OPINION

Can advanced-stage ovarian cancer be cured?

Steven Narod

Abstract | Approximately 20% of women with advanced-stage ovarian cancer survive beyond 12 years after treatment and are effectively cured. Initial therapy for ovarian cancer comprises surgery and chemotherapy, and is given with the goal of eradicating as many cancer cells as possible. Indeed, the three phases of therapy are as follows: debulking surgery to remove as much of the cancer as possible, preferably to a state of no visible residual disease; chemotherapy to eradicate any microscopic disease that remains present after surgery; and second-line or maintenance therapy, which is given to delay disease progression among patients with tumour recurrence. If no cancer cells remain after initial therapy is completed, a cure is expected. By contrast, if residual cancer cells are present after initial treatment, then disease recurrence is likely. Thus, the probability of cure is contingent on the combination of surgery and chemotherapy effectively eliminating all cancer cells. In this Perspectives article, I present the case that the probability of achieving a cancer-free state is maximized through a combination of maximal debulking surgery and intraperitoneal chemotherapy. I discuss the evidence indicating that by taking this approach, cures could be achieved in up to 50% of women with advanced-stage ovarian cancer.

In 2012, an estimated 239,000 women were diagnosed with ovarian cancer worldwide, and 152,000 women died of the disease[1]. These data suggest that almost 65% of all women with ovarian cancer will succumb to the disease — fatality rates are even higher for women who are diagnosed at an advanced disease stage. Indeed, one often hears nowadays that the prognosis of patients with advanced-stage serous ovarian cancer is dismal, but to accept this statement as fact is to overlook the 20% of patients who defy our expectations and survive for 10 years or more, most of whom are effectively cured[2]. Who are these women, and what can we learn from their experience? More importantly, can we use our knowledge to achieve better than a 20% 10-year survival rate? Although the two canonical types of drugs we use to treat ovarian cancer — taxane and platinum-based chemotherapeutic agents — have not been replaced in the past 20 years, debate continues regarding the optimum timing of treatment (neoadjuvant versus adjuvant) and the best route of administration (intravenous versus intraperitoneal). In this Perspectives article, I address the questions posed above, based on the available efficacy data for the various treatment approaches used in patients with advanced-stage ovarian cancer. I argue that — in my opinion, and supported by published evidence — the ideal therapy for women with this disease should comprise optimal debulking surgery and adjuvant intraperitoneal chemotherapy; using this approach, the current cure rate of 20% could be substantially improved, and we might achieve a cure rate closer to 50%.

Survival from ovarian cancer

In the USA, each year, approximately 21,300 women are diagnosed with ovarian cancer and 14,200 women die from this disease (ratio of 1.5:1)[3,4]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that, excluding borderline cases, ovarian cancers are most commonly of serous histology (62% of cases), followed by endometrioid (20%), clear-cell (8%), mucinous (5%), and other histopathological subtypes (5%)[4]. Serous ovarian cancers are responsible for 80% of all deaths from ovarian cancer[4]. The 10-year survival for patients diagnosed with early stage serous ovarian cancer is 55%, versus 15% for those with advanced-stage disease[4] (TABLE 1). Indeed, of the women who die of serous ovarian cancer, 93% present with advanced-stage disease (American Joint Committee on Cancer[4] (AJCC) stages III or IV; TABLE 1). Interestingly, women who received treatment for advanced-stage disease also comprise the majority of all the women who survive 10 years after treatment for serous ovarian cancer (~65%), owing to the high proportion of women diagnosed with stage III–IV disease (TABLE 1). Almost all deaths from ovarian cancer occur within 12 years of diagnosis, and after 12 years the death rate of patients with ovarian cancer approaches that of women in the general population[5,6]. Thus, in this article, I consider 12-year survival to be an indicator of (statistical) cure, although rare exceptions to this rule do exist.

The gynaecological-oncology community is moving towards considering high-grade serous ovarian cancer as a single clinical entity, and in the past decade, much focus has been placed on the pathology, prognosis, and treatment of high-grade serous cancers[7]. Only 13% of serous ovarian cancers are diagnosed in stage I or stage II, and 55% of these patients are alive after 10 years (TABLE 1); therefore, we must make improvements in the treatment of women with advanced-stage disease if we are to increase our ability to cure ovarian cancer. The mainstay of treatment of ovarian cancer is surgery to maximally reduce the tumour burden, followed by chemotherapy to kill as many residual cancer cells as possible. In some patients, neoadjuvant chemotherapy is administered before surgery to reduce the tumour volume and thus improve resectability. The National Comprehensive Cancer Network (NCCN) currently recommends neoadjuvant chemotherapy for

Table 1 | **Mortality from serous ovarian cancer in the USA***

AJCC stages	Definition	Number of cases annually	Proportion of all cases diagnosed	Vital status at 10 years		10-year survival
				Alive (proportion of all survivors)	Dead (proportion of all deaths)	
I and II	Stage I: Tumour confined to one or both ovaries Stage II: Tumour confined to the pelvic tissues (ovaries, fallopian tubes, and/or uterus)	1,716	13%	944 (35.4%)	772 (7.3%)	55%
III and IV	Stage III: Tumour spread beyond the pelvic tissues, to the retroperitoneal lymph nodes or within the peritoneum (including to the liver and spleen capsule) Stage IV: Tumour spread beyond the abdomen (for example, to the liver and/or spleen parenchyma, or pleural effusion containing cancer cells)	11,484	87%	1,723 (64.6%)	9,761 (92.7%)	15%

AJCC, American Joint Committee on Cancer. *On the basis of data from the Surveillance, Epidemiology, and End Results database[4].

patients with high-volume disease who are not surgical candidates (for example, owing to high-risk comorbidity conditions)[8], but in some institutions, its use is more liberally applied[9,10]. Other modern, molecularly targeted treatments, such as the poly(ADP-ribose) polymerase inhibitor olaparib and the anti-VEGF antibody bevacizumab, are aimed at impeding the growth of resistant cancer cells that remain after the first round of chemotherapy in order to delay disease progression, rather than as a means of achieving a cure[11–14]. The efficacies of the various treatments are reviewed in the following sections, and the implications of the various clinical findings are used to propose a model for improving the potential to cure ovarian cancer.

Upfront chemotherapy versus surgery

The authors of two randomized trial reports published in the past 5 years concluded that the survival of women with advanced-stage ovarian cancer after receiving chemotherapy before surgery (neoadjuvant chemotherapy) was not inferior to that of patients who underwent primary debulking surgery followed by chemotherapy (adjuvant chemotherapy)[15,16]; however, neoadjuvant delivery of chemotherapy was associated with less morbidity[15,16]. Only small differences were seen in survival between the treatment arms in both studies, although the 10-year survival rates were universally poor (around 10%)[13,14]. If we accept these studies as definitive, and concede that death from advanced-stage ovarian cancer is inevitable, the use of neoadjuvant chemotherapy to improve a patient's quality of life seems reasonable. As Dr Barbara Ann Goff at the Fred Hutchison Cancer Center, Seattle, Washington, USA, puts it, "doctors think women with ovarian cancer are going to die no matter what you do, so why put them through something that is toxic" (REF. 17).

The results of these randomized trials and their conclusions have been challenged, however, by the findings of several observational studies published in the past 2 years[10,18–20]. For example, Rosen *et al.*[18] found that the 7-year survival of women with advanced-stage ovarian cancer treated with neoadjuvant chemotherapy was only 9%, compared with 41% for women who underwent primary debulking surgery ($P<0.0001$). Women who are offered neoadjuvant chemotherapy are likely to have more-extensive disease than women offered primary debulking surgery[18–20], which might partially explain the disparate results of these observational studies; however, even among women who have no visible residual disease following neoadjuvant chemotherapy, long-term survival has been shown to be universally poor[10,18–20], and is far inferior to that of patients diagnosed with a similar extent of disease who have no residual disease following primary surgery[21,22]. The difference in survival with neoadjuvant chemotherapy versus primary debulking surgery is, therefore, unlikely to be due entirely to differences in disease stage and/or grade.

Findings of many studies have demonstrated that the clinical status of 'no residual disease', which refers to no cancer visible to the naked eye of the surgeon in the abdomen after surgery, is the most-important predictor of long-term survival after a diagnosis of advanced-stage ovarian cancer[21–23]. For women who receive neoadjuvant chemotherapy, the extent of residual disease is assessed after both chemotherapy and surgery have been completed, but for women who undergo primary debulking surgery, the extent of residual disease is measured after surgery — but before chemotherapy. As one might expect, therefore, the proportion of women with a status of no residual disease is usually greater for patients treated with neoadjuvant chemotherapy than for those who undergo primary debulking surgery[15,16]. Typically, intravenous chemotherapy is given after primary debulking surgery, and once adjuvant treatment is complete, the tumour burden is re-evaluated using a combination of imaging assessments and analysis of serum cancer antigen 125 (CA-125) levels. A large proportion of women (50% or more) who have visible residual disease after primary debulking surgery will be rendered to be 'tumour-free' (that is, they will have no objective evidence of disease) after adjuvant chemotherapy[24,25], according to the current clinical criteria (negative findings of physical examination, CA-125 measurements, and CT scans)[8]; for some of these women, all of the cancer cells will, indeed, have been eradicated, but other patients with no detectable residual disease will have undetectable residual cancer cells after chemotherapy. Ultimately, the proportion of patients who have no residual cancer cells after treatment will predict the long-term-survival rate. In the observational study by Rosen *et al.*[18], among women with no visible residual disease after surgery, the 7-year survival was 8% for women who received neoadjuvant chemotherapy and was 74% among the women who underwent primary debulking surgery ($P<0.0001$) — despite the fact that 51% of patients treated with neoadjuvant therapy achieved a status of no residual disease, compared with 42% of patients who underwent primary debulking surgery ($P=0.03$). A possible explanation for the survival difference observed is that each focus of ovarian cancer contains a large number of chemosensitive cells and a small number of chemotherapy-resistant cells, and the latter need to be removed surgically to effect a cure; in the case of neoadjuvant chemotherapy, the chemosensitive cells

that form the bulk of the tumour disappear, thereby rendering the chemoresistant cells invisible to the naked eye, and thus harder to locate and remove during surgery. In this situation, neoadjuvant chemotherapy might provide a false assurance that a status of 'no residual disease' has been achieved, whereas, in reality, microscopic tumour foci remain after surgery.

Intravenous versus intraperitoneal

To date, the best survival rates among women with ovarian cancer have been reported for patients who had no residual disease after primary debulking surgery and who then received intraperitoneal chemotherapy[21,24,25]. Notably, in a retrospective analysis of data from 876 of the patients included in the Gynecologic Oncology Group GOG-114 and GOG-172 trials, Tewari *et al.*[26] demonstrated that the 10-year survival rate among the 78 patients with no residual disease who were treated with intraperitoneal chemotherapy was 50%. In this study, the use of the intraperitoneal chemotherapy regimen was associated with high toxicity and relatively low patient compliance (42% completed all six cycles)[26]; however, several modified intraperitoneal chemotherapy regimens have been used, with better compliance and comparable survival outcomes[27–29]. For example, in the aforementioned study by Rosen and colleagues[18], 19 of 22 patients in this group (86%) survived for at least 7 years.

Typically, authors refer to 'optimal debulking' and to 'no (visible) residual disease' when they describe the clinical status of the patient after surgery to remove ovarian cancer. This nomenclature can be confusing to the uninitiated because the two terms seem to be defining the same outcome, but, in fact, they have different meanings: optimal debulking refers to the situation in which the largest visible post-surgery residual lesion is less than 1 cm in diameter, thus describing achievement of only 'minimal residual disease', as opposed to no visible residual disease. Better outcomes are observed in patients with no residual disease, compared with minimal residual disease. In an early trial by Alberts *et al.*[30], no survival benefit was seen with intraperitoneal chemotherapy versus intravenous chemotherapy; however, in this study, patients with residual disease were included in the analysis. In a later study, Tewari *et al.*[26] reported that a survival benefit for intraperitoneal versus intravenous chemotherapy was present at 10 years for the women who had no residual disease after surgery, but not for those with minimal residual disease. Among women with minimal residual disease ($n = 261$; 126 treated with intraperitoneal and 135 treated with intravenous chemotherapy) the survival curves separated at 5 years in favour of intraperitoneal chemotherapy (45% versus 30%), but by 10 years they had realigned at 18% survival[26]. By contrast, among women with no residual disease, a long-term benefit of intraperitoneal chemotherapy was maintained: as mentioned, the 10-year survival was 50% among the 78 women who received intraperitoneal chemotherapy versus 33% for those treated with chemotherapy via the intravenous route ($n = 75$) — this 17% increase represents a substantial improvement in the cure rate[26]. These data suggest that intraperitoneal chemotherapy only delays recurrence in patients with minimal residual disease, but can improve the cure rate in patients with no residual disease. In a trial by Katsumata *et al.*[31], the 10-year survival rate for Japanese patients with minimal residual disease (up to 1.0 cm) was 65% for conventional intravenous chemotherapy and was 72% for dose-dense intravenous chemotherapy, suggesting that more intensive chemotherapy might also be effective in delaying progression or increasing the cure rate; however, the high survival rates of patients in both arms suggest that the benefit of dose-dense chemotherapy might be at least partially attributable to differences in the disease that are associated with Japanese ethnicity, and these results have not been duplicated in other populations.

Many patients have difficulty tolerating intraperitoneal chemotherapy. Women with ovarian cancer need support to endure the rigours of intraperitoneal chemotherapy, but should be encouraged to do so whenever possible, considering the potential survival benefits. The way the message about outcomes is delivered to them might be important in this regard. Consider the following two statements: the 3-year survival increases from 71% to 81% for patients treated with intraperitoneal chemotherapy[32]; or, the chance of being cured of advanced-stage ovarian cancer increases from 33% to 50% for patients with no residual disease treated with intraperitoneal chemotherapy[26]. Both of these statements are true, but I suspect that the uptake of intraperitoneal chemotherapy might be higher when the information is presented in the second way.

A study published in 2015 has demonstrated that the use of intraperitoneal chemotherapy among eligible women varies enormously between cancer centres in the USA — from 4% to 67% — for reasons that are not completely known[32]. The fact that the proportion of patients who received intraperitoneal chemotherapy exceeded 60% in two of the six centres studied (designated as 'Institutions 1 and 2')[32], is nevertheless a testament to the feasibility of the approach and to the patients' willingness to face adversity if given a chance of cure. Moreover, the fact that in one centre ('Institution 4') this proportion was only 4% warrants explanation[32]; either the doctors at Institution 4 do not believe that intraperitoneal therapy works very well or they are giving up too easily — perhaps they believe that the prognosis of patients with ovarian cancer is poor regardless of the route of treatment, or that the toxicities of intraperitoneal chemotherapy are too numerous. Perhaps they do not have the necessary treatment and supportive-care infrastructure. One assumes that the wide variation in uptake between cancer centres is unlikely to reflect differences in patient preferences. Interestingly, the extent of uptake of intraperitoneal chemotherapy between institutions did not depend on the proportion of patients with residual disease, even though the benefit of intraperitoneal chemotherapy seems to be much greater for patients with no residual disease than for patients with minimal residual disease[26]. On the basis of the findings of Tewari and co-workers[26], patients with no residual disease after primary debulking surgery are ideal candidates for adjuvant intraperitoneal chemotherapy. Patients with residual disease might increase their life expectancy by a year or so by undergoing intraperitoneal chemotherapy, but do not enhance their chance of a cure.

A model for ovarian cancer cure

In the era of molecularly targeted therapy, much effort has been placed on extending the time from disease recurrence to death, or extending the progression-free interval of women with ovarian cancer; use of the newest drugs, bevacizumab and olaparib, delays cancer progression, but offers us very limited or no opportunity to extend the lives of our patients[11–14]. I have long been puzzled by the consistency in the appearance of survival curves for patients with ovarian cancer: when the survival of patients in treatment cohorts is presented graphically, curves that separate at 5 years invariably

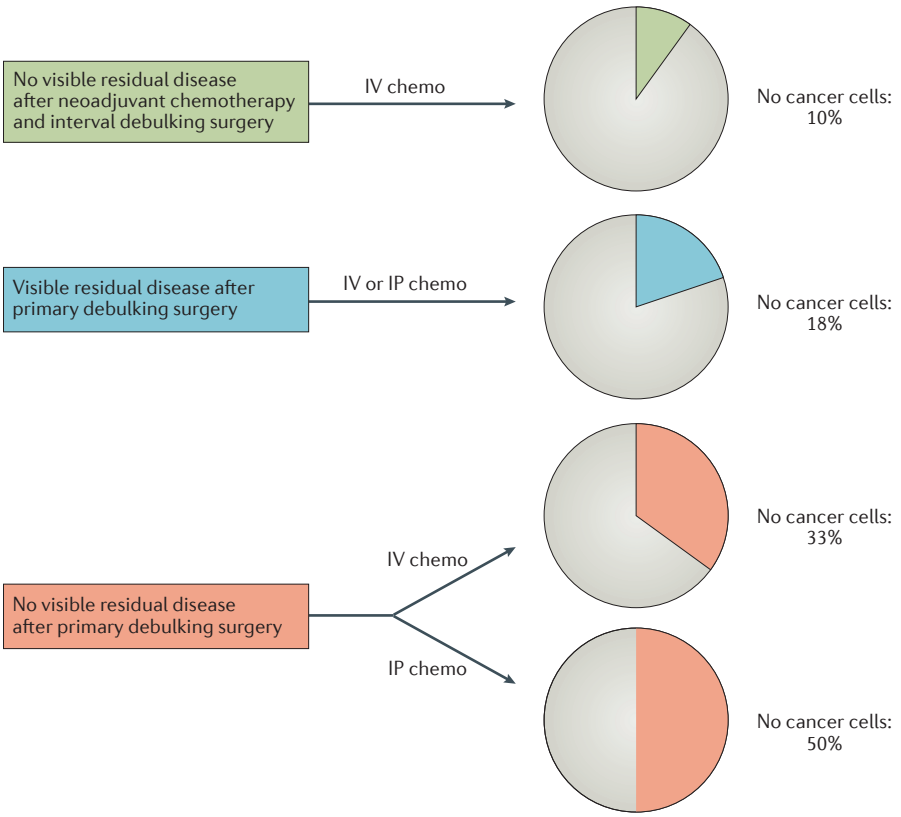

Figure 1 | **A model of ovarian cancer treatment outcome.** Among the women with no visible — that is, clinically detectable — residual disease after treatment of ovarian cancer (by debulking surgery, with or without prior neoadjuvant chemotherapy, and adjuvant chemotherapy), some patients have residual 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. Among the patients with ovarian cancer who achieve a status of no residual disease through neoadjuvant chemotherapy and interval debulking surgery (followed by adjuvant chemotherapy), an estimated 10% have no persisting cancer cells, as approximated from the 10-year survival rates reported by Vergote *et al.*[15] and Kehoe *et al.*[16] Among the patients with visible residual disease in the abdomen after primary debulking surgery who then achieve a status of no detectable residual disease after adjuvant intravenous (IV) or intraperitoneal (IP) chemotherapy, 18% are estimated to have no remaining cancer cells, based on the 10-year survival rates reported by Tewari *et al.*[26] For patients with no visible residual disease after primary debulking surgery, the probability of having no residual cancer cells after adjuvant chemotherapy is estimated to be 33% for those who receive IV chemotherapy and 50% for those who receive IP (together with IV) chemotherapy, again, approximated from the survival data published by Tewari *et al.*[26]

come together at 12 years — regardless of the exposure in question. This pattern holds true for comparisons of survival stratified by year of diagnosis[5,33], by use of chemotherapy versus no chemotherapy[5], and by *BRCA*-mutation status[34,35]. It comes as a surprise to many that standard chemotherapy for ovarian cancer delays recurrence and death, and improves 5-year survival, compared with surgery alone, but does not affect 12-year survival[5]; therefore, chemotherapy decreases the rate of recurrence and the rate of death, but does not reduce the eventual likelihood of death from ovarian cancer *per se*. Once surgery is completed, the patient seems to be fated to survive or to die of the disease, regardless of the best efforts of oncologists, who can delay recurrence, but cannot prevent it. Host factors, such as *BRCA1* and *BRCA2* status, thus predict the frequency and duration of response to chemotherapy, and therefore, the time to recurrence, but do not stave off the inevitable[36]. For example, in an article describing survival patterns of carriers of *BRCA1* or *BRCA2* mutations, Bolton *et al.*[37] reported that a clinically important survival benefit was present at 5 years for women with ovarian cancer who carried a *BRCA1* or *BRCA2* mutation. When this group revisited the dataset at 10 years, however, the survival advantage had disappeared[35]; this effect was similar for all-cause survival and for ovarian-cancer-specific survival[35]. Moreover, many molecular features have been found to predict short-term survival, but not long-term survival. In a whole-genome characterization of chemotherapy-resistant ovarian cancers that was published in 2015 (REF. 38), molecular markers indicative of homologous-recombination deficiency were found to be profoundly predictive of better survival at 5 years, but at 10 years post-diagnosis, the proportion of survivors in the various molecular subgroups was essentially the same.

In statistical terms, the factors that predict cure and the factors that predict death seem to be distinct and separable. At first glance, this appears to be a paradox and will be hard to accept for those of us who have come to assume that recurrence rates (and death rates) are proportional — under the proportional hazards assumption, a separation of the mortality curves at 5 years will be reflected again at 12 years and, ultimately, in the cure rate as well. When hazard rates are not proportional over time, we cannot predict the future based on the past; we need to observe the fate of the patients for ourselves. What explains this consistency in the pattern of survival curves? These various observations can be reconciled under a simple parsimonious model if we make the following 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 both surgery and chemotherapy are completed, these cells will flourish, the cancer will recur, and the patient will eventually die of the disease; third, deaths from ovarian cancer occur within 12 years of diagnosis.

On the basis of the first two principles, we can infer that local (intra-abdominal) recurrence is a necessary and sufficient step towards death from ovarian cancer — that is, women who do not have intra-abdominal recurrence rarely die of ovarian cancer and women who experience a recurrence in the abdomen almost certainly do (in a sense this is a vindication of Halstead's model for the natural history of breast cancer, only for a different cancer)[39]. Indeed, only in exceptional cases is death

Box 1 | **Targets for cure: the three phases of ovarian-cancer treatment**

Resectability

- Aim to achieve a status of no (visible) residual disease through primary debulking surgery
- Factors that predict resectability include the extent and location of disease and, possibly, *BRCA* mutation status

Eradication

- Aim to eliminate all cancer cells present after primary debulking surgery through intravenous and/or intraperitoneal chemotherapy
- Neoadjuvant chemotherapy is associated with a high chance of achieving no visible residual disease but a low chance of cure

Prevention of recurrence

- Attempt to prevent the growth and dissemination of cancer cells that remain present after initial surgery and chemotherapy to delay or prevent recurrence
- Current maintenance therapies include olaparib and bevacizumab — these agents delay disease progression, but do not prevent recurrence or death

from ovarian cancer caused by distant metastatic spread in the absence of intra-abdominal recurrence[40]. Of note, the rate of extra-abdominal recurrence is higher in patients treated with intraperitoneal chemotherapy[41], but the absolute number of patients who recur is lower[42]. By contrast, in patients with breast cancer, local control through surgery is often achieved; however, most women who die of breast cancer are diagnosed with stage I–III disease: women with primary stage IV breast cancer account for only 20% of breast-cancer-related deaths[4]. Why locoregional control of ovarian cancer is paramount for survival, and why debulking of widespread metastases improves outcomes of patients with this disease — contrary to the situation in patients with other cancers — are matters for speculation: perhaps the term 'metastatic' is inaccurate in describing the intra-abdominal spread of ovarian cancer cells[43], and should be replaced by a different term. Nevertheless, the fact that locoregional control determines survival enables us to assume, logically, that if no viable cancer cells persist in the abdomen after treatment, the patient is cured; the pathological features of the cancer (such as mutation status, gene expression, and others) are rendered irrelevant for the fortunate patient in whom no cancer cells are left to proliferate. Conversely, if chemotherapy fails to eradicate all the cancer cells and some remain present post-treatment (even if microscopic), these will ultimately flourish and will lead to death within 12 years of diagnosis. For these less-fortunate patients, the time of death might be influenced by the features of the cancer and any additional treatment given. At 12 years post-diagnosis, the death rate among patients with ovarian cancer approximates that of the general population (statistical cure)[5,6]; thus, under the proposed model, the proportion of women who are alive at 12 years is precisely the proportion of women with no residual cancer cells after treatment.

According to this model, and based on the available survival data[26], after primary debulking surgery, most patients with advanced-stage ovarian cancer will have no clinical (visible) evidence of disease, but within this group at least 50% of women have undetectable deposits of cancer cells that persist after adjuvant chemotherapy. 'No residual disease' is a surgical note — among the women with this outcome, either most have residual cancer cells, with chemoresistant cancer cells remaining present in 50% of patients, or the persistence of residual cells after chemotherapy might be stochastic. In the future, novel therapies might emerge that can be used to render these patients cancer free, but for now, they have a limited chance of cure from treatment in the second-line and beyond. Currently, identification of women with and without microscopic disease is not possible, and the molecular features that discriminate between the two groups remain unknown. Under the model described here, the chance of having no microscopic disease is highest for women treated with primary debulking surgery and intraperitoneal chemotherapy, and is lowest for women who receive neoadjuvant chemotherapy (FIG. 1).

No cancer cell left behind

To cure ovarian cancer, rather than postpone recurrence, we should focus on 12-year survival. The molecular features of the cancer might affect 5-year survival, but have minimal effects on 12-year survival. 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 subsequently by determining whether all (microscopic) cancer cells that remain after surgery are eradicated (through adjuvant chemotherapy) — or, if residual cancer cells are present after surgery and chemotherapy are completed, by affecting the effectiveness of any interventions used to prevent recurrence (BOX 1). Kotsopoulos *et al.*[35] reported that patients with ovarian cancer and a *BRCA1* mutation are less likely to achieve a state of no residual disease than patients without a mutation (19% versus 39%; $P<0.0001$). Furthermore, among women with no residual disease, the presence of a *BRCA* mutation conferred a worse 10-year disease-specific survival, but the difference was not statistically significant (35% versus 54%; $P=0.17$)[35]. Lesnock and colleagues[44] demonstrated that patients harbouring tumours with decreased BRCA1 levels obtained greater benefit from intraperitoneal chemotherapy, compared with patients harbouring tumours with normal BRCA1 expression. The median overall survival of women harbouring tumours with aberrant BRCA1 expression was 84 months in the intraperitoneal chemotherapy cohort and 47 months in the intravenous chemotherapy group ($P=0.0002$), compared with 58 months and 50 months, respectively, for women with normal BRCA1 expression ($P=0.82$). These researchers did not examine survival specifically among patients with no residual disease; however, the data from this study[44] suggest that intraperitoneal chemotherapy might help to improve the long-term survival of patients with no residual disease and a *BRCA1* mutation. Further work is warranted to identify interactions between molecular features, including genetic mutations and gene-expression levels, on tumour resectability, eradication, and outcome.

A synergistic effect seems to exist between intraperitoneal chemotherapy and no residual disease, such that this combination of treatments offers the highest chance of leaving no cancer cell behind. In contrast with current therapies (both those in clinical use and under investigation), we cannot hope to cure patients with ovarian cancer by targeting the prevention of recurrent disease (BOX 1). Some would argue that the association between no residual disease and survival is not a testament to the surgeon's skill, but is instead an expression of the underlying association

between resectability and prognosis; however, 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[21,22]. Some would argue that neoadjuvant chemotherapy will increase the probability of leaving no residual disease and, ultimately, cure, but no data from cohorts of patients treated with neoadjuvant chemotherapy show cure rates of 20% or more[10]. It has become a goal of the gynaecology-oncology community to try to predict the patients in whom complete debulking is likely to be successful, using either a laparoscopic-staging approach[10,45] or a statistical index[46], in order to avoid unnecessary morbidity and to improve surgical efficiency. Neither approach is infallible, however, and consequently a substantial fraction of patients with disease that is judged not to be resectable are nevertheless rendered disease-free by the surgeon. For instance, in the SCORPION trial[45], 45.5% of patients deemed to be unresectable by staging laparoscopy were subsequently resected to no residual disease. At present, I believe that primary surgery should be attempted whenever possible and that the use of neoadjuvant chemotherapy should be restricted to patients with ovarian cancer who cannot undergo extensive surgery or who have clinically significant medical comorbidities.

Conclusions

Clinical experience with ovarian cancer therapies is providing increasing evidence that a cure rate of 50% for women with advanced-stage stage disease is within our reach[26]. This possibility should encourage patients and health-care professionals in their attempts to overcome the disease, which is viewed widely as having a dismal prognosis, and to aim for cure. To cure a patient with advanced-stage ovarian cancer requires the elimination of all cancer cells. I think that the chance of achieving this objective is greatest with resection to no residual disease through maximal debulking surgery, followed by intraperitoneal chemotherapy, and that we should strive to achieve a status of no residual disease whenever possible. Neoadjuvant chemotherapy should be limited to those few patients for whom complete resection is judged to be impossible or who are not candidates for extended surgery owing to the presence of comorbidities. The use of intraperitoneal chemotherapy challenges both physicians and patients, but in spite of the associated morbidities, the available data suggest that we should utilize this route as much as possible, and particularly in patients with no residual disease after surgery. We should seek to understand and to overcome the wide variation in the use of this valuable therapeutic approach[32]. The evidence discussed herein should prompt us to readdress our thinking surrounding the treatment of ovarian cancer. All women should be offered the possibility of cure.

Steven Narod is at the Women's College Research Institute, 76 Grenville Street, Suite 6418, Toronto, Ontario M5S 1B2, Canada.
Steven.Narod@wchospital.ca

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