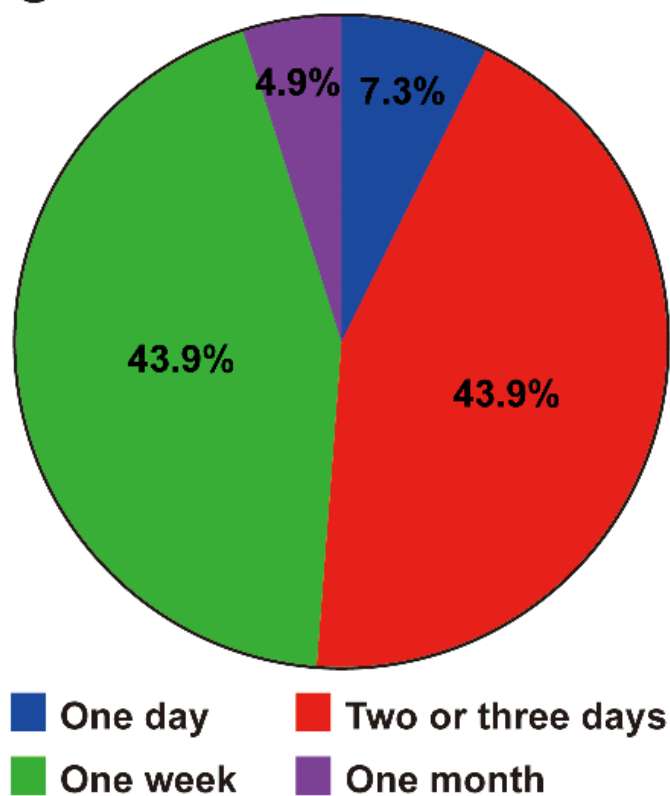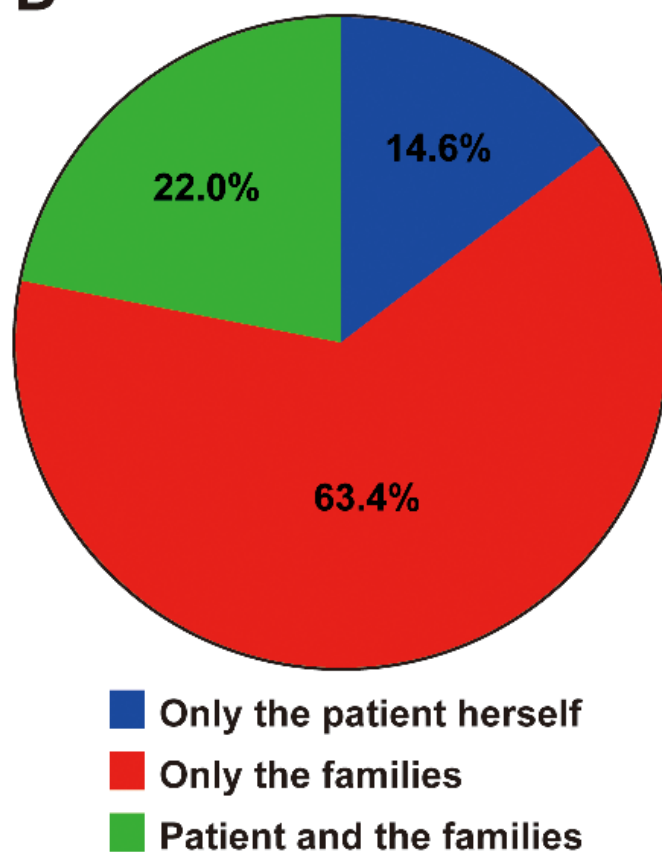
Figure 2

AUROC comparison results.

NNC: neural network cascade; OCMI: ovarian cancer metastasis index, AUROC: area under the receiver operating characteristic curve.
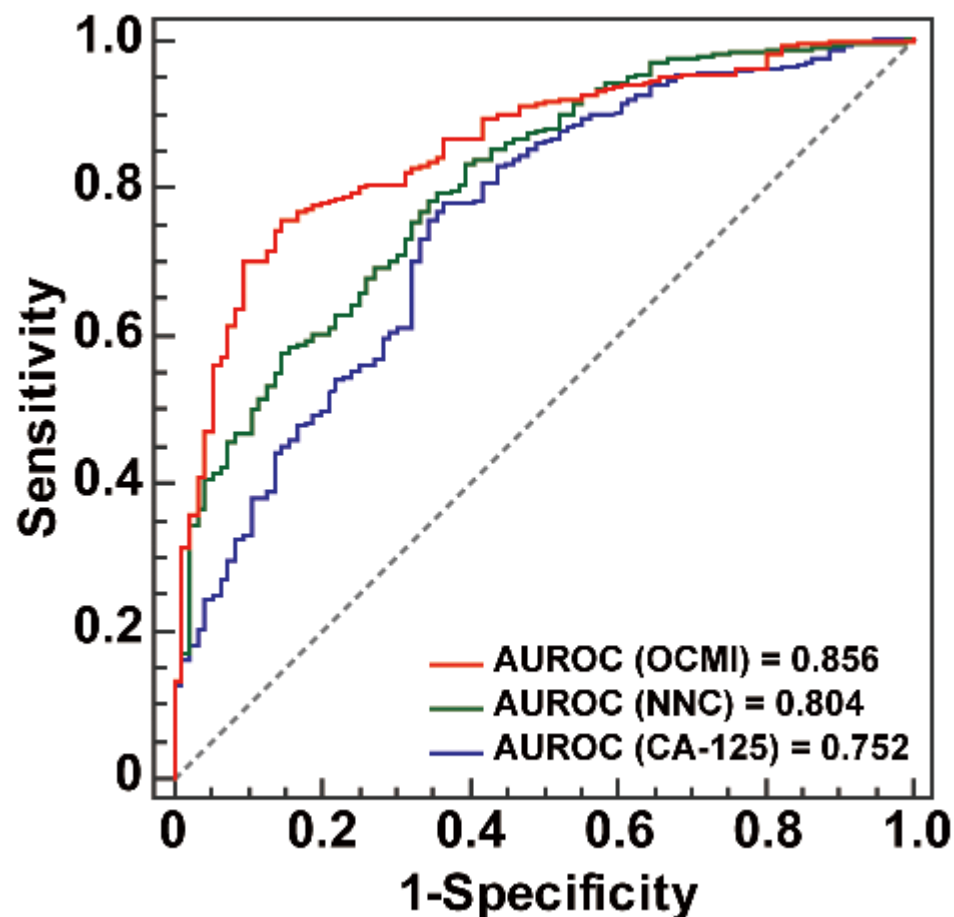
Figure 3

Comparison between CA-125 levels and the OCMI in the early identification of recurrence.

Variation tendencies of CA-125 levels (**A**) and the OCMI (**B**). **C.** Scatter plots of CA-125 values and OCMI values in recurrent patients (five chemotherapy cycles before recurrence). The left dotted line represents the CA-125 metastasis threshold (CA-125 = 313 U/mL) and the right dotted line indicates the metastasis threshold using the OCMI (OCMI = 0.504). OCMI: ovarian cancer metastasis index, CA-125: cancer antigen-125.