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Clinical outcome of patients with high-risk endometrial carcinoma after treatment with chemotherapy only

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Key Words: Endometrial cancer, high-risk, adjuvant chemotherapy, radiotherapy, recurrence, survival

Highlights

- Adjuvant chemotherapy without radiation yields acceptable disease free- and overall survival
- Very few local or loco-regional recurrences detected despite omission of radiotherapy
- Prognosis remains poor for patients with node-positive disease

PRECIS

Surgery followed by chemotherapy only for high-risk endometrial cancer yields acceptable disease free- and overall survival, with few loco-regional recurrences.

ABSTRACT

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/Materials: This is a retrospective study including 230 EC patients with FIGO stage I type II, Ib type I/G3, stage II and IIIc treated at the Oslo University Hospital between 2005-2012. Standard treatment was hysterectomy, bilateral salphingo-ooforectomy and at least pelvic lymphadenectomy followed by adjuvant chemotherapy.

Results: Of the 230 high-risk patients 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% loco-regional 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 DFS was 92% for stage I, 80% for stage II and 60% for stage IIIc disease. In the total population, 55 patients had FIGO stage Ia, 43 Ib, 42 stage II, and 90 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.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in the Western world. The continuously increasing incidence in Western countries is mostly attributable to the increase in prevalence of risk factors in the population such as obesity and diabetes[1]. Patients with early stage disease often have excellent prognosis, with a 10-year overall survival rate exceeding 80%. Still, there are subgroups with a high risk for occult micro-metastatic disease. Traditionally, endometrial cancers 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 overall survival (OS) for this group of patients after chemotherapy compared to whole abdominal irradiation (WAI) in patients with stage III and IV endometrial cancer[2]. Since then, several randomized studies have tried to clarify the role of adjuvant chemotherapy in endometrial cancer. Three subsequent studies compared combination chemotherapy with adjuvant radiation to the pelvis in patients with early stage high-risk or advanced stage disease. All three 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 that may benefit from either of the treatment modalities.

In a pooled analysis of two 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 while 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 stage III and IV[7]. The randomized Portec 3 study randomized patients in stage 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 overall survival[8]. Despite these studies, newly released ESGO guidelines[9,10] advocate for the administration of adjuvant radiotherapy 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 radiotherapy[12] and the omission of adjuvant radiotherapy 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 stage I/II and IIIC EC have since 2005 therefore routinely been treated with chemotherapy only, omitting radiotherapy. Here we report the oncological outcomes of this treatment policy.

MATERIAL AND METHODS

Patients and follow-up

This is an institutional retrospective study of a cohort of all endometrial cancer patients, treated at the 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 work-up, comorbidity, surgical treatment, adjuvant treatment, incident relapse and localization of relapse. All specimens underwent central histopathological 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 ≥ 50%, (2) FIGO stage I serous and clear cell endometrial cancer (pure or mixed with at least 50% serous or clear cell component) of any myometrial invasion, (3) endometrial cancer with cervical stromal invasion of any histology (FIGO stage II) and (4) lymph node positive endometrial cancer of any histology (FIGO stage IIIc). Patients with positive lymph nodes were further analyzed according to histological subtype (grade 1 or 2 endometrioid adenocarcinoma versus

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 three months during the first two years, every six months for the following three years, and then annually at Oslo University Hospital or their local hospital. Visits included thorough clinical examination and vaginal ultrasound, supplemented by CT or MR scan on clinical indication.

Statistical analyses

Continuous variables were descried 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 the chi^2 test.

For disease-free survival (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 overall survival (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 disease-free survival and 3 year overall survival with 95% confidence intervals (CI). All estimates were calculated for the cohort as a whole, and separately for the groups that received and not received adjuvant chemotherapy. For patients with stage IIIc disease, analyses were conducted according to histological subtype (grade 1/2 endometrioid EC versus 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, (Stata Corp LP, Texas, USA).

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

Adherence to institutional guidelines

Omentectomy was performed in 42/54 (77.8%) of patients with serous EC, 17/18 (94.4%) with clear cell EC and 29/42 (69%) of 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), epirubicin single (n=1) and carboplatin single (n=4). Mean number of cycles was 5.5 and 80.7% of the patients received six 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 (25.3%) patients recurred (Table 3). In stage I 6 patients recurred (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 (two patients with lung metastases, one with recurrence in the upper abdomen). In stage II, only one patient (10%) recurred, with extra pelvic disease. In stage III, 30 (39.5%) patients recurred, 6 (7.9%) with recurrence isolated in the vagina and 24 (31.6%) with distant disease. Of the distant metastases only two were restricted to the para-aortic lymph nodes, two were distant metastases only while 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. 1a). 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 histologic 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%) recurred, half of them in the vagina only. In grade 3 endometrioid or type II EC (n=43) 19 (44.2%) patients recurred (p=0.154). One patient recurred in the vagina only and one 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 to 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.

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%) recurred (table 4). Isolated vaginal recurrence occurred in 12 (24.5%), pelvic recurrence in 2 (4.1%) and extra-pelvic disease in 5 (10.2%) of these patients. The 3-year overall DFS and OS was 45% (95% CI: 30-59%) and 71% (95% CI: 55-81%), respectively.

Clinical outcome of the whole cohort

In the whole study cohort 68 (29.6%) patients recurred. Recurrences were localized in the vagina in 9.6% (22/230), in the pelvis in 1.7% (4/230) and extra-pelvic 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. 1b).
Sixty-five patients died during follow-up, and the 3-year overall survival (OS) was 85% for stage I (95% CI: 75-91%), 78% for stage II (95% CI: 63-88%) and 78% (95%CI: 68-85%) for stage IIIc.

DISCUSSION

Our institutional approach of adjuvant chemotherapy only to patients with high-risk endometrial cancer yields acceptable disease free- and overall survival. In particular we observed very few local or loco-regional 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 endometrial cancer still needs to be improved. Although several studies have attempted to identify the best approach, inter-study comparison is hampered by the diversity in patient population. The majority of studies are of non-randomized 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 III 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 loco-regional control, no survival benefit could be demonstrated in any subgroup[8] . The GOG 258 study included more advanced disease and could not

detect any significant improvement of DFS when chemoradiation was added to chemotherapy[7]. Rather, concerns exist regarding toxicity[6] especially when combined with chemotherapy and also regarding the increased risk of secondary malignancy[15]. On the other hand, the risk of loco-regional relapse may be higher when radiotherapy is omitted with reported relapse rates as high as 39% after chemotherapy only in patients with optimally resected stage III disease[11] 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[12]. The recently released ESGO guidelines[9,10] still recommend administration of radiotherapy 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 to these reports. Our figures are comparable to or lower than those reported after pelvic radiation, with loco-regional recurrences in 7-16% of their patients[4,16]. There is evidence that vaginal/pelvic recurrences can be cured with radiotherapy once they occur, although this has only been shown for patients with early stage disease[13,16]. Our excellent survival rates in patients with stage I disease may support this. Another argument for reserving radiotherapy for patients with recurrent disease is the fact that RT will not prevent all loco-regional relapses. So 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 endometrial cancer[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[7,8] and may lead to lower completion rates, especially of the chemotherapy component[6]. In our cohort, completion rate of chemotherapy was high favoring the administration of only one 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 were remarkably low, particularly in patients with high risk disease[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[19]. There is evolving data on the molecular subtypes of endometrial cancer underlining the heterogeneity and overlapping profiles in type 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[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 diversity of adjuvant treatment were 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[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 endometrial cancer. Molecular validation studies with comprehensive clinical data will be necessary to identify patients at truly high risk of relapse.

INTRODUCTION

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DISCUSSION

Our institutional approach of adjuvant chemotherapy only to patients with high-risk endometrial cancer yields acceptable disease free- and overall survival. In particular we observed very few local or loco-regional 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 endometrial cancer still needs to be improved. Although several studies have attempted to identify the best approach, inter-study comparison is hampered by the diversity in patient population. The majority of studies are of non-randomized 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 III 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 loco-regional control, no survival benefit could be demonstrated in any subgroup[8] . The GOG 258 study included more advanced disease and could not

detect any significant improvement of DFS when chemoradiation was added to chemotherapy[7]. Rather, concerns exist regarding toxicity[6] especially when combined with chemotherapy and also regarding the increased risk of secondary malignancy[15]. On the other hand, the risk of loco-regional relapse may be higher when radiotherapy is omitted with reported relapse rates as high as 39% after chemotherapy only in patients with optimally resected stage III disease[11] 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[12]. The recently released ESGO guidelines[9,10] still recommend administration of radiotherapy 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 to these reports. Our figures are comparable to or lower than those reported after pelvic radiation, with loco-regional recurrences in 7-16% of their patients[4,16]. There is evidence that vaginal/pelvic recurrences can be cured with radiotherapy once they occur, although this has only been shown for patients with early stage disease[13,16]. Our excellent survival rates in patients with stage I disease may support this. Another argument for reserving radiotherapy for patients with recurrent disease is the fact that RT will not prevent all loco-regional relapses. So 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 endometrial cancer[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[7,8] and may lead to lower completion rates, especially of the chemotherapy component[6]. In our cohort, completion rate of chemotherapy was high favoring the administration of only one 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 were remarkably low, particularly in patients with high risk disease[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[19]. There is evolving data on the molecular subtypes of endometrial cancer underlining the heterogeneity and overlapping profiles in type 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[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 diversity of adjuvant treatment were 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[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 endometrial cancer. Molecular validation studies with comprehensive clinical data will be necessary to identify patients at truly high risk of relapse.

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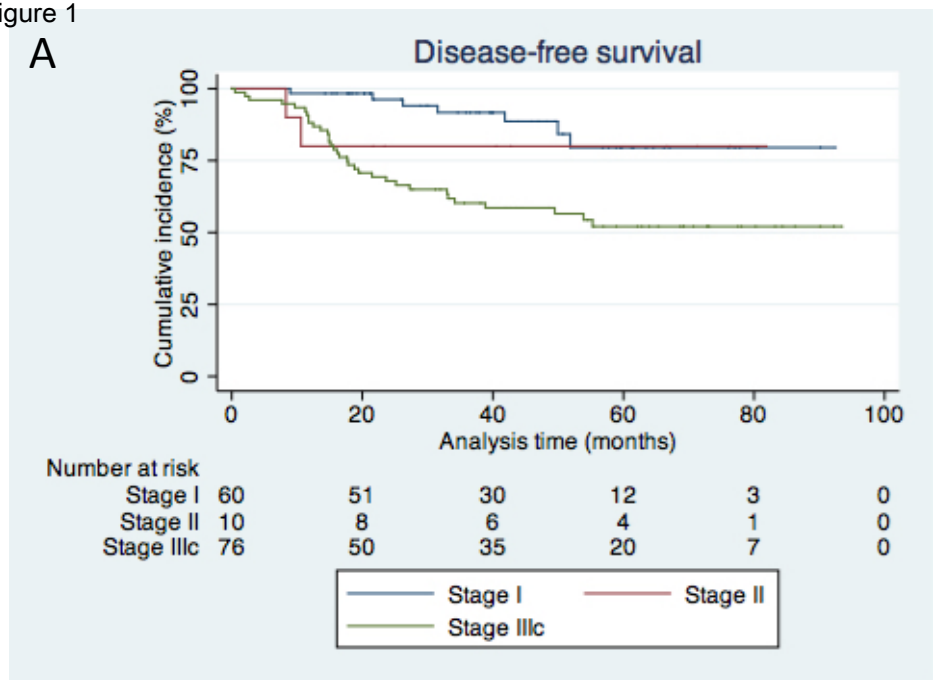
Figure legends

Figure 1a: Kaplan Meier estimates of disease-free survival by FIGO stage in patients treated with at least pelvic lymphadenectomy and adjuvant chemotherapy (N=146)

Figure 1b: Kaplan Meier estimates of disease-free survival by FIGO stage in all patients (N=230)

Figure 1


A
Disease-free survival
Cumulative incidence (%)
0
25
50
75
100
0
20
40
60
80
100
Analysis time (months)
Number at risk
Stage I 60 51 30 12 3 0
Stage II 10 8 6 4 1 0
Stage IIIc 76 50 35 20 7 0
Stage I
Stage II
Stage IIIc

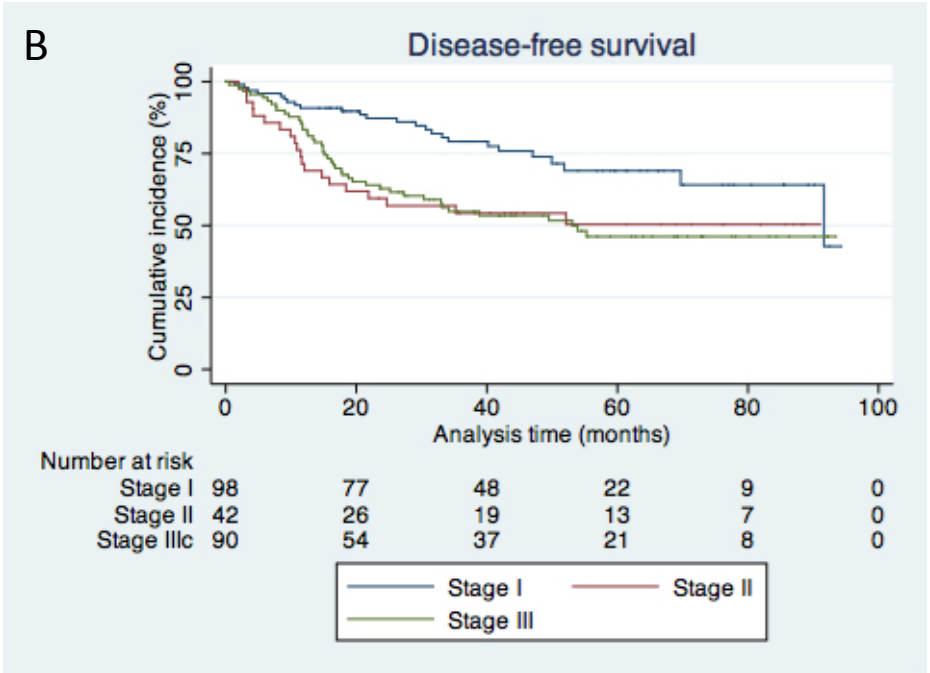

B
Disease-free survival
Cumulative incidence (%)
0
25
50
75
100
0
20
40
60
80
100
Analysis time (months)
Number at risk
Stage I 98 77 48 22 9 0
Stage II 42 26 19 13 7 0
Stage IIIc 90 54 37 21 8 0
Stage I
Stage II
Stage III

Table 1: Baseline characteristics (N=230)

Patient characteristic	**Median (range)**
Age	69 (36-89)
	No of 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 paraaortic 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)
Adjuvant treatment	
No adjuvant treatment	64 (27.8)

Radiotherapy	9 (3.9)
Chemotherapy	155 (67.4)
RT+CT	2 (0.9)

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

Table 2: Compliance with institutional guidelines by stage of disease

Surgical treatment	Adjuvant treatment	Stage I n=98 (%)	Stage II n=42 (%)	Stage III n=90 (%)
Staged	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)
Not staged	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

Abbreviations: CT=Chemotherapy, RT=Radiotherapy

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

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

Stage	**No of patients**	**Localization of relapse**			**Total no of relapses (%)**
		Vagina	**Pelvis**	**Extra-pelvic**	
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)

Table 4. Frequency and localization of relapse in patients treated with at least pelvic lymphadenectomy without adjuvant chemotherapy (n=49)

Stage	**No of patients**	**Localization of relapse**			**Total no of relapses (%)**
		Vagina	**Pelvis**	**Extra-pelvic**	
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)

Table 5: Frequency and localization of relapse in all patients (n=230)

Stage	No of patients	Localization of relapse			Total no of relapses (%)
		Vagina	Pelvis	Extra-pelvic	
Ia	55	4	2	5	11 (20)
Ib	43	2	0	2	4 (9.3)
II	42	8	2	5	15 (35.7)
IIIc	90	8	0	30	38 (42.2)
All stages	230	22	4	42	68 (29.6)