Redefining cancer and cure

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As our understanding of cancer evolves, in parallel, we must evaluate how we define this disease in its simplest terms and what we mean by cure. In the advanced disease setting, downstaging a tumour with neoadjuvant chemotherapy to remove the faster-growing cancer cells and considerably reduce the size of the tumour before surgery seems intuitive and advantageous in terms of patient survival. Certainly, in breast cancer and other cancers, applying neoadjuvant therapy has been shown to improve survival. So, for women with advanced ovarian cancer, in which 20% can survive beyond 10 years, how can we increase this survival rate to 50% with an existing approach? In this issue of the journal, Steven Narod posits that it is possible to significantly increase cure in women with advanced-stage ovarian cancer by using maximal debulking surgery and intraperitoneal chemotherapy. His logic is simple. If no cancer cells remain after initial treatment, then this defines cure. Conversely, recurrence is likely in patients in whom residual cancer cells remain after initial treatment. By assessing survival data and noting that a majority of women with advanced-stage ovarian cancer survive for 10 years following treatment — and that almost all deaths occur within 12 years of diagnosis — he explains that 12-year survival can be a statistical indicator of cure.

By examining data from observational studies and correlating outcomes with residual disease in the context of the treatment employed, Narod begins to unravel how we can achieve cure. In one study, 7-year survival rates of women treated with neoadjuvant chemotherapy were only 9%, whereas, this rate was 41% in women treated with primary debulking surgery. Importantly, in those receiving neoadjuvant treatment, the extent of residual disease is assessed after chemotherapy and surgery; however, for women undergoing primary debulking surgery, residual disease is measured after surgery, but before maintenance chemotherapy. Thus, the proportion of women with 'no residual disease' is usually greater for women treated with neoadjuvant therapy than in situations when primary debulking surgery is used. In observational studies, despite the 'no residual disease' status, the 7-year survival rate was only 8% for women treated with neoadjuvant therapy, but was as high as 74% in those treated with primary debulking surgery.

How can these strikingly different outcomes be reconciled? Narod suggests that larger tumours contain a greater number of chemosensitive cells, but only a few chemoresistant cells. So, if chemotherapy is used early on in the treatment journey to downsize the tumour, it might remove the bulk of the tumour, but the proportion of chemoresistant cells remaining (and that are not macroscopically visible) would be greater in relation to the number of cells remaining if initial surgery is used. Moreover, the remaining cells would be harder to locate and remove during subsequent surgery. Ultimately, in this situation, microscopic disease remains, but the treatment renders the patient status as 'no residual disease'. By scrutinizing the survival curves at 5 years and at 12 years, invariably, at 5 years, the curves separate but then come together at 12 years — a pattern that remains irrespective of the treatment used or tumour biology. In other words, taking 5-year survival as a proxy for cure *per se* is misleading, because although chemotherapy can reduce the rate of recurrence at this juncture, it does not reduce the overall likelihood of death from ovarian cancer.

Is there a common theme that can explain these survival outcomes? Narod proposes three assumptions: first, if no residual cells are present in the abdomen following treatment, then recurrence or death is impossible. Second, if residual cells are present following surgery and chemotherapy, these cells will flourish, and relapse is inevitable. Moreover, death by distant metastases is unlikely in the absence of intra-abdominal recurrence. Third, death from ovarian cancer almost always occurs within 12 years of diagnosis. Thus, to cure ovarian cancer, rather than merely postponing recurrence, achieving 12-year survival should be our goal. The best chance of achieving cure is to resect to the point of no residual disease, and this is more easily achieved with maximal debulking surgery, as hopefully less selective pressure is imposed on any surviving cells, as few or no chemoresistant cells would remain. Although intraperitoneal chemotherapy is harder for women to tolerate, provided no residual disease remains, this is considered the optimal chemotherapy treatment. This is on the basis of data indicating that intraperitoneal chemotherapy might only delay recurrence in patients with minimal residual disease; however, it can improve long-term benefit and cure rates in patients with no residual disease.

By understanding our definition of no residual disease, and by considering the benefits and limitations imposed by different treatment approaches in terms of tumour heterogeneity and the likelihood of the surviving cells repopulating the tumour, Narod offers a parsimonious model that could tangibly improve our view of this disease and ultimately achieve greater cure!

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Competing interests
The author declares no competing interests.