Can advanced-stage ovarian cancer be cured?

Treatment of advanced-stage ovarian cancer should comprise optimal debulking surgery followed by adjuvant intraperitoneal chemotherapy. **Steven Narod**, from Women's College Research Institute, Toronto, Canada, argues that widespread adoption of this model would increase cure rates for advanced ovarian cancers, from the current 20% to half of all patients.

This is an abridged version of S Narod (2016) Can advanced-stage ovarian cancer be cured? ***Nat Rev Clin Oncol*** *13:255–261. It was edited by Janet Fricker and is published with permission ©*
 doi:10.1038/nrclinonc.2015.224

nature REVIEWS CLINICAL ONCOLOGY

In 2012, around 239,000 women worldwide were diagnosed with ovarian cancer and 152,000 died from the disease, suggesting almost 65% of all women with ovarian cancer eventually succumb to the condition (*IARC CancerBase* No 11, 2012). Around two in ten women with advanced-stage ovarian cancer survive 12 years beyond treatment, and are effectively cured (*Obstet Gynecol* 2015, 126: 491–97). Important lessons can be learnt from the experiences of these patients.

Although the main types of drugs used for ovarian cancer (taxanes and platinum-based chemotherapeutics) have not been replaced in 20 years, debate continues over the optimum timing (neoadjuvant versus adjuvant) and best routes of administration (intravenous versus intraperitoneal).

Surviving ovarian cancer

Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate 62% of ovarian cancers have serous histology, 20% endometrioid, 8% clear-cell, 5% mucinous, and 5% other histopathological subtypes, and that serous histology is responsible for 80% of all ovarian cancer deaths. The data also show 10-year survival for patients diagnosed with early-stage serous ovarian cancer is 55%, versus 15% for those with advanced-stage disease.

With studies showing almost all ovarian cancer deaths occur within 12 years of diagnosis, after which death rates approach that of women in the general population (*Gynecol Oncol* 2015, 138:741–49; *JNCI* 2013, 105:141–48), 12-year survival can be considered an indicator of (statistical) cure.

The mainstay of ovarian cancer treatment is surgery to maximally reduce tumour burden, followed by

chemotherapy to kill as many residual cancer cells as possible. In some patients, neoadjuvant chemotherapy (chemotherapy before surgery) is administered to reduce tumour volume and improve resectability.

While the National Comprehensive Cancer Network recommends neoadjuvant chemotherapy for patients with high-volume disease who are not surgical candidates due to high risk comorbidities, some institutions use it more liberally (*Nat Rev Clin Oncol* 2015, 12:239–45; *Gynecol Oncol* 2013, 131:341–46).

Molecularly targeted treatments (olaparib and bevacizumab) are aimed at impeding growth of remaining cancer cells after the first round of chemotherapy to delay disease progression, rather than achieving a cure.

Upfront chemotherapy versus surgery

In advanced-stage ovarian cancer, two randomised trials concluded survival after neoadjuvant chemotherapy was not inferior to primary debulking surgery followed by adjuvant chemotherapy, and found less morbidity in the neoadjuvant group (*NEJM* 2010, 363:943–53; *Lancet* 2015, 386:249–57). With 10-year survival universally poor (around 10%), such data suggest neoadjuvant chemotherapy improves quality of life.

Other observational studies challenge these findings, with one study showing the seven-year survival of advanced–stage ovarian cancer was 9% for neoadjuvant chemotherapy versus 41% for primary debulking surgery ($P<0.0001$) (*Gynecol Oncol* 2014, 134:462–67). One explanation might be that women offered neoadjuvant chemotherapy have more extensive disease, but even among women with no visible residual disease following neoadjuvant chemotherapy, long-term survival has been universally poor, and inferior to that of patients with no residual disease following primary surgery (*Cancer* 2009, 115:1234–44; *JCO* 2015, 33:937–43).

Many studies show that the clinical status 'no residual disease', referring to no cancer visible after surgery, is the best predictor of long-term survival (*JCO* 2015, 33:937–43; *Gynecol Oncol* 2013, 130:493–98).

For women receiving neoadjuvant chemotherapy, residual disease is assessed after completion of chemotherapy and surgery; while for women undergoing primary debulking surgery, residual disease is measured after surgery and before chemotherapy. The proportion with no residual disease is usually greater for those receiving neoadjuvant chemotherapy than those undergoing primary debulking surgery. Fifty percent or more of women with visible residual disease after primary debulking surgery will have no objective evidence of disease after adjuvant chemotherapy (*NEJM* 1996, 334:1–6; *JCO* 2003, 21:3194–200).

In an observational study of women with no visible residual disease after surgery, seven-year survival was 8% for neoadjuvant chemotherapy versus 74% for primary debulking surgery ($P<0.0001$). These results were despite 51% of patients treated with neoadjuvant therapy achieving a status of no residual disease compared with 42% of patients undergoing primary debulking surgery ($P=0.03$).

A possible explanation is that neoadjuvant chemotherapy provides a false assurance of no residual disease, with the chemosensitive cells forming the bulk of the tumour disappearing and thereby rendering chemoresistant cells invisible to the naked eye, and harder to locate and remove in subsequent surgery.

Intravenous versus intraperitoneal chemotherapy

The best ovarian cancer survival rates have been reported in women with no residual disease after primary debulking surgery who then received intraperitoneal chemotherapy .

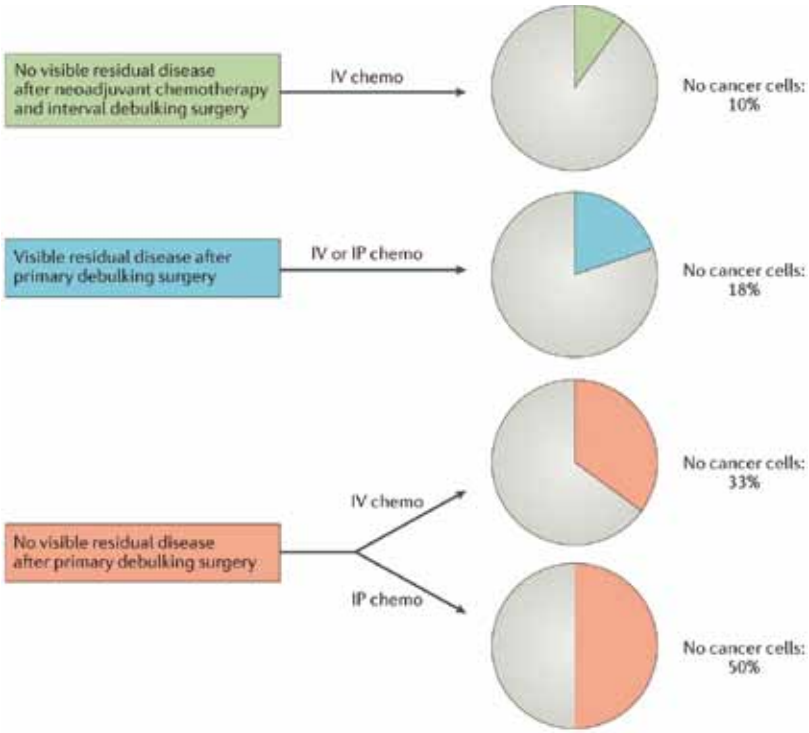
A retrospective analysis of 876 patients included in the Gynecologic Oncology Group GOG-114 and GOG-172 trials demonstrated that, among the 78 patients with no residual disease who underwent intraperitoneal chemotherapy, 10-year survival was 50% (*JCO* 2015, 33:1460–66). Data suggest that intraperitoneal chemotherapy delays recurrence in patients with minimal residual disease, but improves cure in patients with no residual disease.

While patients can have difficulty tolerating intraperitoneal chemotherapy, they should be encouraged to endure the rigours with the message that, for patients with no residual disease, the chance of curing advanced-stage ovarian cancer increases from 33% to 50% (*JCO* 2015, 33:1460–66).

One study of six US centres showed use of intraperitoneal chemotherapy ranged between 4% and 67% (*JCO* 2015, 33:2841–47). That the proportion of patients receiving intraperitoneal chemotherapy exceeded 60% in two centres demonstrates it is possible. That one centre only achieved a 4% uptake suggests that either doctors do not believe the approach works, or they give up too easily, or do not have treatment and supportive care infrastructures.

On the basis of these findings, patients with no residual disease after primary debulking surgery are ideal candidates for adjuvant intraperitoneal chemotherapy. Patients with residual disease may increase life expectancy by a year or so with intraperitoneal chemotherapy, but do not enhance their chance of cure.

A model of ovarian cancer treatment outcome



Among the women with no visible – that is, clinically detectable — residual disease after treatment of ovarian cancer (by debulking surgery, with or without prior neoadjuvant chemotherapy, and adjuvant chemotherapy), some patients have residual microscopic deposits of cancer cells that will eventually cause the disease to recur and, ultimately, lead to death. Those patients who have no residual cancer cells after such treatment are cured. Thus, the percentage of women with no cancer cells remaining post-treatment can be estimated based on the proportion of women who are alive after 12 years of follow up, because the death rate of women with ovarian cancer becomes the same as that of the general population at this time point.

The estimates in the figure are based on survival rates reported by Vergote et al., Kehoe et al., and Tewari et al (NEJM 2010, 363:943–53; Lancet 2015, 386:249–57; JCO 2015, 33:1460–66).

A model for ovarian cancer cure

When ovarian cancer cohort survival is presented graphically, curves that separate at five years invariably come together at 12 years, regardless of the treatment used.

While chemotherapy decreases recurrence and death, it does not reduce the eventual likelihood of death from ovarian cancer *per se*. Once surgery is completed, patients seem fated to survive or die, regardless of the best efforts of oncologists, who can delay recurrence, but not prevent it. Host factors, such as *BRCA1* and *BRACA2* status, predict short-term, but not long-term survival.

In a whole-genome characterisation of chemotherapy-resistant ovarian cancer, molecular markers predicted better five year survivals, but by 10 years the proportion of survivors in molecular subgroups were essentially the same.

Such observations can be reconciled under a simple model making three assumptions. First, if no residual cancer cells are present in the abdomen, recurrence or ovarian-cancer related death is impossible. Second, if residual cancer cells persist in the abdomen after surgery and chemotherapy are completed, these cells will flourish, cancer recur, and patients eventually die of the disease. Third, deaths from ovarian cancer occur within 12 years of diagnosis.

On the basis of the first two principles it can be inferred that local (intra-abdominal) recurrence is a necessary and sufficient step towards death from ovarian cancer, that women who do not have intra-abdominal recurrence rarely die from ovarian cancer and women who experience abdominal recurrence almost certainly do. Only in exceptional cases is death from ovarian cancer caused by distant metastatic spread in the absence of intra-abdominal recurrence (*Int J Gynecol Cancer* 2013, 23:1590–96). Of note, intraperitoneal chemotherapy results in higher rates of extra-abdominal recurrence (*Gynecol Oncol* 2012, 127:51–54), but lower rates of absolute recurrences (*Cancer* 2006, 106: 1624–33).

The fact that locoregional control determines survival allows the assumption that, if no viable cancer cells persist in the abdomen after treatment, the patient is cured. Pathological features of cancer are irrelevant for the fortunate in whom no cancer cells are left to proliferate. Conversely, if chemotherapy fails to eradicate all cancer cells and some remain post-treatment (even if microscopic), these ultimately flourish and lead to death within 12 years of diagnosis. Under the proposed model, the proportion of women who are alive at 12 years is precisely the proportion with no residual cancer cells after treatment.

Under the model, the chance of having no microscopic disease is highest for primary debulking surgery and intraperitoneal chemotherapy, and lowest for neoadjuvant chemotherapy (see figure).

Take home message from the author

Steven Narod is a senior scientist at Women's College Research Institute, in Toronto, and Professor at the Department of Medicine and Dalla Lana School of Public Health, at the University of Toronto, Canada.

"There is much variation in the use of intraperitoneal chemotherapy for ovarian cancer and this can be life-saving. There is a common misconception that women with advanced ovarian cancer are beyond hope and therefore the choice of therapy is not critical. This, however, is not true. Intraperitoneal chemotherapy for ovarian cancer is used sparingly in the UK, but commonly in North America, placing UK patients at a major disadvantage. The differences in treatment approach are due to methods of payment. In the UK doctors are rewarded for doing as little as possible under the NHS, while in the US doctors are rewarded for doing as much as possible in private hospitals.

Clinical implications

From the review, the clinical messages are to avoid neoadjuvant chemotherapy in ovarian cancer wherever possible, and to strive for complete debulking of the tumour with no residual disease. Then patients who have no visible residual disease following primary debulking surgery should be treated with intraperitoneal chemotherapy. The most important endpoint for ovarian cancer studies is 12-year survival; time to progression is of much less importance.

Future studies

I'd like to see studies testing the combination of neoadjuvant chemotherapy and intraperitoneal chemotherapy following debulking surgery among women with no residual disease. Following debulking surgery it would also be valuable to have studies randomising women to intraperitoneal versus intravenous chemotherapy, and finally to have data comparing differences in survival between the UK and USA."

No cancer cell left behind

The pathology and the molecular features of a cancer could possibly affect the chance of cure, either by influencing 'resectability' of the cancer to no residual disease (through primary debulking surgery), or by subsequently determining whether adjuvant chemotherapy eradicates remaining cancer cells.

One study reported ovarian cancer patients with *BRCA1* mutations were less likely to achieve no residual disease status than patients without the mutation (*Gynecol Oncol* 2015), and another that patients harbouring tumours with decreased BRCA1 levels obtain greater benefit from intraperitoneal chemotherapy (*Br J Cancer* 2013, 108:1231–37). Further work is warranted to identify interactions between molecular features, including genetic mutations and gene-expression levels, on tumour resectability, eradication, and outcome.

Synergy seems to exist between intraperitoneal chemotherapy and no residual disease, with this combination offering the highest chance of leaving no cancer cells behind.

Patients who achieve a status of no residual disease through primary debulking surgery have the best long-term survival rates (25–50%, or higher) of all patients with advanced-stage ovarian cancer, irrespective of stage at diagnosis, initial disease burden, surgical complexity, or mutation status.

While it has become a goal to avoid unnecessary morbidity by predicting patients in whom complete debulking is likely to be successful using a laparoscopic-staging or statistical index, neither approach is considered infallible. In the SCORPION trial, 45.5% of patients judged unresectable by staging laparoscopy were subsequently resected to have no residual disease (*Gynecol Oncol* 2015, 138 Suppl. 1:1–4).

In summary

Curing patients with advanced-stage ovarian cancer requires elimination of all cancer cells, with the chance of achieving this objective greatest with resection to no residual disease through maximal debulking surgery, followed by intraperitoneal chemotherapy.

Neoadjuvant chemotherapy should be limited to those for whom complete resection is judged impossible or who are not candidates for extended surgery due to comorbidities. In spite of the morbidity associated with intraperitoneal chemotherapy, data suggest this approach should be used as much as possible, and in particular in patients with no residual disease after surgery.

Overall, there is a need to readdress our thinking around ovarian cancer treatment – all women should be offered the possibility of cure.