Review Article

Why have ovarian cancer mortality rates declined? Part II. Case-fatality

Victoria Sopika a, Javaid Iqbal a, Barry Rosen b, Steven A. Narod a,c,*

a Women’s College Research Institute, Women’s College Hospital, Toronto Canada
b Department of Gynecologic Oncology, Princess Margaret Hospital, Toronto Canada
c Dalla Lana School of Public Health, University of Toronto, Toronto Canada

HIGHLIGHTS

• The decline in ovarian cancer mortality cannot be explained by a reduction in case-fatality.
• New treatments improve short-term survival and median survival, but not long-term survival or cure.
• The greatest potential for cure appears to be aggressive primary surgery to no residual disease followed by intraperitoneal chemotherapy.

ABSTRACT

In the United States, the age-adjusted mortality rate from ovarian cancer declined by 8% from 1975 to 1991 and by 18% from 1992 to 2011. A decline in the incidence rate of ovarian cancer paralleled the decline in mortality (described in Part I). The decline in mortality might also be due to a reduced proportion of ovarian cancer patients who die from their cancer (case-fatality). Here, we examine rates of ovarian cancer case-fatality from the Surveillance Epidemiology and End Results (SEER) registry database, and we consider to what extent advances in treatment also contribute to the observed decline in mortality. From 1973 to 1999, the 5-year case-fatality rate for women with ovarian cancer fell by 7.5%, whereas the 12-year case-fatality rate fell by only 1.2%. The declines in 5-year case-fatality corresponded in time with the introduction and expansion in use of cis-platinum and paclitaxel in clinical practice. However, modest declines in 12-year case-fatality indicate that the introduction of chemotherapy has not contributed to the decline in mortality. Developments in the last two decades include targeted therapies, aggressive surgical techniques, the use of neoadjuvant chemotherapy and intraperitoneal chemotherapy. The impact of these treatment modalities on ovarian cancer mortality still needs to be evaluated.

© 2015 Published by Elsevier Inc.

Contents

1. Introduction ................................................................................................................................. 0
2. Trends in case-fatality ................................................................................................................... 0
3. New treatments ........................................................................................................................... 0
4. Surgery ........................................................................................................................................ 0
5. Neoadjuvant chemotherapy .......................................................................................................... 0
6. Intraoperative chemotherapy ....................................................................................................... 0
7. Synopsis ....................................................................................................................................... 0

Appendix A. Supplementary data .................................................................................................. 0

References ....................................................................................................................................... 0

1. Introduction

Over the past 40 years, the age-adjusted mortality rate from ovarian cancer in the United States has declined by about 23%. In Part I, we
examined rates of ovarian cancer incidence and mortality from the Surveillance, Epidemiology, and End Results (SEER) registry database, and we showed that the observed reduction in ovarian cancer deaths (mortality) paralleled a decrease in the number of cases (incidence). The decline in incidence was largely a consequence of the introduction of oral contraceptives in 1960 and the subsequent expansion in their use (from 0% to 85%) from 1960 to 1990 (discussed in Part I [1]). There was no downward shift in stage at presentation, indicating that early detection (i.e., through screening or better awareness) did not contribute to the decline in mortality.

In the following pages, we examine SEER rates of ovarian cancer case-fatality, with reference to calendar year and tumor stage, and we consider if advances in ovarian cancer treatment also contribute to the decline in mortality. We complement the SEER data analysis with a historical review of the introduction of the various chemotherapy regimens into clinical practice. Finally, we review the evidence that new targeted therapies, aggressive primary surgery, neoadjuvant chemotherapy and intraperitoneal chemotherapy will impact ovarian cancer mortality.

2. Trends in case-fatality

Case-fatality is the proportion of women diagnosed with ovarian cancer in a given year who die from their disease. An improvement in case-fatality may have contributed to the recent decline in ovarian cancer mortality. In turn, a decline in case-fatality might reflect improvements in early detection (stage-shift) or in the treatment of ovarian cancer. Case-fatality is the complement of survival; a reduction in the proportion of patients who die from ovarian cancer can be equivalently described as an increase in the proportion of patients who survive. Case-fatality may be used to describe deaths that occur in a specific follow-up period (i.e., five-year survival) or as the duration of time that patients survive (i.e., median time in months from diagnosis to death). In the SEER database, about 67% of all women diagnosed with ovarian cancer between 1973 and 1991 died of ovarian cancer within 20 years. The majority of deaths (88%) occurred in the first five years, about 7% occurred between year 5 and year 10, 3% between year 10 and year 12, and 1% between years 12 and 15 [3]. In a recent study from Ontario, only one of 309 ovarian cancer patients died from ovarian cancer among those who were alive after 12 years [2]. We propose that the cure rate for ovarian cancer may be approximated by 12-year survival (i.e., the inverse of 12-year case-fatality).

Survival curves depict the experience of a cohort of ovarian cancer patients (from diagnosis to death); comparing these curves from year to year will reveal the impact of advances in treatment of ovarian cancer. The 12-year ovarian cancer-specific survival curves, by year of diagnosis are presented in Fig. 1. From 1973 to 1999, one-year survival increased by 10.3% (66.9% to 77.2%), five-year survival increased by 5.3% (40.2% to 45.5%), ten-year survival increased by 1.0% (36.0% to 37.0%) and 12-year survival increased by 0.4% (35.2% to 35.6%). In all curves, survival plateaus at 12 years, suggesting that 12-year survival is an appropriate surrogate for cure. From 1973 to 1999, the median survival (i.e., the time at which 50% of ovarian cancer patients have died and 50% are alive) increased from 2.3 years to 4.0 years (Fig. 2).

Although ovarian cancer survival curves often separate in the first five years post-diagnosis, in most cases, the curves come together again by year 12, indicating that the hazard rates for death from ovarian cancer (i.e., the probability of death in a specified interval of time) are non-proportional. This means that the relative risk of death from ovarian cancer comparing one patient cohort to another (i.e., the hazard ratio) is not constant over time. For practical reasons, most clinical studies use five-year survival or median survival when they report a survival benefit, but this does not necessarily imply a similar benefit in long-term survival (or cure) [4]. A longer follow-up time (12 years) is required to obtain a complete picture of the impact of any given treatment.

The lack of improvement in the 12-year survival rate of ovarian cancer suggests that the observed decline in mortality cannot be explained by a reduction in case-fatality. It is possible that substantial increases in median survival may cause a shift of some ovarian cancer deaths from one age category to another, and thus influence age-specific mortality rates, but in general, mortality rates do not improve unless there is an increase in the cure rate. To better understand the underlying basis for the trends in survival it is useful to examine five-year and 12-year case-fatality rates by year of diagnosis and by stage at diagnosis. From 1973 to 1999, five-year case-fatality rates for all ovarian cancers fell by 7.5% (from 60.3% to 52.8%) and 12-year case-fatality fell by 1.2% (from 65% to 63.8%) (Fig. 3). The trends in case-fatality for all ovarian cancers are mainly influenced by the trends for advanced (distant) ovarian cancers, which account for 65% of all ovarian cancer diagnoses and 90% of all ovarian cancer deaths. Between 1973 and 1999, the five-year case-fatality of advanced ovarian cancer fell by 14.2% (from 82.2% to 68%) and the 12-year case-fatality fell by 4.7% (from 86.0% to 81.3%) (Figure S1). For patients with localized ovarian cancer (23% of all patients), five-year case-fatality rates fell by 12.5% (from 19.1% to 6.9%) and 12-year case-fatality fell by 12.2% (from 24.4% to 11.9%) (Figure S2). This represents a 12% increase in the proportion of women cured of localized ovarian cancer; however, given the small proportion of cancers that are localized at diagnosis, this improvement has had little effect on the overall cure rate.

Better treatment can influence life expectancy by increasing the proportion of patients who are cured of their disease, or by increasing

![Fig. 1. Ovarian cancer-specific survival curves, by period of diagnosis, 1973 to 1999.](image1)

![Fig. 2. Median survival time, by period of diagnosis, 1973 to 1999.](image2)
survival time for patients who ultimately die. The trends in case-fatality indicate that improvements in treatment have extended the survival time of patients with advanced stage ovarian cancer, but they have not been equally effective at preventing deaths.

The standard treatment for advanced stage ovarian cancer consists of tumor debulking surgery and adjuvant chemotherapy. Treatment advances over the last 40 years include the introduction of cisplatinum (in 1978) and paclitaxel (in 1992), as well as improvements in surgery that have led to greater numbers of patients who, after surgical resection, achieve a status of no residual disease. The declines in five-year case-fatality for advanced ovarian cancer in the SEER database correspond to the timing of the introduction of platinum and paclitaxel and their expansion in use (Fig. 4), but the smaller declines in 12-year case-fatality indicate that the impact of chemotherapy on mortality has been limited (Fig. 5).

Clinical trials have reported significant survival benefits with platinum and taxol. The main outcomes measured by clinical trials in advanced stage ovarian cancer are response to treatment, time to progression (or recurrence) and time to death. The fundamental principal of ovarian cancer is that most patients who progress (or recur) will ultimately die, whereas most patients who do not progress do not die of their cancer. At present, the majority of advanced stage ovarian cancer patients experience disease progression and ultimately die. Among patients who die, overall survival time is composed of two intervals; the time from diagnosis to disease progression (i.e., progression-free survival) and the time from disease progression to death (i.e., survival post-progression). Most reports of clinical trials use median survival, i.e., the time when 50% of patients have died. However, due to non-proportional hazards in advanced stage ovarian cancer, improvements in median survival do not necessarily imply improvements in long-term survival (or cure). Long-term follow-up of patients in clinical trials (i.e., ten years or more) is necessary to reveal all clinically relevant outcomes (i.e., the proportion of patients who recur and the proportion of patients who are ultimately cured of their cancer).

Guidelines for evaluating tumor response to initial treatments and tumor progression have been defined by Response Evaluation Criteria in Solid Tumours (RECIST) and Gynecologic Cancer Intergroup Criteria (GCIG) [5]. Objective response refers to patients with no detectable disease following treatment (a complete response) and patients with reduced but detectable disease (a partial response). Patients with stable disease and patients who progress on treatment are considered non-responders. Disease progression is defined as tumor growth and/or a rise in serum CA125 levels (relative to baseline measures).

In the 1970s, adjuvant treatment for advanced stage ovarian cancer consisted of a single alkylating agent (e.g., melphalan or cyclophosphamide). About 30% of patients responded to the initial treatment, and 15% of patients achieved a complete remission [6,7]. Across studies, median progression-free survival was about six months and median overall survival was about 12 months. After 10 years of follow-up, 95% of patients had progressed and 90% of patients had died [8,9].

Cisplatin was approved for the treatment of ovarian cancer in the United States in 1978. In the 1980s, platinum-based combination therapies became the standard treatment for ovarian cancer. Carboplatin was introduced in 1989 as a less-toxic, but not more effective, analog of cisplatin [10]. Compared to alkylating agents, platinum-based combination therapy doubled response rates to about 60%, and 30% of patients achieved a complete remission [7]. Median progression-free survival increased from six months to 15 months and median overall survival increased from 12 months to 30 months. Five-year survival rates improved from 15% to about 30% [11]. The introduction of platinum was widely viewed as the turning point of ovarian cancer treatment. However, long-term results revealed that after ten years, 90% of patients had developed recurrent disease (versus 95% of patients before cisplatin) and 85% of patients had died (versus 90% before cisplatin) [8]. In SEER, from 1978 to 1984 (following the introduction and expansion in use of cis-platinum), five-year case-fatality rates of advanced ovarian cancer fell by about 6% and 12-year case-fatality fell by only 3.5%.

Paclitaxel was approved for first-line treatment of advanced stage ovarian cancer in 1992. By 1996, approximately 70% of advanced stage ovarian cancer patients were being treated with a platinum–taxane combination therapy [12]. The introduction of taxol increased response rates from 60% to about 75%, and 50% of patients achieved a complete remission [13]. However, the probability of recurrence at ten-years
remained high at about 87% (versus 90% with cisplatin alone), and the case-fatality rate at ten-years was about 80% (versus 85% with cisplatin alone) [14,15]. In SEER, from 1992 to 1999 (following the introduction and expansion in use of taxol), five-year case-fatality for patients with advanced ovarian cancer fell by about 6% and 12-year case-fatality fell by only 2%.

At present, 50% to 75% of patients will achieve a complete remission following surgery and chemotherapy [13,16]. However, 65% of patients who achieve a complete remission will ultimately recur. In reports of clinical trials between 1975 and 1999, the probability of recurrence at 10 years declined by only 5%, from 93% to about 87% and the probability of death at 10 years declined by 10% (from 90% to 80%). In SEER, from 1975 to 1999, 12-year case-fatality fell by about 5% (from about 86% to 81%).

Although improvements in long-term survival have been minimal, there has been a significant increase in median survival for patients with advanced ovarian cancer, from about one year in 1975 to four years in 1999. Patient quality of life has improved as a result, in particular due to the extension in disease-free survival time (i.e., from diagnosis to recurrence) from about six months to about two years [17]. After recurrence, the time to death has increased due to the introduction of several new recurrent therapies, which may delay disease progression/death but cannot prevent it.

3. New treatments

Much of the current research in ovarian cancer is focused on the development of targeted agents and maintenance therapy. Maintenance therapy refers to the administration of treatment for extended periods of time or until the time of relapse, in patients with residual macroscopic disease after surgery or in patients with recurrent ovarian cancer [18]. The goal of maintenance therapy is typically to improve progression-free survival, symptom-free survival or overall survival, but not necessarily cure [19]. In recent years, progression-free survival has replaced overall survival as the primary endpoint of ovarian cancer clinical trials. However, improvements in progression-free survival do not necessarily translate into improvements in overall survival (or cure), and the use of progression-free survival when evaluating the impact of a treatment on patient survival is unclear.

The VEGF inhibitor bevacizumab is currently approved for the treatment of platinum-resistant recurrent ovarian cancer. In one trial, continued administration of bevacizumab in combination with chemotherapy until disease progression improved progression-free survival by 3.3 months compared to chemotherapy alone (from 3.4 months to 6.7 months), but there was no significant increase in overall survival [20]. In the first-line setting, bevacizumab in combination with carboplatin/paclitaxel, followed by maintenance bevacizumab led to an improvement in progression-free survival of 2.4 months (from 17.5 months to 19.9 months), but did not significantly improve overall survival (58.0 months versus 58.6 months) [21].

The poly(ADP-ribose) polymerase (PARP) inhibitor Olaparib (Lynparza) was recently approved as maintenance therapy for women with platinum-sensitive, recurrent ovarian cancer and a BRCA1 or BRCA2 mutation. Compared to chemotherapy alone, patients who received olaparib maintenance therapy following completion of chemotherapy had a seven-month improvement in progression-free survival (from 4.3 months to 11.2 months), and a three-month improvement in overall survival (from 31.9 months to 34.9 months) [22]. It is also important to consider the added toxicities and costs when evaluating new treatments. Although not covered here, these issues have been discussed in great detail elsewhere [23,24].

4. Surgery

The most important factor for predicting long-term survival from advanced stage ovarian cancer is the amount of disease remaining in the abdomen after surgery [16]. The inverse relationship between the extent of residual tumor and prognosis has been widely accepted since 1975 [25]; however, the survival benefit associated with no (versus any) visible residual disease has only recently been established [16]. Patients who achieve a status of no residual disease after primary debulking surgery have a superior median survival (80 to 100 months), compared to patients with 0.1 to 1.0 cm of residual disease (50 months) or patients with more than 1.0 cm of residual disease (35 months) [26]. In 2009, Du Bois et al. reported a 12-year overall survival rate of 40% for patients with no residual disease after primary debulking surgery, compared to 15% for patients with any residual disease [16]. Among patients who recur, overall survival at 12 years was below 5%. This suggests that in order to improve the cure rate of ovarian cancer we must prevent recurrence.

In the last decade, there has been a shift in the paradigm towards aggressive surgery with the goal of no residual disease [27]. On average, 20% to 30% of advanced-stage patients are reported to have no residual disease post-surgery [28,29]. Several reports indicate that since the incorporation of aggressive surgical procedures, the proportion of patients who achieve no residual disease has increased to up to 50% or more [30]. However, the use of aggressive surgical techniques and the proportion of patients with no residual disease post-surgery vary from institution to institution.

The probability of achieving no residual disease depends on the skill and experience of the surgeon as well as on the extent (and location) of disease present at the time of surgery [31]. Not all patients achieve a status of no residual disease through primary debulking surgery. However, many disease sites that have previously been regarded as unresectable (i.e., the diaphragm or the liver) are in fact amenable to surgical resection in appropriately selected patients [32]. The most common factors precluding complete surgical resection are extensive disease involving the upper abdomen, small bowel mesentery or the portal triad. Some have proposed that the probability that surgery will result in no residual disease can be predicted through a pre-operative assessment, which incorporates various factors such as tumor marker expression and the extent of disease detected through imaging or laparoscopy [29,33,34]. However, the ability of pre-operative criteria to reliably predict surgical outcome remains weak.

A recent analysis of patients with stage III/IV ovarian cancer from the Gynecologic Oncology Group 182 randomized trial examined the relative impacts of preoperative disease distribution, surgical complexity and amount of residual disease post-surgery in determining patient outcome [28]. Among patients with low-moderate preoperative disease burden (no upper abdominal disease), survival at nine years was 44% for those with no residual disease after surgery, and was 20% for those with 1–9 mm of residual disease. Among patients with high preoperative disease burden (upper abdominal disease affecting the diaphragm, liver, spleen or pancreas), nine-year survival was 27% for those with no residual disease after surgery and was 15% for patients with 1–9 mm of residual disease. Patients with upper abdominal disease who underwent complex surgical procedures were more likely to achieve a status of no residual disease than patients who underwent less complex procedures, and the long-term survival benefit associated with no residual disease was achieved regardless of surgical complexity. This suggests that patients with extensive disease at presentation may still derive a long-term survival benefit from aggressive surgery if no residual disease can be achieved.

5. Neoadjuvant chemotherapy

Another possible approach to increase the proportion of patients with no residual disease is through neoadjuvant chemotherapy (i.e., chemotherapy before surgery). Patients receiving neoadjuvant chemotherapy are less likely to have any residual disease and to experience surgical complications than patients that undergo primary surgery [35]. In an international trial, there was no difference in median overall survival between patients who received neoadjuvant chemotherapy and those who underwent primary surgery, but the median progression-free survival was longer in the neoadjuvant group [36].
survival between patients who were treated with neoadjuvant chemotherapy followed by interval debulking surgery (29 months) and patients who were treated with primary debulking surgery (30 months) [36]. However, the ten-year actuarial survival rate among patients with no residual disease after either primary debulking surgery or neoadjuvant chemotherapy and interval debulking surgery was poor (8%). Furthermore, 50% of patients randomized to neoadjuvant chemotherapy had no residual disease after surgery compared to 20% of patients randomized to primary debulking surgery, yet there was no increase in survival associated with neoadjuvant chemotherapy. This is contrary to what we would expect if the survival of patients with no residual disease after surgery were equivalent, whether achieved through primary debulking surgery or neoadjuvant chemotherapy and interval debulking surgery. Similar results were observed in the United Kingdom randomized trial of neoadjuvant chemotherapy versus primary surgery [37].

From 1990 to 2010 the use of neoadjuvant chemotherapy increased from 20% of patients to 40%, while the use of primary debulking surgery decreased from 70% of patients to 50% [38]. Currently, neoadjuvant chemotherapy is often administered to patients who, by pre-operative assessment, appear to have unresectable disease (i.e., extensive upper abdominal disease or stage IV cancer) or are considered to be poor candidates for aggressive surgery (i.e., elderly or obese women) [29,39].

The National Comprehensive Cancer Network (NCCN) currently recommends primary debulking surgery for patients with ovarian cancer that is potentially resectable; however, neoadjuvant chemotherapy may be considered for patients with high-volume disease who are not surgical candidates (i.e., due to high-risk comorbidities) [40]. At present, it is not possible to accurately predict the resectability of disease based on a pre-operative assessment. The proportion of women with advanced ovarian cancer who have a severe medical co-morbidity is much smaller than the proportion of women who currently receive neoadjuvant chemotherapy.

A number of recent studies report that the survival of patients who achieve no residual disease after treatment with neoadjuvant chemotherapy is inferior to that of patients who achieve no residual disease through primary debulking surgery. In one study, patients who received neoadjuvant chemotherapy and had no residual disease after interval debulking surgery had a higher rate of recurrence than patients who had no residual disease after primary debulking surgery [41]. Rosen et al. (2014) reported a seven-year survival rate of 8% for women with no residual disease following neoadjuvant chemotherapy and interval debulking surgery, compared to 74% for women with no residual disease after primary debulking surgery [42]. Colombo et al. found that patients who achieved a status of no residual disease through interval debulking surgery after four or more cycles of neoadjuvant chemotherapy had relatively poor survival at seven years (20%) compared to those who received fewer than four cycles of neoadjuvant chemotherapy (45%) or patients who had no residual disease after primary debulking surgery (55%) [43].

6. Intraperitoneal chemotherapy

Most ovarian cancer recurrences are confined to the peritoneal cavity. The conventional rationale for intraperitoneal chemotherapy is that drugs clear the peritoneal cavity slowly, allowing for the drugs to achieve concentrations 20- to 1000-fold higher than typically achieved with intravenous chemotherapy regimens, with low systemic exposure [44,45]. An alternate theory is that the intraperitoneal administration affects the mesothelium such that it no longer readily supports tumor growth [46]. The penetration of intraperitoneal chemotherapy is limited to 1 to 2 mm of the tumor surface; therefore, the survival benefit of intraperitoneal chemotherapy is expected to accrue to patients with no (or little) residual disease.

In 2006, Armstrong et al. reported a median overall survival of 66 months for stage III ovarian cancer patients with less than 1.0 cm of residual disease after primary debulking surgery who received intraperitoneal chemotherapy, compared to 50 months for patients who received intravenous chemotherapy [47]. Among patients with 0.1 to 1.0 cm of residual disease, intraperitoneal chemotherapy was associated with a 13.5-month improvement in median survival compared to intravenous chemotherapy. However, patients were followed for only five years, which is not sufficient to assess cure, and median survival had not yet been reached for patients with no residual disease after surgery who received intraperitoneal chemotherapy. In 2013, Landrum et al. reported that among patients in the trial who had no residual disease after primary debulking surgery, those who received intraperitoneal chemotherapy had a median survival of 128 months, and those who received intravenous chemotherapy had a median survival of 82 months [48]. One-half of all patients who had no residual disease after primary debulking surgery and who subsequently received intraperitoneal chemotherapy were alive ten years after diagnosis (the majority of patients who are alive ten years after diagnosis will be cured of their disease).

Recently, Tewari et al. (2015) reported long-term survival data for patients from two Gynecologic Oncology Group (GOG) randomized trials of intraperitoneal chemotherapy versus intravenous chemotherapy (GOG 114 reported by Markman et al. in 2001 and GOG 172 reported by Armstrong et al. in 2006) [49]. The ten-year actuarial survival rate among patients with no residual disease after primary debulking surgery was 50% for those who received intraperitoneal chemotherapy and was 35% for those who received intravenous chemotherapy. The ten-year actuarial survival rate among patients with 0.1 to 1.0 cm of residual disease was 15%, both for patients who received intraperitoneal chemotherapy and for patients who received intravenous chemotherapy.

In a recent retrospective study, women with stage IIC/IV ovarian cancer who had no residual disease after primary debulking surgery and who received intraperitoneal chemotherapy had a seven-year survival of 90%, whereas those who received intravenous chemotherapy had a seven-year survival of 74% [42]. In the same study, among women with 0.1 to 0.9 cm of residual disease after primary debulking surgery, the seven-year survival rate was 30% for women who received intraperitoneal chemotherapy compared to 20% for women who received intravenous chemotherapy. Intraperitoneal chemotherapy has several side effects, including abdominal pain, port-site infections and catheter blockages. In the initial studies, 50% of women who started intraperitoneal chemotherapy completed the recommended six-cycles of treatment [50]. With modified treatment regimens, experience and better supportive care, this percentage has increased to more than 70% of patients [51,52].

Another approach that is currently being evaluated involves combining intraperitoneal chemotherapy with hyperthermia (hyperthermic intraperitoneal chemotherapy; HIPEC) [53]. HIPEC is administered during surgery. It is proposed that the hyperthermia increases the cytotoxic effects of the chemotherapy and together with the continuous circulation improves tumor penetration and may lead to improved survival rates [55]. One randomized trial in recurrent ovarian cancer has reported an increase in median overall survival for patients treated with secondary debulking surgery and HIPEC versus surgery alone [54]. No randomized trials in the first-line setting have been completed. It is too early to evaluate the impact of HIPEC on ovarian cancer mortality.

Current guidelines for the primary treatment of advanced stage ovarian cancer from the NCCN include aggressive primary debulking surgery with the goal of achieving no visible residual disease, followed by adjuvant systemic therapy with intravenous or intraperitoneal (combined with intravenous) chemotherapy [40]. Since 2006, the NCCN recommends intraperitoneal chemotherapy for women with stage III ovarian cancer that has been reduced to less than one centimeter of residual disease. However, the use of intraperitoneal chemotherapy has not been widely adopted. Although most patients now have less than 1 cm of residual disease after surgery, only 20% to 30% of stage III
patients in the United States are treated with intraperitoneal chemotherapy [56,57]. This may be due to the challenges associated with the treatment and with the management of side effects. Also, as discussed above, intraperitoneal chemotherapy improves median survival for patients with no or minimal residual disease after primary debulking surgery, but the improvement in long-term survival appears to be restricted to patients with no residual disease [49]. However, it is not yet clear to what extent the 12-year survival rate (i.e., the cure rate) for women with no residual disease after primary debulking surgery is increased for those women who receive intraperitoneal chemotherapy, compared to those who receive intravenous chemotherapy. It is hoped that future studies will address this question.

This analysis has some limitations. SEER does not provide information on treatment (i.e., debulking surgery and chemotherapy). The implications of surgery and chemotherapy on survival are based on time trends (taken from the literature) rather than individual usage data. It is too early to evaluate the impact of new treatment modalities on survival based on SEER data. Other general limitations of the SEER dataset are discussed in Part I of this series [1].

7. Synopsis

From 1975 to 2011, ovarian cancer mortality fell by 23%. The greatest period of decline (18%) was between 2001 and 2011, when mortality fell from 9.0 per 100,000 per year to 7.5 per 100,000 per year. This cannot be explained by a reduction in case-fatality; new treatments have extended the survival time of ovarian cancer patients but have not been effective at preventing deaths from ovarian cancer. Radical surgery and the introduction of cis-platinum has prolonged survival time in Europe, but not in the ultimate cure rate of women with advanced ovarian cancer [58]. Despite the introduction of taxanes, targeted therapies and aggressive surgery, the cure rate at 12 years has not improved. The decline in mortality is the consequence of a decline in ovarian cancer incidence, which was largely due to the introduction of oral contraceptives in 1960 and the expansion in their use until 1990 [1]. In Part III, we discuss potential approaches to standardize the treatment of ovarian cancer using an optimal combination of surgery and chemotherapy in order to improve the cure rate of ovarian cancer [59].

Transparency documents

The Transparency documents associated with this article can be found, in online version.

Conflicts of interest

The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.06.016.

References
