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Comparative Effectiveness Research in Gynecologic Oncology

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Abstract

The field of gynecologic oncology is faced with a number of challenges including how to incorporate new drugs and procedures into practice, how to balance therapeutic efficacy and toxicity of treatment, how to individualize therapy to particular patients or groups of patients, and how to contain the rapidly rising costs associated with oncologic care. In this chapter we examine three common and highly debated clinical scenarios in gynecologic oncology: the initial management of ovarian cancer, the role of lymphadenectomy in the treatment of endometrial cancer, and the choice of adjuvant therapy for ovarian cancer.

Keywords

Gynecologic cancer; Endometrial cancer; Ovarian cancer; Chemotherapy; Lymphadenectomy

1 Introduction

Gynecologic oncology incorporates a diverse group of diseases of the female genital tract. Some tumor types, such as endometrial cancer, are commonly detected early and associated with a high cure rate. In contrast, other malignancies, such as ovarian cancer, are more commonly diagnosed after dissemination and are accompanied by a poorer overall prognosis. Treatment for nearly all of the gynecologic cancers incorporates a multimodal approach utilizing various combinations of surgery, chemotherapy, and radiation.

The field of gynecologic oncology is faced with a number of challenges including how to incorporate new drugs and procedures into practice, how to balance therapeutic efficacy and toxicity of treatment, how to individualize therapy to particular patients or groups of patients, and how to contain the rapidly rising costs associated with oncologic care. In this chapter we examine three common and highly debated clinical scenarios in gynecologic oncology: the initial management of ovarian cancer, the role of lymphadenectomy in the treatment of endometrial cancer, and the choice of adjuvant therapy for ovarian cancer.

2 Initial Management of Ovarian Cancer

2.1 Background

Epithelial ovarian cancer is a major cause of cancer-related mortality in women. The high mortality associated with ovarian cancer is due in large part to the lack of effective screening tests for the disease. While potential screening tests such as transvaginal ultrasonography and serum screening with CA125 have been evaluated in a number of prospective trials, these tests are associated with low specificity and often fail to detect ovarian tumors when they are confined to the ovary and potentially curable. The difficulty in diagnosis is further compounded by the fact that most women with early-stage tumors are asymptomatic and, as such, the majority of women already have dissemination of the tumor within the abdominal cavity and often beyond (stage III or IV), at the time of diagnosis.

Traditional management for advanced-stage ovarian is surgical. Surgery for ovarian tumors relies a procedure known as cytoreduction or debulking. The goal of cytoreductive surgery is removal of all gross tumor within the abdominal cavity. In addition to hysterectomy and bilateral salpingo-oophorectomy, the procedure often requires omentectomy, peritoneactomy and frequently resection of the abdominal viscera including small bowel resection, colectomy, rectosigmoid colectomy, splenectomy, partial hepatectomy, and diaphragm resection. Surgery is typically followed by chemotherapy, most commonly employing a platinum-based regimen. Survival is highly correlated with the amount of residual tumor at the completion of surgery [1, 2]. Patients are classified as having undergone optimal cytoreduction if the greatest dimension of the largest residual tumor nodule is <1 cm and as having undergone suboptimal cytoreduction if the largest residual tumor is >1 cm in diameter.

Despite the oncologic benefits of cytoreduction, the procedure can be associated with substantial perioperative morbidity [3]. One population-based report noted that major perioperative complications occurred in nearly a quarter of women who undergo surgery for ovarian cancer [3]. Further, a systematic review reported that the perioperative mortality rate was nearly 4 % in women who underwent surgery [4]. Additional work has also shown that those women who experience major perioperative complications often have delayed receipt of chemotherapy, thereby potentially negating the beneficial effects of cytoreductive surgery [5, 6].

An alternative to primary cytoreductive surgery is neoadjuvant chemotherapy. Women who undergo neoadjuvant chemotherapy typically receive primary platinum and taxane based chemotherapy followed by interval cytoreduction and additional cytotoxic therapy

postoperatively. Institutional series have noted that perioperative morbidity is often reduced in women who undergo neoadjuvant chemotherapy compared to those treated with a strategy of primary cytoreductive surgery [7, 8]. However, the reported survival rates in these observational studies are often inferior to survival outcomes from cooperative group trials and from some tertiary centers [9, 10].

2.2 Evidence

2.2.1 Evidence for Primary Cytoreduction—Despite the fact the surgical cytoreduction is the standard of care for advanced stage ovarian cancer, the procedure is not based on randomized controlled trial data. The concept of surgical cytoreduction originated in the 1970s with the goal of resecting all visible tumor within the abdominal cavity [11]. The rationale for tumor debulking was to not only improve symptoms for bulky abdominal disease, but also to reduce the potential of residual chemotherapy resistant tumor clones and improve response to chemotherapy [12].

The efficacy of surgical cytoreduction was based in large part on retrospective studies that suggested that survival was improved in women with lower residual tumor burden after surgery [1, 2]. The Gynecologic Oncology Group (GOG) performed a number of analyses that helped demonstrate this concept [2]. In one report of 294 patients with stage III ovarian cancer, the relative risk of death increased sequentially as the diameter of the largest residual tumor nodule increased. Compared to women with a residual disease <2 cm, the relative risk of death in those with a residual tumor diameter of 2–2.9 cm was 1.90 while the relative risk in those with the largest tumor nodule measuring 3–3.9 cm was 1.91 [2].

The importance of cytoreduction has been demonstrated in multiple institutional series as well as a meta-analysis of available data that suggested similar findings [1, 13–18]. Among 81 studies including women with advanced-stage ovarian cancer, each 10 % increase in maximal cytoreduction was associated with a 5.5 % increase in median survival [1]. One single institution study compared survival in their patients before and after a programmatic change in surgical approach that adopted aggressive primary surgery including upper abdominal surgery when necessary. Five-year survival improved from 35 to 47 % after the paradigm shift [15].

Cytoreductive surgery not only involves resection of the ovaries and uterus, but also often requires removal of other pelvic viscera. One concern with aggressive surgery is the risk of perioperative morbidity and mortality. A number of studies have attempted to model factors associated with perioperative complications including age, functional status and extent of cytoreduction [19, 20]. After completion of cytoreduction most women receive adjuvant chemotherapy.

2.2.2 Evidence for Neoadjuvant Chemotherapy—Much of the evidence describing the outcomes of neoadjuvant chemotherapy is based on retrospective institutional reports that have compared the outcomes of primary cytoreduction to a strategy of neoadjuvant chemotherapy [7, 8, 21–26]. Many of these studies have noted that neoadjuvant chemotherapy is associated with less perioperative morbidity and a higher rate of optimal cytoreduction than primary cytoreduction. A meta-analysis of 21 studies found that patients

who received neoadjuvant chemotherapy were less likely to undergo a sub-optimal cytoreduction (pooled odds ratio 0.50; 95 % CI, 0.29–0.86) [22].

One report comparing 109 patients who underwent primary surgery to 63 women treated with neoadjuvant chemotherapy noted a higher rate of optimal cytoreduction in those treated with neoadjuvant chemotherapy (95 % vs. 71 %). Further, aggressive surgery was required in only 5 % of those women who received neoadjuvant chemotherapy compared to 25 % in the primary surgery group. The median overall survival in the neoadjuvant therapy group was 46 months, similar to the 47 months noted in the primary surgery patients [8].

A second institutional series identified 200 patients with advanced stage epithelial ovarian cancer and included 98 patients who had initial chemotherapy and 102 who underwent surgery. Surgical morbidity was similar between the two groups, however, optimal cytoreduction was more often achieved in patients who underwent neoadjuvant chemotherapy (86 % vs. 54 %, $P < 0.001$). In the survival analysis, optimal cytoreduction was the only independent predictor of improved survival. Timing of cytoreduction, either as primary surgery or after neoadjuvant chemotherapy, was not associated with survival [7].

The only randomized controlled trial of primary surgery versus neoadjuvant chemotherapy was undertaken by the European Organization for Research and Treatment of Cancer (EORTC) and reported in 2010. The study randomized 670 patients with stage IIIC-IV epithelial ovarian cancer to primary cytoreduction followed by platinum-based chemotherapy or neoadjuvant platinum-based chemotherapy (Table 1). Optimal cytoreduction to a largest tumor diameter of <1 cm was achieved in 41.6 % of patients who underwent primary debulking compared to 80.6 % of those who received neoadjuvant therapy. Perioperative morbidity was lower in those who underwent neoadjuvant chemotherapy and the postoperative mortality rate was 0.7 % in patients who received neoadjuvant chemotherapy compared to 2.5 % in those randomized to primary surgery. Median overall survival was comparable between the two arms, 29 months in those who underwent primary surgery and 30 months in women who received neoadjuvant chemotherapy. The investigators concluded that neoadjuvant surgery was not inferior to primary cytoreduction [26].

2.3 Areas of Uncertainty

Despite the data describing the potential benefits of neoadjuvant chemotherapy for advanced stage ovarian cancer, the topic remains controversial [27–29]. A survey of gynecologic oncologists in the US found that most used neoadjuvant chemotherapy infrequently with the majority of participants reporting use in <10 % of cases. Further, the majority of respondents to the survey reported that they felt that the evidence supporting neoadjuvant chemotherapy was insufficient [27].

An important argument against the use of neoadjuvant chemotherapy stems from comparison of outcomes of patients treated with primary surgery [9]. Survival estimates of many observational studies as well as the randomized controlled trial of neoadjuvant therapy have been inferior to survival data reported for primary surgery documented from institutional series and cooperative group trials [9, 10, 30]. For example, the GOG recently

reported data from a phase III trial of women with stage III and IV ovarian cancer randomized to intravenous or intraperitoneal platinum and taxane based chemotherapy. Median overall survival in this trial was 50 months for intravenous chemotherapy and 66 months for intraperitoneal treatment [10]. Survival estimates from this and other trials is substantially longer than reported for either the neoadjuvant (30 months) or primary surgery arms of the EORTC trial [10, 30, 31].

The relatively poor survival as well as low overall rate of optimal cytoreduction in the EORTC trial have raised the concern that the results of this data are not applicable to patients in the US who have access to gynecologic oncologists skilled in performance of aggressive cytoreductive surgery [29]. A single institution report identified patients who met the eligibility criteria for the EORTC trial and who underwent primary cytoreductive surgery. In this report, the median overall survival was 50 months, superior to the overall survival of both the neoadjuvant and primary surgery arms of the EORTC study [9, 31].

A major limitation of the currently available data is that many observational studies comparing the outcomes of primary surgery and neoadjuvant chemotherapy are limited by strong selection bias [7, 8, 21–25, 32, 33]. Patients with poor prognostic factors including advanced age, higher grade, and stage and more medical comorbidities are often preferentially treated with neoadjuvant chemotherapy. In addition, more subtle differences in patient characteristics such as the volume and distribution of tumor often influence decision making. Measurement of these more subtle factors is problematic not only in studies using administrative data, but also in studies that directly abstract data from medical records. The strong selection bias in treatment choice and comparison to highly selected patients enrolled in cooperative group trials and treated at tertiary centers may result in biased conclusions [26].

2.4 Areas of Future Study

Clearly, additional randomized controlled trials comparing primary cytoreduction and neoadjuvant chemotherapy with interval surgery would be of great value. Trials that compare outcomes at tertiary referral centers where patients are treated by high-volume gynecologic oncologists as well as trials in community settings would both be of utility. Ideally these studies would include both “favorable” prognosis patients with advanced stage disease as well as women with larger volume disease.

While randomized controlled trials in this setting would be of great utility, undertaking these trials is challenging. First, among gynecologic oncologists there is often a strong bias towards one treatment approach over another, potentially limiting referral to trials. Second, enrollment into clinical trials in which patients are randomized to either a surgical intervention or to a non-surgical alternative is often problematic. Lastly, ovarian cancer is often a disease that is treated over the course of many years. Initial surgery and chemotherapy, regardless of the sequence, is typically followed by multiple lines of cytotoxic chemotherapy and often secondary surgery for recurrent disease. Imbalances in downstream treatment often make interpretation of trials focused on initial therapy difficult [34].

Given the difficulty in performing prospective, randomized trials, there has been great interest in using observational data to explore primary treatment for ovarian cancer. Studies using observational in this setting are limited by both selection bias and the influence of multiple measured and unmeasured confounders that influence both treatment selection and outcomes. Recent studies attempted to overcome some of these limitations using statistically methodology such as propensity score matching and instrumental variable analysis to limit the influence of selection bias and confounding. One report examined treatment outcomes in over 9,500 women with advanced-stage ovarian cancer. Using traditional regression analysis, survival was inferior in women who received neoadjuvant chemotherapy. However, after leveraging geographic variation in treatment as an instrumental variable to limit the effects of unmeasured confounding, there was no statistically significant difference in survival between those who received neoadjuvant chemotherapy and those women treated with primary cytoreduction. Further, in this report of unselected patients the median survival for both groups was approximately 24 months, much lower than what has been reported from tertiary centers in the US [35].

Ultimately, better screening tests are needed for ovarian cancer to help reduce the burden of advanced-stage disease. For those women with advanced-stage tumors, newer therapeutic strategies may help prolong survival and increase the chance of cure. Further prospective clinical trials as well as novel methods of analyzing population-based data will help to shed light on how best to individualized the treatment of women with newly diagnosed, advanced stage tumors.

3 The Role of Lymphadenectomy in Endometrial Cancer

3.1 Background

Endometrial cancer is the most common gynecologic cancer in the United States. In 2014, it is estimated that 52,630 women will be diagnosed with the disease and 8,590 women will die from uterine cancer [36]. For the vast majority of women primary treatment entails surgery. Surgical management of endometrial cancer consists of hysterectomy and usually bilateral salpingo-oophorectomy [37]. Lymphadenectomy, or removal of the regional lymphatics, may be a part of the primary surgical effort as well. Hysterectomy for endometrial cancer can be performed via laparotomy, or, more recently using minimally invasive surgery with either laparoscopy or robotic assistance [38].

The surgical treatment of endometrial cancer has evolved over the last four decades. Historically, treatment for all women with endometrial cancer was initiated with intracavitary radiation [39]. Intracavitary radiation was most frequently administered using capsules loaded directly into the uterine cavity. Radiation was followed by hysterectomy. In the 1980s, treatment paradigms began to shift. In lieu of primary radiation, hysterectomy was often employed as initial therapy and followed by tailored, adjuvant radiotherapy. Lymphadenectomy was performed in some women to help guide adjuvant radiotherapy [39]. This treatment shift and the recognition of the role of lymphadenectomy in endometrial cancer was recognized in 1988 when a revised surgical staging system for endometrial cancer was introduced by the International Federation of Obstetrics and Gynecology [40].

A series of surgical pathology studies have demonstrated that women with high-risk uterine features including higher tumor grade, greater depth of myometrial invasion, and lymphovascular space invasion were at higher risk for nodal metastasis [41]. Further, these studies suggested that the presence of nodal metastases was among the strongest adverse predictors of survival in women with endometrial cancer [42]. The primary goal of lymphadenectomy is to identify occult metastatic disease to help guide adjuvant therapy. Women identified with metastatic disease could thus be triaged to adjuvant therapy in the form of chemotherapy and radiation and those women without nodal disease could forego additional therapy and its associated toxicity [43]. In addition to treatment planning, some studies have suggested that lymphadenectomy has a therapeutic role [44, 45]. The therapeutic role of lymphadenectomy may be the result of resection of microscopic nodal disease.

The potential benefits of lymphadenectomy are weighed against the increased operative time and morbidity associated with performance of the procedure. Currently, debate around lymphadenectomy centers on whether lymphadenectomy should be performed universally in all patients, or, whether the procedure should be performed selectively in high-risk patients or omitted entirely [46]. More recently, sentinel lymph node biopsy has been described for endometrial cancer [47].

3.2 Evidence

Observational studies have defined a strong rationale for performance of lymphadenectomy in women with apparent uterine-confined endometrial cancer. First, it is well accepted that the presence of nodal metastasis is highly prognostic for endometrial cancer. International data as well as studies from the National Cancer Database have suggested that survival for stage I–II endometrial cancer is >80 % but decreases to approximately 40–50 % in women with nodal disease [48–50]. Identification of occult nodal metastasis therefore provides important prognostic information for patients, and ideally would identify a subset of patients who could receive adjuvant therapy.

The argument for universal lymphadenectomy for endometrial cancer is further bolstered by the difficulty in accurately identifying women with nodal disease without pathologic assessment. The premise of selective lymphadenectomy relies on classification of patients based on preoperative and intraoperative factors into a high-risk group that would undergo lymphadenectomy and similarly, a population at low-risk for lymph node metastases that could safely forego lymphadenectomy [50]. Risk stratification relies on utilization of pathologic factors, most commonly tumor grade, depth of myometrial invasion, and size. Investigators from the Mayo Clinic have identified a subgroup of patients at very low-risk for lymph node metastasis. In a series of 328 patients with grade 1 or 2 endometrioid tumors, 2 cm in diameter and <50 % myometrial invasion, the rate of nodal metastasis was 5 % and 5-year survival was 97 % [51]. These criteria were further examined prospectively as well as through a multi-institutional evaluation that noted a negative predictive value of 98.2 % [52, 53].

Despite the high negative predictive value of utilizing preoperative and intra-operative assessment to stratify patients, concern has been raised that data available to surgeons at the

time of decision making frequently changes after complete pathologic evaluation of the surgical specimens. For example, in the GOGs surgicopathology study, 20 % of tumors classified as grade 1 preoperatively were upgraded and frequently myoinvasive [41]. A prospective, blinded study of the accuracy of frozen section in women with endometrial cancer found an overall poor correlation between frozen section findings in the operating room and final pathology. These investigators noted that tumor grade at frozen section correlated with final pathology in only 58 % of cases while depth of invasion correlated in 67 % of patients. Overall, 28 % of patients were upstaged from the intraoperative assessment to final pathology [54]. Similarly, a report of 181 women with a diagnosis of grade 1 endometrial cancer who underwent staging lymphadenectomy found that 19 % of the neoplasms were upgraded, 18 % upstaged while adjuvant therapy was affected by the results of lymphadenectomy in 26 % of women [55]. Lastly, intraoperative gross inspection and palpation of the lymph nodes has very poor sensitivity in identifying nodal metastases [41]. Proponents of lymphadenectomy have argued that universal lymphadenectomy saves women from re-exploration when unexpected pathologic findings are noted postoperatively.

The theoretic benefit of lymphadenectomy is to identify women with positive nodes who can undergo adjuvant therapy and increase the chance of cure as well as to spare lower risk women potentially toxic therapy. This argument depends on two factors. First, there must be an effective treatment that improves survival for women with nodal metastasis. Second, a large portion of women without nodal metastases should be at low enough risk to be able to forego adjuvant therapy, or, alternatively, undergo a less toxic intervention than patients with nodal disease. Historically, pelvic radiotherapy was the treatment of choice for women with nodal disease from endometrial cancer. More recently, the GOG has demonstrated that combination chemotherapy is superior to radiation therapy [56]. In practice, multimodal therapy employing both chemotherapy and radiation is often utilized for women with node positive endometrial cancer [57].

Several observational reports have suggested that the results of lymphadenectomy are associated with decision making for adjuvant therapy [55, 58, 59]. An analysis of over 58,000 patients with stage I–II endometrioid adenocarcinomas in the Surveillance, Epidemiology, and End Results database noted that lymphadenectomy was performed in approximately 44 % of patients. Among low-risk women with tumors confined to the endometrium, performance of lymphadenectomy was not associated with patterns of adjuvant therapy. Among women with myoinvasive tumors, lymphadenectomy was associated with treatment with women who underwent lymphadenectomy being more likely to receive brachytherapy and those women who did not undergo lymphadenectomy more frequently receiving pelvic radiation. For example, among women <60 years of age with grade 2 tumors invading >50 % of the myometrium, whole pelvic radiation was used in 40 % of women who underwent lymphadenectomy versus 61 % of those who did not, while vaginal brachytherapy was used in 11 and 2 %, respectively [59]. Similarly, a single institution study of 95 patients found that 13 % of patients received extended field radiation due to para-aortic nodal disease while 52 % of patients had negative nodes and avoided treatment [58].

A fourth argument for the performance of universal lymphadenectomy stems from the potential therapeutic benefit of the procedure [44, 45, 60, 61]. The potential therapeutic benefit of lymphadenectomy for women with negative lymph nodes was first described by Kilgore and colleagues in 1995. In this report of 649 patients, there was a trend toward increased survival in women who underwent multi-site sampling [45]. A single institution analysis of 509 patients with endometrial cancer noted that removal of >11 nodes was associated with improved survival in women with grade 3 tumors, but node count had no impact on survival in those with grade 1 and 2 neoplasms [44]. Data on over 12,000 patients registered in the Surveillance, Epidemiology, and End Results database suggested that more extensive lymphadenectomy improved survival for intermediate and high-risk patients (<50 % myoinvasion and grade 3, > 50 % myoinvasion, and stages II–IV). Lymph node count remained significant after adjustment for clinical and demographic variables as well as receipt of adjuvant radiotherapy [60]. In contrast, several retrospective reports have shown no association with lymphadenectomy and survival, particularly among low-risk patients [51, 62, 63].

Despite potential benefits in prognostication and treatment planning, the most important question is whether lymphadenectomy ultimately improves survival in women with apparent early-stage endometrial cancer. Two randomized controlled trials have now directly addressed this issue [64, 65] (Table 2). The first study examined 514 women with endometrial cancer apparently confined to the uterus. Patients were randomized to either systematic pelvic lymphadenectomy or no lymphadenectomy. Removal of bulky lymph nodes was permitted in the no lymphadenectomy arm. Adjuvant therapy was based on the discretion of the treating clinician. The study was powered to detect an 8 % difference in 5-year survival. The median number of pelvic lymph nodes removed in the lymphadenectomy arm was 26, while 22 % of patients in the no lymphadenectomy arm had enlarged nodes and underwent resection. Only 14 % of the 56 patients with enlarged nodes in the no lymphadenectomy arm had metastatic disease. Choice of adjuvant therapy did not differ statistically between the two arms ($P = 0.07$). Early and late postoperative complications were more common in the lymphadenectomy arm. After a median follow-up of 49 months, the recurrence rate was 12.9 % in the lymphadenectomy arm versus 13.2 % in the no lymphadenectomy arm. Similarly, there was no difference in survival; 5-year overall survival was 86 % in the lymphadenectomy arm versus 90 % in the no lymphadenectomy arm ($P = 0.50$) [64].

A second RCT examining the role of lymphadenectomy, A Study in the Treatment of Endometrial Cancer (ASTECC), analyzed 1,408 women treated in 85 centers across 4 countries. ASTECC randomized women with apparent uterine confined disease to either lymphadenectomy or standard surgery without lymphadenectomy. Patients underwent a second randomization after surgery for adjuvant therapy. The study was powered to detect a 10 % improvement in 5-year survival. The median number of nodes removed in the standard surgery group was 12 while 5 % of women in the no lymphadenectomy arm had some nodal tissue removed. Operative time and complications were longer in the lymphadenectomy arm. 5-year recurrence-free survival was 79 % in the no lymphadenectomy arm versus 73 % in the lymphadenectomy arm while 5-year overall survival was 81 % in the no

lymphadenectomy compared to 81 % in the no lymphadenectomy arm and 80 % in the lymphadenectomy cohort. The authors concluded that pelvic lymphadenectomy had no benefit on survival and should not be recommended outside of clinical trials [65].

3.3 Areas of Uncertainty and Future Study

Despite the publication of 2 randomized trials, the role of lymphadenectomy for early-stage endometrial cancer remains actively debated [43, 46, 66]. A number of methodologic concerns have been raised regarding the design of the two clinical trials. While both trials included quality control, neither trial required para-aortic lymphadenectomy and the node counts, particularly in ASTEC, were relatively low overall [43, 66]. There is growing recognition that isolated para-aortic node metastases are not infrequent among women with endometrial cancer [52]. Similarly, both trials included a relatively low-risk population in which the overall rates of lymph node metastases were low. While actively debated, it has been argued that any benefit of lymphadenectomy is more likely to be detected in a higher risk patient population. A decision analysis that reviewed many of the statistical assumptions of the 2 RCTs suggested that a survival difference of 10 % was only detectable if the rate of isolated pelvic nodal metastasis rose to 15 %. This analysis concluded that the populations studied in these trials rendered both studies underpowered to detect a difference in survival [43, 46].

Finally, neither trial had a standard protocol for adjuvant therapy and, as such, differences in outcome may be due not only to lymphadenectomy, but also to differences in postoperative treatment. This concern focuses not just on lymphadenectomy, but also on endometrial cancer in general where recommendations for adjuvant therapy are highly variable. Most women with advanced stage disease (including nodal metastasis) are treated with chemotherapy often combined with radiation [57]. However, there is now greater recognition that uterine factors may be nearly as important in prognosis as nodal disease [67, 68]. This awareness has led to increased use of chemotherapy, often combined with vaginal brachytherapy, for early-stage tumors [69]. If adjuvant therapy is similar for patients whether or not they undergo lymphadenectomy then any survival benefit for the procedure would require a benefit to the resection of microscopic metastatic disease. The changing patterns of adjuvant therapy may thus further confound trials of lymphadenectomy.

There is much debate about how to proceed to further study the role of lymph node dissection in apparent early-stage endometrial cancer. To achieve adequate power, it appears that analysis of a higher-risk patient population enriched for nodal metastasis will be required to achieve statistical significance [43, 46]. Future prospective trials will likely also need to include sentinel lymph node dissection, translational science endpoints and quality of life evaluations [43]. However, as has been pointed, using various treatment appropriations to endometrial cancer, 3-year survival rates range from 88 to 93 %. The overall favorable prognosis of the disease raises question as to the value of large scale, randomized trials in this scenario as these trials, even if designed optimally, would result in very small differences in survival [43, 46].

Given the difficulties in conducting large-scale randomized trials there is also clearly room for alternative study designs. Previous observational studies of endometrial cancer and

lymphadenectomy are strongly influenced by selection bias and likely unmeasured confounding. Particularly as endometrial cancer patients are elderly and often have substantial comorbidity, a number of measured and unmeasured factors undoubtedly influence decision making and influence outcomes. Statistical analysis with newer methodology such as instrumental variable analysis may help mitigate some of these confounding factors. Large, population-based studies can not only analyze survival in real world populations but also assess the impact of lymphadenectomy on downstream decision making. Ultimately further work is needed to develop novel imaging strategies and biomarkers that can perhaps identify high-risk patients without the need for a surgical intervention such as lymphadenectomy [43].

4 Adjuvant Therapy for Ovarian Cancer

4.1 Background

At the time of diagnosis nearly three quarters of women with ovarian cancer present with advanced stage disease (stage III or IV). For these women, standard treatment entails either primary surgery or neoadjuvant chemotherapy. Surgery is typically followed by adjuvant chemotherapy.

The last three decades have seen significant improvement in the chemotherapeutic treatment options for women with ovarian cancer [10, 70–72]. In the 1970s and 1980s treatment often employed agents such as doxorubicin and cyclophosphamide. In the 1980s platinum-analogue showed efficacy for ovarian cancer and are still considered the most active agents for the disease. A series of studies completed by the GOG in the United States and by cooperative groups throughout the world have explored the incorporation of a number of chemotherapeutic drugs, examined alternative strategies to administer these agents, and tested how novel biologic agents can be used for the treatment of ovarian cancer.

Despite the advances in the chemotherapeutic armamentarium for ovarian cancer, how to choose the best therapy for individual patients often remains elusive. Increased efficacy of chemotherapy is often accompanied by increased toxicity. A major challenges for oncologists is how to balance efficacy, toxicity, and quality of life in decision making.

4.2 Evidence

The standard of care for the adjuvant therapy of advanced stage ovarian cancer changed rapidly in the mid-1990s with presentation of data examining taxanes in the treatment of ovarian cancer. GOG protocol 111 randomized 386 women who underwent suboptimal tumor cytoreduction (>1 cm residual tumor) to 6 cycles of chemotherapy with either cyclophosphamide and cisplatin or cisplatin and paclitaxel (Table 3). The overall response rate was 60 % in the cisplatin/cyclophosphamide group compared to 73 % in the cisplatin/paclitaxel arm. With a median follow-up of 37 months, the median progression free survival in was 13 months in cisplatin/cyclophosphamide arm compared to 18 months in the cisplatin/paclitaxel arm ($P < 0.0001$). Median overall survival was 24 versus 38 months, respectively [72]. A similar, confirmatory trial (OV10) was conducted by investigators in Europe and Canada to compare cisplatin/cyclophosphamide to cisplatin/paclitaxel. In this

analysis of 680 patients the response rate as well as progression-free and overall survival were superior in the paclitaxel-treated patients [73].

Subsequent work by the GOG was focused on reducing the toxicity and enhancing convenience of platinum and taxane based therapy. GOG protocol 158 randomized 792 patients to treatment with either cisplatin and paclitaxel or carboplatin and paclitaxel. The study followed a non-inferiority design and found that the carboplatin/paclitaxel combination was less toxic, easier to administer, and not inferior to the cisplatin-containing doublet. With these findings the combination of carboplatin and paclitaxel has remained the most frequently used regimen for ovarian cancer [30]. Subsequent modifications of the carboplatin/paclitaxel backbone for ovarian cancer focused on adding additional cytotoxic agents to upfront therapy. An international trial of over 4,300 women led by the GOG (protocol 182) randomized patients to carboplatin and paclitaxel with some combination of gemcitabine, liposomal doxorubicin, or topotecan given either as triplets or sequential doublets. The final analysis revealed no difference in survival for any of the combinations [74].

While the addition of additional cytotoxic agents to initial therapy appears to be of little value, there has been great interest in alternate ways to deliver cytotoxic chemotherapy. Intraperitoneal chemotherapy allows the administration of chemotherapy directly into the abdominal cavity. Given that ovarian cancer predominately spreads within the peritoneal cavity, there is a strong rationale for this method of delivery. Numerous preclinical studies have demonstrated that intraperitoneal administration of chemotherapy results in a higher cellular concentration of a number of agents. Similarly, the feasibility of intraperitoneal chemotherapy has been shown in a number of phase II and phase III trials [10, 75, 76].

One of the first large randomized trials of intraperitoneal chemotherapy was reported by the Southwest Oncology Group (SWOG) in 1996. In this randomized controlled trial, 654 patients with optimally cytoreduced ovarian cancer were randomized to intravenous cyclophosphamide and cisplatin or an experimental regimen of intravenous cyclophosphamide with intraperitoneal cisplatin. The intraperitoneal chemotherapy arm was associated with an 8 month improvement in overall survival (49 vs. 41 months) [75]. Despite the survival benefit demonstrated with intraperitoneal chemotherapy, there was little attention to this method of treatment delivery until the publication of GOG protocol 172 in 2006. In this protocol, 429 women with optimally cytoreduced ovarian cancer were randomized to intravenous cisplatin and paclitaxel or an experimental arm of intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2 and intraperitoneal paclitaxel on day 8 (intraperitoneal arm). Intraperitoneal chemotherapy was associated with an improvement in both progression-free (24 vs. 18 months) and overall (66 vs. 50 months) survival. The improved survival was however, accompanied by greater toxicity. Within the cohort of women who received intraperitoneal chemotherapy, only 42 % were able to complete all 6 intraperitoneal cycles. Grade 3–4 myelosuppression, renal, neurologic, infectious, metabolic and hepatic toxicity as well as fatigue and metabolic events were all more frequent in the intraperitoneal chemotherapy arm. While quality of life was worse during treatment for those women in the intraperitoneal therapy arm, there was no difference in quality of life 1 year after treatment [10].

There has also been interest in incorporating novel, molecularly targeted agents into the upfront treatment of ovarian cancer. To date, the greatest interest has focused on bevacizumab, a humanized anti-vascular endothelial growth factor [71]. GOG protocol 218 randomized 1,873 women with incompletely resected stage III and IV ovarian cancer to chemotherapy with carboplatin and paclitaxel to three arms: placebo, bevacizumab for 6 cycles or bevacizumab during chemotherapy and as consolidation therapy for a total of 22 cycles. The median progression-free survival was 10.3 months in the control group, 11.2 in the bevacizumab during chemotherapy arm and 14.1 in the prolonged bevacizumab arm. PFS was statistically significantly longer in the prolonged bevacizumab arm compared to the control arm. Median overall survival was 39.3, 38.7, and 39.7 months respectively [71]. A second study of bevacizumab reported similar results; bevacizumab was associated with improved progression-free survival [70]. The benefits were greatest in patients at highest risk for recurrence.

Lastly, as an alternative to delivery of the maximum tolerated dose of intravenous chemotherapy, recently studies have explored combinations using more frequent, lower doses of these agents (dose dense chemotherapy). The Japanese Gynecologic Oncology reported long-term results of a dose dense chemotherapy regimen for adjuvant therapy (JGOG protocol 3016). In this study, 631 women with stage II–IV ovarian cancer were randomly assigned to carboplatin and paclitaxel every weeks or to carboplatin on day 1 and paclitaxel on days 1, 8 and 15 of a 3 week cycle. With a median follow-up of 77 months, the investigators found an improvement in both progression free (28 months vs. 17 months) and overall (101 months vs. 62 months) survival for women who received dose dense treatment. The improvement in survival was most pronounced in those women with suboptimally cytoreduced tumors. Grade 3–4 anemia was more common in the dose dense group, but both regimens were relatively well tolerated [77, 78].

4.3 Areas of Uncertainty and Future Study

Data from a variety of sources and using a number of study designs can help inform the debate regarding the best adjuvant therapy for advanced stage ovarian cancer. Currently, standard therapy remains carboplatin and paclitaxel administered every 3 weeks. Intraperitoneal chemotherapy has been consistently associated with improved overall survival but also accompanied by substantial toxicity [10]. The addition of bevacizumab appears to improve progression-free survival, particularly if administered for a prolonged course, but this therapy has not resulted in improved overall survival, is associated with added toxicity and substantial cost [70, 71]. Finally, dose dense paclitaxel resulted in impressive survival improvements but this data is based on one study outside of the United States [77, 78].

To help tailor a number of prospective, phase III trials are currently underway. Many of these studies are cooperative group trials and are comparing strategies of standard intravenous chemotherapy, dose dense chemotherapy, intraperitoneal chemotherapy and bevacizumab in various combinations. Many of these trials are also focused on developing less toxic regimens to enhance the therapeutic profile and minimize impact on quality of life.

While randomized controlled trials are optimal for minimizing bias, a major concern is that these trials often lack generalizability to “real world” populations. Particularly in the cooperative group setting, trial inclusion criteria are often extensive with exclusion of elderly patients and those with comorbid medical conditions. While RCTs maximize precision, the results may not be directly applicable to the daily practice of oncology. A recent analysis compared eligibility and outcomes of patients treated on 21 SWOG trials to non-trial participants from throughout the United States captured through analysis of SEER. The analysis noted that trial participants were significantly younger than non-trial participants with similar tumors. Among 11 good-prognosis studies trial participation was not associated with survival. However, among 10 poor-prognosis studies survival was better in trial participants. The impact of trial participation was predominately noted in the first year after treatment likely due to the exclusion of patients with comorbidity [79].

To help design treatment strategies for real world populations, observational data and comparative effectiveness studies are of great utility [80]. Unlike randomized trials, these studies can show actual treatment trends in community practice and examine risks and benefits in specific patient populations or groups of subjects with particular characteristics. A major limitation of observational data is confounding, both measured and unmeasured. Newer methodology to help limit this bias is now more commonly employed for oncology studies [81–83].

In oncology there is now a greater focus on quality of life. One aspect of measuring quality of life is specifically examining outcomes that matter to patients. While patient-reported outcomes (PROs) are now being more frequently described, many oncology trials are still designed with insufficient focus on PROs. A recent systematic review examined PROs in randomized trials of brain tumors. Among 14 RCTs including over 3,000 patients, only 2 studies incorporated PROs that sufficiently satisfied methodologic criteria to provide high-quality PROs [84]. Use of PROs in gynecologic oncology remains in its infancy and clearly this will be a focus of study over the next decade.

Finally, there is growing concern about the cost of incorporating new therapeutic agents into the treatment regimens. In particular, controversy has surrounded use of bevacizumab for solid tumors [85, 86]. In a cost-effectiveness analysis of treatment strategies using bevacizumab for ovarian cancer based on the results of GOG 218, the costs of treatment for patients on each arm were approximately \$2.5 million for carboplatin/paclitaxel, \$21.4 million for carboplatin/paclitaxel and initial bevacizumab and \$78.3 million for carboplatin, paclitaxel and extended bevacizumab. This translated into an incremental cost-effectiveness ratio of \$479,712 per progression-free life-year saved for initial bevacizumab and \$401,088 per progression-free life-year saved for prolonged bevacizumab [85]. These studies highlight the difficulty in utilizing costly new drugs of uncertain value. Clearly moving forward with cost constraints on oncology, decision analyses and cost effectiveness studies will play an important role in helping to shape public policy for the treatment of gynecologic malignancies (Tables 1, 2 and 3).

References

1. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002; 20:1248–1259. [PubMed: 11870167]
2. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol.* 1994; 170:974–980. discussion 9-80. [PubMed: 8166218]
3. Wright JD, Lewin SN, Deutsch I, et al. Defining the limits of radical cytoreductive surgery for ovarian cancer. *Gynecol Oncol.* 2011; 123:467–473. [PubMed: 21958535]
4. Gerestein CG, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: a systematic review. *Gynecol Oncol.* 2009; 114:523–527. [PubMed: 19344936]
5. Wright JD, Herzog TJ, Neugut AI, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. *Obstet Gynecol.* 2012; 120:871–881. [PubMed: 22996105]
6. Wright J, Doan T, McBride R, Jacobson J, Hershman D. Variability in chemotherapy delivery for elderly women with advanced stage ovarian cancer and its impact on survival. *Br J Cancer.* 2008; 98:1197–1203. [PubMed: 18349836]
7. Everett EN, French AE, Stone RL, et al. Initial chemotherapy followed by surgical cytoreduction for the treatment of stage III/IV epithelial ovarian cancer. *Am J Obstet Gynecol.* 2006; 195:568–574. discussion 74-6. [PubMed: 16890558]
8. Hou JY, Kelly MG, Yu H, et al. Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease. *Gynecol Oncol.* 2007; 105:211–217. [PubMed: 17239941]
9. Chi DS, Musa F, Dao F, et al. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS versus neoadjuvant chemotherapy (NACT). *Gynecol Oncol.* 2012; 124:10–14. [PubMed: 21917306]
10. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006; 354:34–43. [PubMed: 16394300]
11. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr.* 1975; 42:101–104. [PubMed: 1234624]
12. Hoskins WJ. Epithelial ovarian carcinoma: principles of primary surgery. *Gynecol Oncol.* 1994; 55:S91–S96. [PubMed: 7835815]
13. Aletti GD, Dowdy SC, Gostout BS, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol.* 2006; 107:77–85. [PubMed: 16394043]
14. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? *Gynecol Oncol.* 2006; 103:559–564. [PubMed: 16714056]
15. Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol.* 2009; 114:26–31. [PubMed: 19395008]
16. Chi DS, Franklin CC, Levine DA, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. *Gynecol Oncol.* 2004; 94:650–654. [PubMed: 15350354]
17. Chi DS, Liao JB, Leon LF, et al. Identification of prognostic factors in advanced epithelial ovarian carcinoma. *Gynecol Oncol.* 2001; 82:532–537. [PubMed: 11520151]
18. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol.* 1998; 69:103–108. [PubMed: 9600815]
19. Aletti GD, Eisenhauer EL, Santillan A, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. *Gynecol Oncol.* 2011; 120:23–28. [PubMed: 20933255]

20. Gerestein CG, Nieuwenhuyzen-de Boer GM, Eijkemans MJ, Kooi GS, Burger CW. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer*. 2010; 46:102–109. [PubMed: 19900801]
21. Inciura A, Simavicius A, Juozaityte E, et al. Comparison of adjuvant and neoadjuvant chemotherapy in the management of advanced ovarian cancer: a retrospective study of 574 patients. *BMC Cancer*. 2006; 6:153. [PubMed: 16759398]
22. Kang S, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. *Ann Surg Oncol*. 2009; 16:2315–2320. [PubMed: 19517192]
23. Morice P, Dubernard G, Rey A, et al. Results of interval debulking surgery compared with primary debulking surgery in advanced stage ovarian cancer. *J Am Coll Surg*. 2003; 197:955–963. [PubMed: 14644284]
24. Morrison J, Haldar K, Kehoe S, Lawrie TA. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database Syst Rev*. 2012; 8:CD005343. [PubMed: 22895947]
25. Schwartz PE, Rutherford TJ, Chambers JT, Kohorn EI, Thiel RP. Neoadjuvant chemotherapy for advanced ovarian cancer: long-term survival. *Gynecol Oncol*. 1999; 72:93–99. [PubMed: 9889037]
26. Vergote I, Leunen K, Amant F. Primary surgery or neoadjuvant chemotherapy in ovarian cancer: what is the value of comparing apples with oranges? *Gynecol Oncol*. 2012; 124:1–2. [PubMed: 22153125]
27. Dewdney SB, Rimel BJ, Reinhart AJ, et al. The role of neoadjuvant chemotherapy in the management of patients with advanced stage ovarian cancer: survey results from members of the society of gynecologic oncologists. *Gynecol Oncol*. 2010; 119:18–21. [PubMed: 20673970]
28. Vergote I, Amant F, Leunen K. Neoadjuvant chemotherapy in advanced ovarian cancer: what kind of evidence is needed to convince US gynaecological oncologists? *Gynecol Oncol*. 2010; 119:1–2. [PubMed: 20833283]
29. Chi DS, Bristow RE, Armstrong DK, Karlan BY. Is the easier way ever the better way? *J Clin Oncol*. 2011; 29:4073–4075. [PubMed: 21931018]
30. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*. 2003; 21:3194–3200. [PubMed: 12860964]
31. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010; 363:943–953. [PubMed: 20818904]
32. Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. *Gynecol Oncol*. 2007; 104:480–490. [PubMed: 17166564]
33. Vergote I, Trope CG, Amant F, Ehlen T, Reed NS, Casado A. Neoadjuvant chemotherapy is the better treatment option in some patients with stage IIIC–IV ovarian cancer. *J Clin Oncol*. 2011; 29:4076–4078. [PubMed: 21931032]
34. Herzog TJ, Armstrong DK, Brady MF, et al. Ovarian cancer clinical trial endpoints: society of gynecologic oncology white paper. *Gynecol Oncol*. 2014; 132:8–17. [PubMed: 24239753]
35. Wright JD, Ananth CV, Tsui J, et al. Comparative effectiveness of upfront treatment strategies in elderly women with ovarian cancer. *Cancer*. 2014; 120:1246–1254. [PubMed: 24443159]
36. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014; 64:9–29. [PubMed: 24399786]
37. Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. *J Clin Oncol*. 2009; 27:1214–1219. [PubMed: 19171707]
38. Wright JD, Burke WM, Wilde ET, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. *J Clin Oncol*. 2012; 30:783–791. [PubMed: 22291073]
39. Wright JD, Medel NIB, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management of endometrial cancer. *Lancet*. 2012; 379:1352–1360. [PubMed: 22444602]

40. Creasman W. Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet.* 2009; 105:109. [PubMed: 19345353]
41. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: a gynecologic oncology group study. *Cancer.* 1987; 60:2035–2041. [PubMed: 3652025]
42. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1991; 40:55–65. [PubMed: 1989916]
43. McMeekin DS. Designing the next lymphadenectomy trial: what should we learn for our prior experiences. *Gynecol Oncol.* 2012; 126:1–2. [PubMed: 22713367]
44. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol.* 2005; 23:3668–3675. [PubMed: 15738538]
45. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol.* 1995; 56:29–33. [PubMed: 7821843]
46. Naumann RW. The role of lymphadenectomy in endometrial cancer: was the ASTEC trial doomed by design and are we destined to repeat that mistake? *Gynecol Oncol.* 2012; 126:5–11. [PubMed: 22555109]
47. Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. *Gynecol Oncol.* 2011; 122:251–254. [PubMed: 21570109]
48. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. *Int J Gynaecol Obstet.* 2003; 83(Suppl 1):79–118. [PubMed: 14763170]
49. Partridge EE, Shingleton HM, Menck HR. The national cancer data base report on endometrial cancer. *J Surg Oncol.* 1996; 61:111–123. [PubMed: 8606542]
50. Chan JK, Kapp DS. Role of complete lymphadenectomy in endometrioid uterine cancer. *Lancet Oncol.* 2007; 8:831–841. [PubMed: 17765192]
51. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? *Am J Obstet Gynecol.* 2000; 182:1506–1519. [PubMed: 10871473]
52. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. *Gynecol Oncol.* 2008; 109:11–18. [PubMed: 18304622]
53. Convery PA, Cantrell LA, Di Santo N, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. *Gynecol Oncol.* 2011; 123:65–70. [PubMed: 21742369]
54. Case AS, Rocconi RP, Straughn JM Jr, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol.* 2006; 108:1375–1379. [PubMed: 17138769]
55. Ben-Shachar I, Pavelka J, Cohn DE, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol.* 2005; 105:487–493. [PubMed: 15738013]
56. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study. *J Clin Oncol.* 2006; 24:36–44. [PubMed: 16330675]
57. Secord AA, Havrilesky LJ, O'Malley DM, et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. *Gynecol Oncol.* 2009; 114:442–447. [PubMed: 19560193]
58. Lo KW, Cheung TH, Yu MY, Yim SF, Chung TK. The value of pelvic and para-aortic lymphadenectomy in endometrial cancer to avoid unnecessary radiotherapy. *Int J Gynecol Cancer.* 2003; 13:863–869. [PubMed: 14675325]
59. Sharma C, Deutsch I, Lewin SN, et al. Lymphadenectomy influences the utilization of adjuvant radiation treatment for endometrial cancer. *Am J Obstet Gynecol.* 2011; 205(562):e1–e9.

60. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*. 2006; 107:1823–1830. [PubMed: 16977653]
61. Mohan DS, Samuels MA, Selim MA, et al. Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. *Gynecol Oncol*. 1998; 70:165–171. [PubMed: 9740684]
62. Carey MS, O'Connell GJ, Johanson CR, et al. Good outcome associated with a standardized treatment protocol using selective postoperative radiation in patients with clinical stage I adenocarcinoma of the endometrium. *Gynecol Oncol*. 1995; 57:138–144. [PubMed: 7729725]
63. Eltabbakh GH, Piver MS, Hempling RE, Shin KH. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. *Int J Radiat Oncol Biol Phys*. 1997; 38:373–380. [PubMed: 9226326]
64. Panici PB, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst*. 2008; 100:1707–1716. [PubMed: 19033573]
65. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*. 2009; 373:125–136. [PubMed: 19070889]
66. Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? *Gynecol Oncol*. 2010; 116:293–294. [PubMed: 19897230]
67. Kwon JS, Qiu F, Saskin R, Carey MS. Are uterine risk factors more important than nodal status in predicting survival in endometrial cancer? *Obstet Gynecol*. 2009; 114:736–743. [PubMed: 19888029]
68. Medel NIB, Herzog TJ, Deutsch I, et al. Comparison of the prognostic significance of uterine factors and nodal status for endometrial cancer. *Am J Obstet Gynecol*. 2011; 204:248.e1–e7. [PubMed: 21247552]
69. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese gynecologic oncology group study. *Gynecol Oncol*. 2008; 108:226–233. [PubMed: 17996926]
70. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011; 365:2484–2496. [PubMed: 22204725]
71. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011; 365:2473–2483. [PubMed: 22204724]
72. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*. 1996; 334:1–6. [PubMed: 7494563]
73. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst*. 2000; 92:699–708. [PubMed: 10793106]
74. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the gynecologic cancer intergroup. *J Clin Oncol*. 2009; 27:1419–1425. [PubMed: 19224846]
75. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996; 335:1950–1955. [PubMed: 8960474]
76. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001; 19:1001–1007. [PubMed: 11181662]
77. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial

- ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol.* 2013; 14:1020–1026. [PubMed: 23948349]
78. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet.* 2009; 374:1331–1338. [PubMed: 19767092]
79. Unger JM, Barlow WE, Martin DP, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst.* 2014; 106:dju002. [PubMed: 24627276]
80. Hershman DL, Wright JD. Comparative effectiveness research in oncology methodology: observational data. *J Clin Oncol.* 2012; 30:4215–4222. [PubMed: 23071228]
81. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA.* 2007; 297:278–285. [PubMed: 17227979]
82. Earle CC, Tsai JS, Gelber RD, Weinstein MC, Neumann PJ, Weeks JC. Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. *J Clin Oncol.* 2001; 19:1064–1070. [PubMed: 11181670]
83. Hadley J, Yabroff KR, Barrett MJ, Penson DF, Saigal CS, Potosky AL. Comparative effectiveness of prostate cancer treatments: evaluating statistical adjustments for confounding in observational data. *J Natl Cancer Inst.* 2010; 102:1780–1793. [PubMed: 20944078]
84. Dirven L, Taphoorn MJ, Reijneveld JC, et al. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. *Eur J Cancer.* 2014; 50(14):2432–2448. [PubMed: 25034656]
85. Cohn DE, Kim KH, Resnick KE, O'Malley DM, Straughn JM Jr. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *J Clin Oncol.* 2011; 29:1247–1251. [PubMed: 21383297]
86. Dawood S, Shaikh AJ, Buchholz TA, et al. The use of bevacizumab among women with metastatic breast cancer: a survey on clinical practice and the ongoing controversy. *Cancer.* 2012; 118:2780–2786. [PubMed: 22614656]

Table 1
Randomized control trial of neoadjuvant chemotherapy versus primary cytoreduction for advanced stage ovarian cancer

Study	Arms	Subjects	Optimal cytoreduction (1 cm residual tumor) (%)	Perioperative mortality (%)	Median progression-free survival (months)	Median overall survival (months)
<i>Vergote (2010)</i>						
	Primary surgery	336	42	2.5	12	29
	Neoadjuvant chemotherapy	334	81	0.7	12	30

Table 2
Outcomes of randomized controlled trials of lymphadenectomy for endometrial cancer

Study	Arms	Subjects	Lymphadenectomy (median nodes removed)	Operating room time (median) (min)	Radiation received (%)	Recurrence (%)	5-year recurrence free survival (%)	5-year overall survival (%)
<i>Benedetti Panici (2008)</i>								
	No pelvic lymphadenectomy	264	22 %	120	25	13.2	82	90
	Pelvic lymphadenectomy	273	100 % (30)	180	17	12.9	81	86
<i>ASTEC (2009)</i>								
	No pelvic lymphadenectomy	704	5 %	60	33	Not reported	79	81
	Pelvic lymphadenectomy	704	92 % (12)	90	33	Not reported	73	80

Table 3

Sentinel studies of adjuvant therapy for advanced stage ovarian cancer

Study	Arms	Subjects	Completed all scheduled therapy (%)	Response rate (%)	Median progression-free survival (months)	Median overall survival (months)
<i>GOG 111 (1996)</i>						
	Cisplatin and cyclophosphamide	202	78	60	13	24
	Cisplatin and paclitaxel	184	87	73	18	38
<i>OV10 (2000)</i>						
	Cisplatin and cyclophosphamide	338	–	45	12	26
	Cisplatin and paclitaxel	342	–	58	16	36
<i>GOG 158 (2003)</i>						
	Cisplatin and paclitaxel	400	85	–	19	49
	Carboplatin and paclitaxel	392	87	–	22	57
<i>GOG 172 (2006)</i>						
	Intravenous cisplatin and paclitaxel	210	90	–	18	50
	Intraperitoneal cisplatin and paclitaxel	205	42 (intraperitoneal)	–	24	66
<i>GOG 218 (2011)</i>						
	Carboplatin and paclitaxel	625	16	–	10	39
	Carboplatin and paclitaxel and bevacizumab	625	17	–	11	39
	Carboplatin and paclitaxel and prolonged bevacizumab	623	24	–	14	40
<i>JGOG 3016 (2009)</i>						
	Carboplatin and paclitaxel every 3 weeks	320	73	–	18	62
	Carboplatin and dose dense paclitaxel	317	62	–	28	101