A randomized trial in ovarian cancer (OC) of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials)

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Background
- **Ovarian cancer** is the second most common gynecological malignancy in the United States with nearly 22,000 cases diagnosed annually. More than 15,000 of these patients will die of their disease, making ovarian cancer the fifth most common cause of cancer death in women in the United States.
- CA-125 is a glycoprotein whose serum values are elevated in over 80% of women with ovarian cancer with excellent sensitivity for stage II or greater cancers.
- For women receiving treatment for their ovarian cancer, serum CA-125 levels often rise several months before women have symptoms or clinical signs of disease relapse.
- 80% of women ultimately relapse after treatment with first line chemotherapy but most will benefit from further cytotoxic therapy.
- It is currently unclear whether second line chemotherapy should be deployed based on rise in serum markers or clinical relapse.
- OV05/EORTC 55955 is a randomized trial examining whether benefit is derived in patients treated for suspected clinical relapse based on their CA-125 levels as compared to patients whose treatment is delayed until clinically indicated.

Materials and Methods
- Eligible patients included women with ovarian cancer in clinical complete remission following first-line platinum-based chemotherapy and a normal CA-125. Randomizable histologies include: epithelial ovarian cancers, fallopian tube cancers or primary serous peritoneal carcinoma.
- Serum CA-125 was measured every three months but patients and investigators were blinded to the results, which were only available to the trials units.
- Patients whose serum CA-125 levels exceeded twice the upper limit of normal were randomized to receive immediate treatment or to continue to obtain every three month blinded measurements of CA-125 until relapse was documented clinically or symptomatically.
- Relapses, regardless of modality of detection, were treated according to local standard practice by the gynecological oncologist.
- The primary outcome measurement was overall survival and the trial was designed to detect a 10% improvement in 2-year overall survival in the immediate treatment arm with at least 85% power and 5% significance level. Secondary outcomes included times to second and third line chemotherapies or death and patient quality of life (QOL).

Results
- A total of 1,442 patients were registered from 59 centers from 10 countries between 1996 and 2005 (MRC began enrolling patients in 1996 and the EORTC 1999).
- Registration closed on March 31, 2008 with a total of 527 randomized patients (264 immediate and 263 delayed) when the targeted number of deaths were reached.
915 patients were not randomized, of which 48% had no CA-125 rise and no evidence of relapse, 14% withdrew from the trial and 2% were not randomized for other reasons. 421 of these women were not randomized as they had persistent elevations of CA-125 less than twice the upper limit of normal.

Among patients randomized, baseline characteristics were well balanced between the two groups. Median age at registration was 61 years. 81% were FIGO stage III/IV. Second line chemotherapy began a median of 5 months earlier in the immediate arm. Predominant histologies were serous and endometrioid, involving 53% and 17%, respectively, among randomized patients.

With a median follow-up of 49 months from randomization and a total of 351 deaths, there was no evidence of a difference in overall survival between the immediate and delayed arms with a hazard ratio of 1.00 and a p value of 0.98.

Third line chemotherapies were used in 68% of the early and 56% of the delayed treatment arms, which was statistically significant with a HR of 0.69 and a p value of 0.0001.

Quality of life estimates revealed that women randomized to the immediate treatment arm had less time with a ‘good’ quality of life as estimated by validated QOL measurements.

Early treatment based on rise in CA-125 occurred on average 4.8 months earlier in the immediate arm with respect to second line therapies and 4.6 months earlier in third line therapy.

**Author's Conclusions**

- Overall, there is no survival advantage from early treatment based on a raised serum marker level alone
- Therefore, there is no value in the routine quarterly measurement of CA125 in the follow-up of ovarian cancer patients after clinical complete remission following first-line platinum-based chemotherapy.
- Early treatment negatively impacted quality of life. Women treated in the immediate treatment arm received on average 12 more total cycles of chemotherapy (30 vs. 18 months in the immediate versus delayed treatment arms, respectively).
- Authors conclude that treatment may be safely delayed until there is evidence of clinical relapse.

**Clinical/Scientific Implications**

- This investigation examines whether the common practice of routine quarterly checks of serum CA-125 is routinely warranted following clinical complete remission following first-line platinum-based chemotherapy.
- The study does not question whether CA-125 measurement is an accurate surrogate of early relapse but rather whether an intervention based on biochemical relapse improves outcomes.
- Interestingly, this study provides level one evidence that women treated in the immediate treatment arm receive addition cycles of chemotherapy and have a decreased quality of life despite suffering from identical clinical outcomes. The decrease in QOL may be attributable to additional cycles of chemotherapy resulting in additional toxicity (e.g., neuropathy or hospital admissions secondary to neutropenias), more time spent in physicians’ offices, and may result in hastened demise due to these toxicities. Furthermore, additional cycles of chemotherapy represent an increased cost to society due to the costs of cytotoxic medications and possibly through increased radiographic studies.
- Although an excellent study design overall, some weaknesses warrant discussion: there were no standardized second or third line chemotherapeutic regimens and available agents evolved over the ten year accrual period. Furthermore, there were no surgical considerations in terms of optimal versus suboptimal primary or secondary cytoreductive surgeries or whether the tumors were platinum sensitive or resistant.
- Bottom line: CA-125 levels should not be measured quarterly and only clinical relapse or development of symptoms should justify the use of chemotherapy.

See **Patient Summary**