Clinical Outcome of Patients With High-Risk Endometrial Carcinoma After Treatment With Chemotherapy Only

Elisabeth Smogeli, MD,*† Milada Cvancarova, PhD,‡ Yun Wang, MD, PhD,* Ben Davidson, MD, PhD,†§ Gunnar Kristensen, MD, PhD,*|| and Kristina Lindemann, MD, PhD*†

Objectives: Adjuvant treatment of high-risk endometrial cancer (EC) is still controversial. Several studies have tried to clarify the best treatment strategy, and guidelines have been made, but no study to date has shown a survival benefit for radiation over chemotherapy. We aimed to evaluate the outcome of high-risk EC patients treated with adjuvant chemotherapy only in a population where the routine administration of adjuvant radiotherapy was omitted.

Methods: This is a retrospective study including 230 EC patients with International Federation of Gynecology and Obstetrics stage I type II, stage Ib type I/G3, stage II, and IIIc treated at Oslo University Hospital between 2005 and 2012. Standard treatment was hysterectomy, bilateral salpingo-oophorectomy and at least pelvic lymphadenectomy followed by adjuvant chemotherapy.

Results: Of the 230 high-risk patients, standard treatment was given to 146 patients (63.5%): 60 patients in stage I, 10 patients in stage II, and 76 patients in stage IIIc. Only 10% of patients with stage I disease relapsed, with 3.3% locoregional relapses and 6.7% distant relapses. Recurrence rate in stage IIIc was 39.5%, with 7.9% isolated vaginal and 31.6% distant relapses. The 3-year disease-free survival was 92% for stage I, 80% for stage II, and 60% for stage IIIc disease. In the total population, 55 patients had International Federation of Gynecology and Obstetrics stage Ia, 43 Ib, 42 stage II, and 90 stage IIIc disease. Recurrence rate in the total population was 29.6%, with 9.6% isolated vaginal recurrences, 1.7% recurrences located in the pelvis, and 18.3% distant recurrences.

Conclusions: Patients with high-risk EC have acceptable vaginal/pelvic control rates after adjuvant chemotherapy. However, prognosis remains poor for patients with stage IIIc disease, also after chemotherapy.

Key Words: Adjuvant chemotherapy, Endometrial cancer, High risk, Radiotherapy, Recurrence, Survival

Received April 20, 2018, and in revised form June 30, 2018. Accepted for publication July 20, 2018.

(Int J Gynecol Cancer 2018;28: 1789–1795)
survival (OS) rate exceeding 80%. Still, there are subgroups with a high risk of occult micrometastatic disease. Traditionally, ECs have been considered to be resistant to chemotherapy, and most high-risk patients have been treated with adjuvant radiotherapy (RT). This view has gradually changed since the publication of GOG-122 reporting improved both disease-free survival (DFS) and OS for this group of patients after chemotherapy compared with whole abdominal irradiation in patients with stages III and IV EC.2 Since then, several randomized studies have tried to clarify the role of adjuvant chemotherapy in EC. Three subsequent studies compared combination chemotherapy with adjuvant radiation to the pelvis in patients with early-stage high-risk or advanced-stage disease. All 3 studies failed to show significant differences in DFS or OS between the arms,3–5 but they were not designed to potentially identify a subgroup of patients who may benefit from either of the treatment modalities.

In a pooled analysis of 2 randomized trials (NSGOEC-9501/EORTC-55991 and MaNGO ILIADE-III), it was shown that the addition of chemotherapy sequential to RT versus RT alone significantly increased DFS, whereas the increase in OS did not reach statistical significance.6 The combined treatment was associated with increased morbidity and a higher rate of treatment discontinuation. There was no significant difference in the patterns of relapse between the arms. A large randomized study (GOG-258) failed to show a difference in survival between chemotherapy versus chemoradiation followed by chemotherapy in optimally debulked stages III and IV.7 The randomized PORTEC-3 study randomized patients in stages I, II, and III without residual disease to radiation alone or chemoradiation followed by chemotherapy. The benefit in 5-year failure-free survival with the combination was mainly driven by the positive results for patients with stage III disease but did not translate into a benefit in OS.8 Despite these studies, newly released European Society of Gynaecological Oncology (ESGO) guidelines9,10 advocate for the administration of adjuvant RT in high-risk disease.

There have been constant concerns about the potentially increased risk of pelvic/vaginal relapse in patients treated with chemotherapy only. In a retrospective study where patients with stage IIIC disease treated with either chemotherapy alone, radiation alone, or a combination of both, pelvic relapse rates were 39%, 29%, and 27%, respectively.11 However, most relapses in high-risk EC patients occur outside the pelvis irrespective of the kind of adjuvant treatment.11 Vaginal recurrences can be effectively salvaged by modern RT,12 and the omission of adjuvant RT at least in early-stage EC has not been shown to diminish long-term survival.13

At the Norwegian Radium Hospital, patients with high-risk stages I/II and IIIC EC have since 2005 therefore routinely been treated with chemotherapy only, omitting RT. We report the oncological outcomes of this treatment policy.

MATERIALS AND METHODS

Patients and Follow-up

This is an institutional retrospective study of a cohort of all EC patients, treated at Oslo University Hospital (the Norwegian Radium Hospital, Ullevål University Hospital and Rikshospitalet) between November 2005 and October 2012. Patients were selected from a validated quality assurance database, providing detailed information on the primary diagnosis, the preoperative workup, comorbidity, surgical treatment, adjuvant treatment, incident relapse, and localization of relapse. All specimens underwent central histopathologic review by a pathologist specialized in gynecologic pathology at the Norwegian Radium Hospital at the time of diagnosis. Individual survival data were available through linkage to Statistics Norway. Stage of the disease at initial surgery was recoded to match the International Federation of Gynecology and Obstetrics (FIGO) 2009 revised staging.14 We included all patients with (1) FIGO stage I, grade 3, endometrioid endometrial carcinoma with myometrial invasion of 50% or greater; (2) FIGO stage I serous and clear cell EC (pure or mixed with at least 50% serous or clear cell component) of any myometrial invasion; (3) EC with cervical stromal invasion of any histology (FIGO stage II); and (4) lymph node–positive EC of any histology (FIGO stage IIIc). Patients with positive lymph nodes were further analyzed according to histological subtype (grade 1 or 2 endometrioid adenocarcinoma vs grade 3 endometrioid adenocarcinoma or serous and clear cell carcinomas). Sarcomas or carcinosarcomas were excluded from the analyses, as well as patients with synchronous ovarian cancer (n = 6) or neoadjuvant chemotherapy (n = 4). All patients underwent surgical treatment with at least total hysterectomy and bilateral salpingo-oophorectomy. Institutional guidelines considered standard treatment to be pelvic lymphadenectomy and para-aortic lymphadenectomy up to the renal veins for high-risk stage I, omentectomy for serous and clear cell histology, and radical hysterectomy with pelvic and para-aortic lymphadenectomy for stage II.

Adjuvant platinum-based chemotherapy was considered the standard treatment for high-risk patients. For different reasons, not all patients received adjuvant chemotherapy. Clinical outcomes are reported for the entire cohort and separately for patients treated with hysterectomy, bilateral salpingo-oophorectomy, and at least pelvic lymphadenectomy with or without adjuvant chemotherapy. Patients were monitored every 3 months during the first 2 years, every 6 months for the following 3 years, and then annually at Oslo University Hospital or their local hospital. Visits included thorough clinical examination and vaginal ultrasound, supplemented by computed tomography or magnetic resonance imaging scan on clinical indication.

Statistical Analyses

Continuous variables were described with median and range. Categorical variables were presented with counts and proportions. Crude recurrence rates are given as the proportion of patients diagnosed with relapse during follow-up time. Differences between proportions were assessed by χ² test.

For DFS, follow-up time was calculated from the date of EC diagnosis until the date of relapse, date of death from any cause, or end of follow-up, August 31, 2014, whichever occurred first. Death without prior relapse was treated as event in the analysis of DFS. For OS, follow-up time was calculated from the date of EC diagnosis until date of death from any cause or end of follow-up, whichever occurred first. Survival curves were plotted with the Kaplan-Meier method. We calculated 3-year DFS and 3-year OS with 95%
confidence intervals (CIs). All estimates were calculated for the cohort as a whole and separately for the groups who received and did not receive adjuvant chemotherapy. For patients with stage IIIc disease, analyses were conducted according to histological subtype (grade 1/2 endometrioid EC vs grade 3 endometrioid-type II EC).

The analyses were performed using IBM SPSS version 23 (SPSS, Chicago, IL) and the STATA statistical package, version 11.0 (StataCorp LP, College Station, TX).

RESULTS

The entire database comprised 934 surgically managed EC patients. Of those, 230 patients with median age of 69 years (range, 36–89 years) fulfilled the inclusion criteria for this analysis.

Baseline characteristics and treatment details are given in Table 1. Median follow-up time was 4.16 years (range, 0.4–8.8). Among those who underwent lymphadenectomy, the median number of removed lymph nodes was 17 (range, 0–47) in the pelvis and 6 (0–27) in the para-aortic region. The total number of patients who underwent pelvic lymphadenectomy was 203/230 (88.2%), and 136/230 (59.1%) underwent para-aortic lymphadenectomy.

Postoperatively, 155 (67.4%) were treated with chemotherapy alone, 64 patients (27.8%) were observed without further treatment, 9 (3.9%) were treated with external beam radiation therapy (EBRT) (1 with EBRT and brachytherapy), and 2 (0.9%) received both chemotherapy (one of those received only 1 cycle) and EBRT.

TABLE 1. Baseline characteristics (n = 230)

| Patient Characteristic | Median (Range) |
|------------------------|----------------|
| Age, y                 | 69 (36–89)     |
| No. Patients (%)       |                |
| Diabetes               |                |
| Yes                    | 25 (10.9)      |
| No                     | 201 (87.4)     |
| Missing                | 4 (1.7)        |
| Smoking                |                |
| Yes                    | 31 (13.5)      |
| No                     | 141 (61.3)     |
| Missing                | 58 (25.2)      |
| Histology              |                |
| Endometrioid           | 109 (47.4)     |
| Serous/clear cell/mixed| 114 (49.6)     |
| Other                  | 5 (2.2)        |
| Unclassified           | 2 (0.9)        |
| Stage                  |                |
| Ia                     | 55 (23.9)      |
| Ib                     | 43 (18.7)      |
| II                     | 42 (18.3)      |
| IIIc                   | 90 (39.1)      |
| Lymphadenectomy by stage|              |
| Ia                     | n = 55         |
| Not staged             | 7 (12.7)       |
| At least pelvis        | 48 (87.3)      |
| Pelvis/PA              | 34 (61.8)      |
| Ib                     | n = 43         |
| Not staged             | 9 (20.9)       |
| At least pelvis        | 34 (79.1)      |
| Pelvis/PA              | 25 (58.1)      |
| II                     | n = 42         |
| Not staged             | 9 (21.4)       |
| At least pelvis        | 33 (78.6)      |
| Pelvis/PA              | 17 (51.5)      |
| IIIc                   | n = 90         |
| Not staged*            | 2 (2.2)        |
| At least pelvis        | 88 (97.8)      |
| Pelvis/PA              | 60 (66.7)      |
| Total pelvic lymphadenectomy | 203 (88.2) |
| Total para-aortic lymphadenectomy | 136 (59.1) |
| Type of surgery        |                |
| Abdominal procedure    | 187 (81.3)     |
| Laparoscopic procedure (included robot) | 41 (17.9) |
| Removed uterus earlier | 2 (0.8)        |

TABLE 1. (Continued)

| Patient Characteristic | Median (Range) |
|------------------------|----------------|
| Adjuvant treatment     |                |
| No adjuvant treatment  | 64 (27.8)      |
| Radiotherapy           | 9 (3.9)        |
| Chemotherapy           | 155 (67.4)     |
| RT + computed tomography | 2 (0.9)      |

*Not completely staged, but both patients had 1 metastatic lymph node removed, 1 pelvic and 1 para-aortic, respectively.

PA, Para-aortic lymphadenectomy.

Compliance with institutional guidelines related to FIGO stage is shown in Table 2. In stage I, 16% were not staged, and

Adherence to Institutional Guidelines

Omentectomy was performed in 42 (77.8%) of 54 patients with serous EC, 17 (94.4%) of 18 with clear cell EC, and 29 (69%) of 42 patients with mixed histology with a serous or clear cell component. For patients who received postoperative chemotherapy alone (67.4%), the following chemotherapy regimens were administered: paclitaxel/carboplatin (TC) (n = 79), paclitaxel/epirubicin/carboplatin (TEC) (n = 61), epirubicin/carboplatin (n = 1), cisplatin/paclitaxel (n = 1), and carboplatin single (n = 4). Mean number of cycles was 5.5, and 80.7% of the patients received 6 cycles.

Compliance with institutional guidelines related to FIGO stage is shown in Table 2. In stage I, 16% were not staged, and
31% did not receive any adjuvant treatment. In stage II, 21% were not staged, and 60% did not receive any adjuvant treatment. In stage IIIC, 10% did not receive adjuvant treatment.

Clinical Outcome of Patients Treated According to Institutional Guidelines

Of the 230 patients, 146 (63.5%) received treatment according to institutional guidelines with at least pelvic lymphadenectomy and adjuvant chemotherapy with a median age at diagnosis of 67 years (range, 35–84 years).

In total, 37 patients (25.3%) had a recurrence (Table 3). In stage I, 6 patients had a recurrence (10%), with 2 (3.3%) isolated recurrences either in the vagina or in the pelvis and 4 (6.7%) distant failures. Three of the distant recurrences involved distant sites only (2 patients with lung metastases, 1 with recurrence in the upper abdomen). In stage II, only 1 patient (10%) had a recurrence, with extrapelvic disease. In stage III, 30 patients (39.5%) had a recurrence, 6 (7.9%) with recurrence isolated in the vagina and 24 (31.6%) with distant disease. Of the distant metastases, only 2 were restricted to the para-aortic lymph nodes, and 2 were distant metastases only, whereas the remaining vast majority developed both distant and pelvic/vaginal metastases. The 3-year DFS was 92% for stage I (95% CI, 79%–97%), 80% (95% CI, 41%–95%) for stage II, and 60% (95% CI, 48%–70%) for stage IIIC disease (Fig. 1). The 3-year OS was 98% for stage I (95% CI, 87%–100%), 80% for stage II (95% CI, 41%–95%), and 83% (95% CI, 73%–90%) for stage IIIC.

The localization of recurrence in patients with stage IIIC disease was further analyzed according to histological subtype. Both frequency and localization of relapse seem to differ by histological subtype, although the differences did not reach statistical significance. In patients with grade 1/2 endometrioid EC (n = 28), 8 (28.6%) had a recurrence, half of them in the vagina only. In grade 3 endometrioid or type II EC (n = 43) 19 patients (44.2%) had a recurrence (P = 0.154). One patient had a recurrence in the vagina only, and 1 had a recurrence restricted to the para-aortic lymph nodes. The remaining vast majority developed distant disease. The 3-year DFS was 71% (95% CI, 50%–84%) for grade 1/2 endometrioid tumors compared with 54% (95% CI, 38%–68%) for patients with grade 3/type II tumors. The 3-year OS for grade 1/2 tumors was 92% (95% CI, 73%–98%) and 76% (95% CI, 60%–86%) for grade 3/type II EC tumors.

### TABLE 2. Compliance with institutional guidelines by stage of disease

| Surgical Treatment | Adjuvant Treatment | Stage I (n = 98), n (%) | Stage II (n = 42), n (%) | Stage III (n = 90), n (%) |
|--------------------|--------------------|-------------------------|-------------------------|-------------------------|
|                    | CT                 | 60 (66.7)               | 10 (23.8)               | 76 (84.4)               |
|                    | RT                 | 2 (2.2)                 | 3 (7.1)                 | 2 (2.2)                 |
|                    | CT + RT            | 0                       | 0                       | 1 (1.1)                 |
|                    | No adjuvant treatment | 20 (21.7)             | 20 (47.6)               | 9 (10)                  |
|                    | CT                 | 6 (6.7)                 | 1 (2.4)                 | 2 (2.2)*                |
|                    | RT                 | 0                       | 2 (4.8)                 | 0                       |
|                    | CT + RT            | 0                       | 1 (2.4)                 | 0                       |
|                    | No adjuvant treatment | 10 (11.1)            | 5 (11.9)                | 0                       |

*Not completely staged, but both patients had 1 metastatic lymph node removed, 1 pelvic and 1 para-aortic, respectively.

CT, chemotherapy; RT, radiotherapy.

### TABLE 3. Frequency and localization of relapse in patients treated with at least pelvic lymphadenectomy and adjuvant chemotherapy (n = 146)

| Stage | No. Patients | Vagina | Pelvis | Extrapelvic | Total No. Relapses (%) |
|-------|--------------|--------|--------|-------------|------------------------|
| Ia    | 35           | 0      | 1      | 2           | 3 (8.6)                |
| Ib    | 25           | 1      | 0      | 2           | 3 (12)                 |
| II    | 10           | 0      | 0      | 1           | 1 (10)                 |
| IIIc  | 76           | 6      | 0      | 24          | 30 (39.5)              |
| G1/G2 | 28           | 4      | 0      | 4           | 8 (28.6)               |
| G3/type II | 43     | 1      | 0      | 18          | 19 (44.2)              |
| All stages | 146      | 7      | 1      | 29          | 37 (25.3)              |
Clinical Outcome of Patients After Surgical Treatment Only

In our cohort, 49 patients underwent pelvic lymphadenectomy but did not receive adjuvant chemotherapy. The reasons, when given in the medical records, mainly included complicating comorbidities or age. These patients were consequently considered unfit for any adjuvant treatment. Four patients refused all further treatment. A total of 19 patients (38.8%) had a recurrence (Table 4). Isolated vaginal recurrence occurred in 12 (24.5%), pelvic recurrence in 2 (4.1%), and extrapelvic disease in 5 (10.2%) of these patients. The 3-year overall DFS and OS were 45% (95% CI, 30%–59%) and 71% (95% CI, 55%–81%), respectively.

Clinical Outcome of the Whole Cohort

In the whole study cohort, 68 patients (29.6%) had a recurrence. Recurrences were localized in the vagina in 9.6% (22/230), in the pelvis in 1.7% (4/230), and extrapelvic in 18.3% (42/230) of the patients (Table 5). The 3-year DFS was 79% for stage I (95% CI, 69%–86%), 54% (95% CI, 38%–68%) for stage II, and 55% for stage IIIc (95% CI, 44%–65%) (Fig. 2).

DISCUSSION

Our institutional approach of adjuvant chemotherapy only to patients with high-risk EC yields acceptable DFS and OS. In particular, we observed very few local or locoregional recurrences. Nevertheless, the prognosis of node-positive patients remains poor, also after chemotherapy. It seems that patients with stage IIIC disease of endometrioid type with poor differentiation or type II histology were at particularly high risk of distant recurrence and death despite chemotherapy.

The treatment for patients with high-risk EC still needs to be improved. Although several studies have attempted to identify the best approach, interstudy comparison is hampered by the diversity in patient population. The majority of studies are of nonrandomized design with heterogeneous treatment regimens applied. Our institutional guidelines are building on the fact that no study to date has provided evidence that adjuvant RT increases survival. The PORTEC-3 study reported significant improvement in 5-year failure-free survival from 68.6% to 75.5%, mainly driven by the positive results in stage III disease. Besides the improvement in locoregional control, no survival benefit could be demonstrated in any subgroup. The GOG-258 study included more advanced disease and could not detect any significant improvement of DFS when chemoradiation was added to chemotherapy. Rather, concerns exist regarding toxicity especially when combined with chemotherapy and also regarding the increased risk of secondary malignancy. On the other hand, the risk of locoregional relapse may be higher when RT is omitted, with reported relapse rates as high as 39% after chemotherapy only in patients with optimally resected stage III disease, with half of them being located in the pelvis/vagina. Brachytherapy, which is associated with less toxicity, may be sufficient to prevent vaginal relapse in some patients. The recently released ESGO guidelines still recommend administration of RT despite the lack of benefit for survival and regard brachytherapy as an alternative for node-negative high-risk stage I and selected stage II patients. Our rates of vaginal/pelvic recurrence of 3% in stage I and 8% in stage IIIc after chemotherapy were low compared with these reports. Our figures are comparable to or lower than those reported after

| Stage | No. Patients | Vagina | Pelvis | Extrapelvic | Total No. Relapses (%) |
|-------|--------------|--------|--------|-------------|------------------------|
| Ia    | 13           | 3      | 1      | 0           | 4 (30.8)               |
| Ib    | 7            | 0      | 0      | 0           | 0                      |
| II    | 20           | 7      | 1      | 3           | 11 (47.8)              |
| IIIc  | 9            | 2      | 0      | 2           | 4 (36.4)               |
| All stages | 49    | 12     | 2      | 5           | 19 (38.8)              |
pelvic radiation, with locoregional recurrences in 7% to 16% of their patients.\textsuperscript{4,16} There is evidence that vaginal/pelvic recurrences can be cured with RT once they occur, although this has been shown only for patients with early-stage disease.\textsuperscript{13,16} Our excellent survival rates in patients with stage I disease may support this. Another argument for reserving RT for patients with recurrent disease is the fact that RT will not prevent all locoregional relapses. Thus, if these patients are irradiated upfront, relapses may then be hard to cure.

The vast majority of recurrences in our study sample were distant metastases despite chemotherapy, which is in line with previous reports on high-risk early-stage and stage IIIC EC.\textsuperscript{6,11,17} The poor survival of patients with positive lymph nodes at the time of diagnosis despite treatment with chemotherapy highlights the need for improved systemic treatment strategies in these patients.

Intensification of the regimen by combining chemotherapy and radiation did not improve survival but rather increased toxicity\textsuperscript{7,8} and may lead to lower completion rates, especially of the chemotherapy component.\textsuperscript{6} In our cohort, completion rate of chemotherapy was high, favoring the administration of only 1 modality. The fact that a considerable proportion of patients in our study did not receive the institutional standard treatment is in line with recent reports from the Dutch Cancer Registry where compliance of physicians to adjuvant therapy guidelines was remarkably low, particularly in patients with high-risk disease.\textsuperscript{18} The poor outcome of patients with stage II disease is worrying and highlights the importance of compliance to treatment guidelines. Toxicity is obviously a concern in patients with high-risk EC who often belong to an elderly, comorbid patient population mainly due to limited data on chemotherapy tolerance in these patients. In line with the ESGO guidelines, brachytherapy may be discussed with selected patients unfit for systemic therapy, but the benefit for local control only needs to be balanced against careful observation with treatment at the time of relapse.

Our subgroup analysis according to histology confirmed the particular aggressive behavior of type II and poorly differentiated endometrioid tumors.\textsuperscript{19} There are evolving data on the molecular subtypes of EC underlining the heterogeneity and overlapping profiles in types I and II EC. Copy-number-high tumors have been pointed out as a group with high prevalence of p53 mutation and poor prognosis in several data sets.\textsuperscript{20,21} Understanding the molecular drivers in high-risk patients may eventually enable us to develop targeted treatment options.

The strength of this study is the pathological review of all cases at the time of diagnosis by a pathologist specialized in gynecologic pathology (B.D.). Our hospital is the referral center for patients with relapsed disease in the region, and we are therefore confident that our follow-up data for recurrence are complete. The study is limited by its retrospective design and the low number of patients available for analysis when the cohort is broken down to subgroups. A variety of adjuvant treatment was given, and a variety of chemotherapy regimens were applied, but the vast majority included a platinum-paclitaxel combination, which is considered standard of care for this patient group.\textsuperscript{10} The analysis by histological subtype of lymph node–positive patients is hampered by small numbers and precludes definite conclusions.

In light of the acceptable pelvic recurrence rates, adjuvant treatment with chemotherapy alone seems safe. Rather than intensifying current treatment with radiation, there is an urgent need for prospective studies evaluating novel treatment strategies for patients with high-risk EC. Molecular validation studies with comprehensive clinical data will be necessary to identify patients at truly high risk of relapse.

**REFERENCES**

1. Lindemann K, Eskild A, Vatten LJ, et al. Endometrial cancer incidence trends in Norway during 1953–2007 and predictions for 2008–2027. *Int J Cancer*. 2010;127:2661–2668.

---

TABLE 5. Frequency and localization of relapse in all patients (n = 230)

| Stage | No. Patients | Vagina | Pelvis | Extrapelvic | Total No. Relapses (%) |
|-------|--------------|--------|--------|-------------|------------------------|
| Ia    | 55           | 4      | 2      | 5           | 11 (20)                |
| Ib    | 43           | 2      | 0      | 2           | 4 (9.3)                |
| II    | 42           | 8      | 2      | 5           | 15 (35.7)              |
| IIc   | 90           | 8      | 0      | 30          | 38 (42.2)              |
| All stages | 230 | 22 | 4 | 42 | 68 (29.6) |

**FIGURE 2.** Kaplan-Meier estimates of DFS by FIGO stage in all patients (n = 230).
2. 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.

3. 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.

4. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer*. 2006;95:266–271.

5. Kuoppala T, Maenpaa J, Tomas E, et al. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. *Gynecol Oncol*. 2008;110:190–195.

6. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. *Eur J Cancer*. 2010;46:2422–2431.

7. Matei D, Filiaci VL, Randall M, et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. *J Clin Oncol*. 2017;35(suppl 15):5505–5505.

8. De Boer SM, Powell ME, Milesklinik LR, et al; PORTEC Study Group. Final results of the international randomized PORTEC-3 trial of adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer. *J Clin Oncol*. 2017;35(suppl; abstr 5502).

9. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:16–41.

10. Colombo N, Preti E, Landoni F, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24.

11. Secord AA, Geller MA, Broadwater G, et al. A multicenter evaluation of adjuvant therapy in women with optimally resected stage IIIC endometrial cancer. *Gynecol Oncol*. 2013;128:65–70.

12. Vargo JA, Kim H, Houser CJ, et al. Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification. *Radiother Oncol*. 2014;113:126–131.

13. Ortoft G, Hansen ES, Bertelsen K. Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: the Danish Endometrial Cancer Study. *Int J Gynecol Cancer*. 2013;23:1429–1437.

14. Pecorelli S, Zigliani L, Odicino F, et al. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105:103–104.

15. Onsrud M, Cvanarova M, Hellebust TP, et al. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. *J Clin Oncol*. 2013;31:3951–3956.

16. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81:e631–e638.

17. Randall ME, Spirtos NM, Dvoretsky P. Whole abdominal radiotherapy versus combination chemotherapy with doxorubicin and cisplatin in advanced endometrial carcinoma (phase III): Gynecologic Oncology Group study no. 122. *J Natl Cancer Inst Monogr*. 1995:13–15.

18. Eggink FA, Mom CH, Boll D, et al. Compliance with adjuvant treatment guidelines in endometrial cancer: room for improvement in high risk patients. *Gynecol Oncol*. 2017;146:380–385.

19. Bakkum-Gamez JN, Mariani A, Dowdy SC, et al. Efficacy of contemporary chemotherapy in stage IIIC endometrial cancer: a histologic dichotomy. *Gynecol Oncol*. 2014;132:578–584.

20. Kandoth C, Schultz N, Cherniack AD, et al; Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497:67–73.

21. Le Gallo M, Bell DW. The emerging genomic landscape of endometrial cancer. *Clin Chem*. 2014;60:98–110.