Beyond evidence: reappraising use of CA-125 as post-therapy surveillance for ovarian cancer

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Reconsidering the place of disease monitoring after treatment

Women who have completed primary chemotherapy for ovarian cancer commonly have serial assessment of the serum tumour marker cancer antigen 125 (CA-125).[1] This practice has been based on the proven utility of CA-125 in diagnostic algorithms and as a marker of response to therapy. Serial CA-125 assessment is also used because there is evidence that in women who have completed treatment for ovarian cancer, the serum CA-125 rises 2–6 months before symptoms or signs of relapse develop. The assumption underlying this and other similar studies is that serial monitoring of CA-125 would enable early diagnosis and treatment of relapse. This would thus lead to delay or reduction of cancer-related symptoms, psychological reassurance and, in theory, improved survival.[1]

Some studies have suggested that CA-125 may have some benefit in post-treatment surveillance. However, many others have demonstrated that although a rising CA-125 level is highly predictive of relapse, surveillance monitoring of CA-125 levels after remission from primary chemotherapy confers little benefit over standard clinical examination and does not improve duration of survival or quality of life.[2,3]

There are many possible explanations for the apparently conflicting data regarding the merits of CA-125 surveillance following initial ovarian cancer therapy. These include the stage of the primary cancer, the choice of chemotherapy, the definition of remission, and the timing and frequency of surveillance testing. In spite of this, those caring for women with ovarian cancer have no clear guidance regarding the place of CA-125 surveillance.

The results of a recent randomised controlled trial (RCT) published in *The Lancet* present a further challenge to the routine practice of CA-125 surveillance.[4] This study, by Rustin and colleagues, included 1442 women from 59 medical centres across Europe with stage I–IV ovarian cancer in clinical complete remission and with a normal CA-125 following initial therapy. It found that using CA-125 surveillance every 3 months as the basis for recommencing treatment did not improve survival or quality of life. Importantly, it also found that women who received delayed treatment following the onset of symptoms reported a higher quality of life than those treated earlier.[4]

This study has been the subject of extensive analysis, with critics identifying several potential confounding factors in the study design and analysis and questioning the results.[5] These include the heterogeneity of the study population, the time taken to complete the study (10 years), the number of collaborators (128), the statistical analysis, the lack of standardisation of surgical debulking and management of recurrence, and the choice of outcome measures. Although there are unquestionably deficiencies in the Rustin study, it was a blinded RCT that directly assessed the effect of treatment decisions made on the basis of CA-125 testing on health outcomes (mortality and quality of life). This means that it should be taken seriously and that we should (re)consider how it is that CA-125 surveillance became part of the routine management of ovarian cancer.

Understanding the "drivers" of CA-125 surveillance

A review of follow-up testing of patients with lung cancer suggested several reasons why doctors may use more intensive follow-up testing than can be justified. These include an overoptimistic assessment of the benefits of early diagnosis of relapse and/or the value of follow-up testing, and an explicit or implicit desire to avoid discussions about futility and the active management of terminal illness.[6] Thus, using only clinical examination and the patient's history may seem inconsistent with good medical practice (regardless of the evidence), when, for example, in the case of ovarian cancer, a doctor can also use a CA-125 test to gain further information about the patient's disease.

Doctors may also feel that their patients lack faith in the validity of their own symptoms, and want objective, scientific data about their disease. They want to be reassured that close monitoring may enable early diagnosis and treatment of a relapse. Finally, doctors may feel that most women with ovarian cancer know (or will find out) that CA-125 testing exists, and believe that its level correlates with disease status, and so will expect surveillance testing to be done.

Similarly, patients may simply go along with the management plan developed by their doctor because they fear recurrence or progressive disease more than the anxiety associated with surveillance. They may also be willing to experience any inconvenience, side effect or toxicity for even a small chance of benefit.[6] Women with advanced ovarian cancer, in particular, may also deeply distrust their own body and feel (often rightly) that relapse is inevitable.

Qualitative studies of patients who have completed treatment for other cancers support the idea that patients may wish to make use of post-therapy surveillance because it assists them in dealing with uncertainty and with the anxiety of relapse.[7]

Serial CA-125 testing may allow women to "manage" the uncertainty and anxiety surrounding their disease

status, their bodies and their lives, because a "good" result will be reassuring, and even a "bad" result may provide some ordered foreknowledge that some women may find helpful.[7] The results of CA-125 tests may therefore help predict the future of the disease, determine interventions, provide a framework for action and legitimise the illness. CA-125 test results may help a patient achieve a sense of order in a body she may have learnt not to trust, and help her define her social roles and relationships.[7]

Implications for practice

What role does CA-125 surveillance have in asymptomatic women with ovarian cancer? Intensive surveillance, including CA-125 monitoring, would be desirable if early recognition and treatment of relapse produced a meaningful survival benefit or improved quality of life. The evidence suggests that it does not, so there appear to be two options for the use of CA-125 in surveillance outside clinical trials.

The first option is to recommend that CA-125 monitoring should not be routinely performed following treatment for ovarian cancer. This approach is consistent with the published clinical and epidemiological evidence and would be economically prudent. It would undoubtedly attract some controversy, but would be consistent with similar recommendations against the use of other tumour markers such as carcinoembryonic antigen, cancer antigen 15-3 and cancer antigen 27.29 in surveillance after primary treatment of breast cancer.[8]

The second option would be to accept that oncologists and patients may reasonably make a shared decision to incorporate CA-125 monitoring into their post-treatment care, on the understanding that CA-125 monitoring may not confer any advantage to survival or quality of life. This approach recognises the many reasons why a patient or doctor may want to perform surveillance testing. It also recognises that, although rising CA-125 levels alone should not dictate therapy, they may provide a point when goals of care can be re-examined. This approach explicitly acknowledges that women may make very different decisions about their care. Some may choose to have diagnostic testing and treatment only when they become symptomatic, and others may choose to have CA-125 surveillance and to have treatment even when they are asymptomatic, and irrespective of adverse effects.[9]

This second approach to post-treatment use of CA-125 surveillance is consistent with clinical guidelines (currently being revised in the light of emergent data on CA-125 surveillance).[10] The ongoing use of a surveillance measure for reasons other than improving survival or quality of life may also be more acceptable to patients, clinicians and the health system if, as suggested by Rettenmaier and colleagues, it is not economically prohibitive.[2]

Rustin and colleagues from the European Organisation for Research and Treatment of Cancer deserve congratulation for designing and completing a seminal study, not only in ovarian cancer, but in oncology generally. The conclusion that earlier therapy of relapse detected by CA-125 with current treatments does not prolong survival seems rock solid, and demands an end to the practice of routine CA-125 surveillance in ovarian cancer.

This does not mean, though, that CA-125 testing has no role in surveillance, as it may provide some benefit beyond mortality and morbidity — something that should now be the focus of rigorous qualitative study. In the interim, oncologists should openly discuss the options for monitoring disease following primary therapy with their patients, and should use clinical follow-up and the results of surveillance testing (if they choose to do it) in advance care planning.

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