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Aloisi, Alessia

Casanova, Joao

Tseng, Jill

et al.

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PATTERNS OF FIRST RECURRENCE OF STAGE IIIC1 ENDOMETRIAL CANCER WITH NO PARAAORTIC NODAL ASSESSMENT

Alessia Aloisi[a], **João Miguel Casanova**[a,1], **Jill H. Tseng**[a,2], **Kristina A. Seader**[a,3], **Nancy Thi Nguyen**[a,4], **Kaled M. Alektiar**[a,b], **Vicky Makker**[a,b], **Sarah Chiang**[a], **Robert A. Soslow**[a,b], **Mario M. Leitao Jr.**[a,b], and **Nadeem R. Abu-Rustum**[a,b]

[a]Memorial Sloan Kettering Cancer Center, New York, NY

[b]Weill Cornell Medical College, New York, NY

[1]Current Affiliation: Gynecologic Oncology Unit, Champalimaud Clinical Center, Lisbon, Portugal

[2]Current Affiliation: University of California Irvine, Irvine, CA

[3]Current Affiliation: Newark Beth Israel Medical Center, Newark, NJ

[4]Current Affiliation: Kaiser Permanente, Department of Obstetrics and Gynecology, Oakland, CA

Abstract

Objective: To assess the rates and distribution of first recurrence in patients with FIGO stage IIIC1 endometrial cancer (EC) who did not undergo paraaortic dissection at surgical staging.

Corresponding Author: Nadeem R. Abu-Rustum, MD , Chief, Gynecology Service , Vice Chair for Technology Development, Department of Surgery , Avon Chair in Gynecologic Oncology , Memorial Sloan Kettering Cancer Center , 1275 York Avenue , New York, NY 10065, USA , Phone: 212-639-7051 , abu-rusn@mskcc.org.

Author Contributions:

Alessia Aloisi: Data collection; interpretation of data and statistics; writing of manuscript; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Joao Miguel Casanova: Data collection; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Jill H. Tseng: Interpretation of data and statistics; approval of version to be submitted.

Kristina A. Seader: Data collection; approval of version to be submitted.

Nancy Thi Nguyen: Writing of manuscript; approval of version to be submitted.

Kaled M. Alektiar: Interpretation of data; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Vicky Makker: Interpretation of data; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Sarah Chiang: Interpretation of data; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Robert A. Soslow: Interpretation of data; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Mario M. Leitao, Jr.: Interpretation of data and statistics; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Nadeem R. Abu-Rustum: Interpretation of data; critical revision of manuscript for important intellectual content; approval of version to be submitted.

Conflict of interest statement: None of the authors declare conflicts of interest.

Methods: We retrospectively selected all (n=207) stage IIIC1 patients treated at a single institution from 5/1993–1/2017. Sites of first recurrence were identified, disease-free (DFS) and overall survival (OS) calculated, multivariate logistic regression performed to identify factors associated with recurrence.

Results: Three-year DFS and OS were 66.5% and 85.7%, respectively. The most common histology was endometroid (64.2%). Three-year DFS was 81% (SE+/−3.8%) endometrioid vs. 39.5% (SE+/−6.6%) non-endometrioid (P<0.001). Three-year OS was 96.9% (SE+/−1.8%) endometrioid vs. 65.6% (SE+/−6.7%) non-endometrioid (P<0.001). Sixty-two (30.1%) patients recurred. Patterns of recurrence were: 14 (8.3%) multiple sites, 17 (8.2%) abdominal, 14 (6.8%) extra-abdominal, 17 (8.3%) isolated nodal (8 of these (3.9%) paraaortic). Patients with isolated tumor cells (ITCs) in lymph nodes only had 12/71 (17%) recurrence rate vs. 50/135 (37%) for patients with micro- /macrometastasis. On univariate analysis, grade (HR 4.67 95%CI 1.5–14.5, P=0.008), histology (HR 4.9 95%CI 2.6–9.3, P<0.001), myometrial invasion (HR 1.9 95%CI 1.043.5, P=0.04), pelvic washing (HR 2.2 95%CI 1.1–4.5, P=0.03), tumor volume in pelvic LNs (ITC vs. micro-/macrometastasis; HR 0.3 95%CI 0.2–0.7, P=0.003) were associated with recurrence. On multivariate analysis, only histology was associated with recurrence

(HR 7.88 95%CI 3.43–18.13, P<0.001).

Conclusions: Isolated paraaortic recurrence in stage IIIC1 EC is uncommon. Micro/macrometastasis were associated with twice the recurrence rate compared to ITC. These data will help clinicians counsel patients with stage IIIC1 EC regarding paraaortic assessment.

Keywords

: Endometrial cancer; recurrence; Stage IIIC1; isolated tumor cells; ITC

BACKGROUND

Endometrial cancer is the most common gynecologic malignancy in the United States, with 63,230 new cases and 11,350 deaths anticipated in 2018 [1]. Surgical staging of endometrial cancer typically includes a total hysterectomy, bilateral salpingooophorectomy, and lymph node dissection with either sentinel node mapping or removal of pelvic and/or paraaortic lymph nodes. Lymph node metastases can be found in approximately 10% of women with apparent uterine-confined disease, resulting in approximately 25% poorer overall survival (OS) [2,3]. Lymphadenectomy poses a significant risk of surgery-related morbidities, such as vascular or nerve injury, or lymphedema/lymphocele formation. However, upstaging to Stage IIIC with positive pelvic or paraaortic lymph nodes can influence decisions about adjuvant treatments that can be tailored according to the pathologic findings at surgery [4–6].

The role of paraaortic lymphadenectomy in staging is controversial [7]. Truly isolated paraaortic node metastasis occurs in only about 3% of women undergoing staging for endometrial cancer [2,8]. Currently, there is a lack of international guideline consensus (ACOG, SGO, NCCN, ESMO-ESGO-ESTRO) on how to best assess pelvic lymph nodes (elective omission, sampling with sentinel lymph node biopsy, or systematic

lymphadenectomy). Additionally, there is limited guidance on the role and necessity of paraaortic evaluation at the time of pelvic lymphadenectomy.

It is well documented that pelvic lymph node metastases are an important marker of paraaortic involvement. There will be paraaortic nodal metastases in 50–60% of women who have pelvic nodal metastases, and some have proposed that this information be used as a parameter when tailoring adjuvant therapy [8]. However, there is very limited data on patterns of disease recurrence in the setting of positive pelvic lymph nodes (FIGO stage IIIC1 disease) when paraaortic lymphadenectomy is not performed. Understanding the recurrence patterns of pelvic lymph node-positive patients can help surgeons decide whether surgical re-staging with paraaortic lymph nodes is really necessary, or if it can be omitted without compromising oncologic outcomes. The purpose of this study was to analyze 1) the rates of first recurrence and its distribution within specific sites, and 2) the clinical outcomes of patients with FIGO stage IIIC1 endometrial cancer who did not undergo paraaortic dissection.

METHODS

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC). We identified all patients with a diagnosis of endometrial cancer who underwent surgical treatment at the Gynecologic Oncology Service of MSKCC, from May 1993 to January 2017. We included all patients with FIGO stage IIIC1 (positive pelvic lymph nodes) who did not undergo any surgical sampling of paraaortic lymph nodes at the time of surgical staging. It was not our practice to return patients to surgery for paraaortic dissection, if the pelvic nodes were found to be positive on final pathology. All patients diagnosed with more advanced disease (FIGO stage IVA or IVB) were excluded from the analysis. For the purposes of this study, we analyzed cases showing any amount of nodal disease, including those with isolated tumor cells (ITCs).

Patients' characteristics (age, BMI, race, CA-125) and perioperative characteristics (type of procedure, conversion rates, uterine size, number and location of pelvic lymph nodes removed) were identified from a review of medical records. We included all identified patients regardless of age, race, type of surgical approach (laparotomy or minimally invasive) or type of lymph node assessment (lymphadenectomy or sentinel lymph node biopsy) in our analysis. All surgeries were performed by fellowship-trained gynecologic oncologists assisted by gynecologic oncology fellows.

All histological characteristics including tumor type, grade, depth of invasion, lymphovascular invasion (LVI), pelvic washing, extent of disease, number and characteristics of the positive pelvic lymph nodes, were identified retrospectively through a review of patients' medical records. Tumor grading was not assigned in the case of serous, clear cell, carcinosarcoma or mixed histotypes, because these are classified as poorly differentiated but are no longer graded by pathologists [9].

All pathologic evaluation was performed by specialized gynecologic pathologists. In patients with successful mapping of at least one sentinel lymph node, the ultrastaging protocol

(previously described by Kim et al.) was used [10]. ITCs were defined as tumor foci ≤ 0.2 mm, or fewer than 200 cells in the nodes. We included only cases in which ITCs were identified on both Hematoxylin and Eosin (H&E) stain and immunohistochemistry (IHC). Micrometastasis was defined as tumor involvement ≤ 2 mm but > 0.2 mm. Macrometastasis was defined as presence of tumor > 2 mm.

In this group of pelvic node-positive endometrial cancer cases, all patients underwent postoperative imaging, usually with computed tomography (CT) of the chest, abdomen, and pelvis. These scans were repeated during the first 3 years of postoperative follow-up, at the discretion of the attending oncologist. All patients' medical records were reviewed until the last identified follow-up at our institution. We determined whether patients received any adjuvant treatment after surgery, including chemotherapy, radiotherapy, hormones, or a combination of those.

Disease-free survival (DFS) was calculated from the date of surgery to the first documented recurrence, or death from disease. OS was calculated from the date of surgery to date of death, or last follow-up. The Kaplan-Meier method was used to estimate DFS and OS, and estimates were compared with the Logrank test. In order to identify potential factors associated with recurrence, we compared patients with disease recurrence (Group 1) to patients without recurrence (Group 2). We also compared recurrence rates for patients with only ITCs versus those with micrometastasis/macrometastasis. Characteristics of patients within the two groups were analyzed using the Chi square test for categorical variables and the Mann-Whitney U Test for continuous variables. Univariate and multivariate logistic regression analyses were performed to identify factors associated with recurrence. Statistical significance was set at P>0.05. Statistical analysis was done using SPSS software.

RESULTS

Four thousand five hundred and thirty-three endometrial cancer patients undergoing initial surgical treatment at our institution were identified. Of these 4533 women, 229 (5%) were diagnosed as having at least FIGO stage IIIC1 disease, and did not undergo surgical assessment of the paraaortic lymph nodes at initial staging. Twenty-two women were excluded from our final analysis due to insufficient data. In all, 207 FIGO stage IIIC1 endometrial cancer patients were included in the final analysis.

Patients' characteristics are reported in Table 1. The median age was 66 years (range, 3189 years). Median BMI was 30.2 kg/m2 (range, 15.1–61.7 kg/m2). The majority of patients were white (N=163; 78.7%). Preoperative CA-125 was assessed in 103 (49.8%) women; the median CA-125 level was 17 U/ml (range, 4–1029 U/ml). A minimally invasive surgical approach was used in 149 (72%) patients, with a conversion rate of 1.9% (n=3). Endometrioid histology was noted in 133 (64.2%) cases; 72 (51.8%) of the endometrioid and mucinous cases were FIGO grade1.

The median number of pelvic lymph nodes removed was 5 (range, 1–34) and the median number of total positive pelvic lymph nodes was 1 (range, 1–11). In 71 (34.3%) patients, ITCs-only were identified in the pelvic lymph nodes; micrometastases were identified in 8

(3.9%) patients. The pattern of distribution of positive pelvic lymph nodes is reported in Table S1. The most common site of pelvic lymph node metastasis was the external iliac (39.4%), and the least common site was the presacral (0.6%).

Information on adjuvant treatment was available for 206 women; 1 patient was lost to follow-up postoperatively (Table 2). Adjuvant therapy was administered to 198 (96.1%) patients. Systemic chemotherapy combined with radiotherapy was used in 141 (68.4%) patients. Overall, 103 patients underwent external beam radiotherapy. Extended field radiation therapy to the paraaortic nodal basin was used in only 8 of these patients, and 3 (37.5%) of the 8 suffered recurrence: 1 extra-abdominal (lung and supradiaphragmatic lymph nodes); 1 isolated pelvic; 1 multisite (lung, spine, pelvic lymph nodes).

Most patients with ITC received adjuvant treatment (2 women did not receive any adjuvant treatment, and were observed). Five patients received chemotherapy only, 53 received chemotherapy with radiation therapy (brachytherapy ± EBRT), and 11 underwent radiotherapy (brachytherapy ± EBRT).

The median postoperative follow-up was 32 months (range, 1–279 months). At last follow-up, 29 (14.1%) patients were alive with recurrent disease, 137 (66.5%) were disease-free, and 40 (19.4%) had died. The overall 3-year DFS and OS were 66.5% (SE +/−3.7%) and 85.7% (SE +/−2.9%), respectively. When stratified by histotype (endometrioid vs. non-endometrioid), the 3-year DFS was 81% (SE +/−3.8%) for endometrioid versus 39.5% (SE +/−6.6%) for non-endometrioid (P<0.001). The 3-yr OS was 96.9% (SE +/−1.8%) for endometrioid versus 65.6% (SE +/−6.7%) for nonendometrioid (P<0.001). When stratified by volume of lymph node metastasis (ITC versus micro-/macrometastasis) the 3-year DFS was 80.6% (SE +/−5.4%) for ITC versus 59.2% (SE +/−4.7%) for micro-/macrometastasis (P=0.003; Figure 1A). The 3-year OS was 94.9% (SE +/−3.6%) for ITC versus 81% (SE +/−3.9%) for micro-/macrometastasis (P=0.026; Figure 1B).

Overall, 62 (30.1%) of 206 patients (30.1%) recurred, with a median disease-free interval of 14.5 months (range, 1–43 months). As shown in Table 3, patients who suffered a recurrence were less likely to have endometroid histotope (P<0.001), and more likely to have a grade 3 tumor (P=0.02), positive pelvic washing (P=0.03), myometrial invasion >50% (P=0.04), or micro-/macrometastasis in the pelvic lymph nodes (P=0.003). There was no difference in disease recurrence with respect to age, BMI, mode of surgery, uterine size, or presence of lymphovascular involvement (LVI). The number of pelvic lymph nodes removed, or the number of positive nodes identified, did not appear to make a difference in the incidence of recurrence.

On univariate analysis, grade 3 (HR 4.67, 95%CI 1.5–14.5, P=0.008), non-endometrioid histology (HR 4.9, 95%CI 2.61–9.33, P<0.001), myometrial invasion >50% (HR 1.92, 95%CI 1.04–3.55, P=0.04), positive pelvic washing (HR 2.21, 95%CI 1.1–4.51, P=0.03), and tumor volume in pelvic lymph nodes (ITC vs. micro-/macrometastasis (HR 0.35, 95%CI 0.17–0.7, P=0.003)) were associated with recurrence. We decided not to include grade in the multivariable analysis because non-endometrioid histotypes (serous, clear cell, mixed, carcinosarcoma) are, by definition, no longer graded [9]; however, had all the non-

endometrioid cases been excluded by our multivariate analysis, it would have constituted a critical bias.

On multivariate logistic regression analysis, the only factor associated with recurrence was histology (endometrioid vs. non-endometrioid), with adjusted HR 5.99, 95%CI 2.7513.06, P<0.001. There was no difference in recurrence with respect to the different types of adjuvant treatments (Table 4).

Patterns of first recurrences are shown in Table 5. Overall, 17 (8.3%) of the 206 patients had isolated lymph nodal recurrence. Only 8 (3.9%) were isolated paraaortic nodal recurrences; 3 (1.5%) were isolated pelvic; 1 (0.5%) was isolated porta hepatis; and in 5 (2.4%) cases, recurrence was identified in both pelvic and paraaortic lymph nodes. Eight (3.9%) patients had local recurrence either in the pelvic soft tissue or in the vaginal cuff. Seventeen (8.3%) patients had multisite recurrence. Twelve (5.8%) had isolated relapse in the lung, 7 (3.4%) in the abdomen, and 1 (0.5%) in the liver.

The characteristics of the 8 patients with isolated paraaortic nodal recurrence were as follows: 2 women had endometrioid G2 endometrial cancer; 1 had endometrioid G1 cancer; 2 had endometrioid G2 cancer; 1 had serous carcinoma; 1 had carcinosarcoma; and 1 patient had endometrial stromal carcinoma. Of these patients, 2 had ITC in pelvic lymph nodes and the remaining patients had macrometastasis.

When stratified by lymph node status, the incidence of recurrence was 17% (n=12/71) in patients with ITC and 37% (n=50/135) in those with micro-/macrometastasis. In the 12 ITC cases that recurred, the primary histologies were as follows: 6 endometrioid (2 cases, grade 1; 2 cases, grade 2; 2 cases, grade 3); 2 carcinosarcoma; 4 serous. Ten of these 12 patients had a biopsy-proven recurrence, and in all cases, it was consistent with the known uterine primary.

DISCUSSION

In the current era of minimally invasive surgery, the main goal of treatment is to achieve the best oncologic results possible, while preventing adverse events and related morbidities that deleteriously impact the patient’s quality of life. These concerns are especially true in endometrial cancer, in which the role of lymphadenectomy--particularly paraaortic lymphadenectomy, and particularly in patients with stage IIIC1 disease who did not have paraaortic dissection at staging--is still a matter of debate.

In stage IIIC disease, the reported 5-year DFS ranges from 54% to 79%, and the 5-year OS ranges from 53.9% to 81.0% [4,6,11–18]. Our results (DFS 66.5%, OS 85.7%) are consistent with previously published outcomes in this cohort of patients. Published 3-year DFS ranges from 53% to 64%, and 3-year OS ranges from 68% to 80.5% [19–21].

In the current study, DFS and OS differed by histology. Endometrioid-type tumors had better DFS and OS compared to non-endometrioid tumors, and the difference was statistically significant. These findings are similar to those of Sueoka et al. [16], who reported a 5-year OS of 90.2% for endometrioid versus 56.7% for non-endometrioid carcinomas. Young et al.

[19] also noted a superior 3-year progression-free survival (PFS) (92.4% vs. 58.0%) and 3-year OS (97.2% vs. 65.8%) for endometrioid versus nonendometrioid carcinomas. Our results are consistent with these reports. However, other reports have failed to detect a prognostic relevance with respect to histological type [12, 13].

The presence of ITC-only was associated with a lower recurrence rate (17%) compared to micro-/macrometastasis (37%). Both DFS and OS were better in patients with ITC-only compared to those with micro-/macrometastasis in pelvic lymph nodes. To our knowledge, this is the largest case series on stage IIIC1 endometrial cancer to focus on the presence of ITC-only. Many would not consider ITC-only to be stage IIIC disease, and there is still debate regarding the significance of ITC-only in the lymph nodes. Smaller studies have also noted better oncologic outcomes in the setting of low-volume nodal metastases, but these studies have included both ITCs and micrometastases in the same category [22–24]. In our analysis, the advantage in oncologic outcome seems to be associated with ITCs and *not* micrometastasis; however, it is important to emphasize that only a small number of patients (n=8) had micrometastasis, limiting our ability to make definitive conclusions. Of interest, we registered some recurrences in patients with ITConly, in a setting in which its clinical/prognostic role and definition remain uncertain. The definition of ITCs must be standardized if we are to gain a better understanding of sentinel lymph node mapping results, and determine optimal treatments. We defined cases as ITC-only if the cells were appreciated on both IHC and on corresponding H&E slides. The 17% recurrence rate we noted in ITC-only cases may also reflect the fact that we did not include IHC-only cases. The identification of ITCs may have implications in outcome and treatment decisions. This will require further investigation.

In the current study, the most common site of positive pelvic lymph nodes on initial surgical staging was in the external iliac area (39.4%), followed by the obturator area (27.6%). These findings are similar to those of previous studies assessing patterns of lymph node metastasis in endometrial cancer [26–28], (although Hirahatake et al. reported that the obturator nodes were the most frequent site of nodal disease) [29]. These patterns of spread can help surgeons focus their efforts on the lymph nodes most likely to be involved by tumor.

The overall rate of recurrence in our study was 30%. This is comparable to the recurrence rates reported in the literature at 3 years (32–49%) and at 5 years (26–44%) in stage IIIC disease [11,14,18–20]. Isolated paraaortic recurrences were uncommon (3.9%). Again, our data appear to be consistent with previous reports on stage IIIC patients, in which relapse in the paraaortic area ranges from 12–20% at 3 years, and from 6–20% at 5 years [4,11,19,20,30].

When stratifying by the type of adjuvant treatment received after surgery, we found no difference in rates of recurrence. Only 8 patients received extended field radiation to the paraaortic area; 3 of these patients recurred but none recurred in the aortic area, so we do not know if adding a paraaortic radiation field would potentially reduce the risk of a paraaortic recurrence. However, in light of the patterns of first recurrence, it seems reasonable to continue focusing adjuvant therapy on both local and distant disease control. In our dataset

the impact of adjuvant therapy could not be conclusively assessed, as the majority of patients received some form of adjuvant therapy.

The strengths of our study include the relatively large cohort of patients available for analysis. The study does have some limitations, including those inherent in any retrospective study. We were not able to compare our cohort to patients who underwent paraaortic node assessment. Thus, we observed the outcomes of patients who underwent pelvic but not paraaortic lymphadenectomy. We did not compare these oncologic outcomes with patients who underwent both pelvic and paraaortic lymphadenectomy (which would have enabled us to do a direct comparison of patterns of recurrence); rather, we compared our results to the literature. However, this study may help delineate recurrence patterns in stage IIIC1 endometrial cancer, and provide data on the true risk of omitting paraaortic lymph nodes that, on initial staging, may have been identified as positive. Lastly, the study was based on data from a single institution, and the results may not be generalizable to all centers. Larger, multicenter, prospective studies will be needed to confirm these results.

In summary, isolated paraaortic recurrence is uncommon (≈4%) in stage IIIC1 endometrial cancer patients who have not undergone paraaortic dissection and have received postoperative adjuvant therapy. Non-endometrioid histology is associated with risk of recurrence. Stage IIIC1 disease with micro- or macrometastasis appears to carry twice the risk of recurrence compared to ITC-only. These data are informative for clinicians who must counsel patients with stage IIIC1 disease regarding paraaortic assessment. The presence of positive pelvic lymph nodes may be sufficient to guide decisions about adjuvant treatment for both pelvic and distant disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics 2018. CA Cancer J Clin 2018;68:7–30. [PubMed: 29313949]
2. 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(8 Suppl):2035–41. [PubMed: 3652025]
3. Lewin SN, Herzog TJ, Barrena Medel NI, Deutsch I, Burke WM, Sun X, et al. Comparative performance of the 2009 International Federation of Gynecology and Obstetrics' staging system for uterine corpus cancer. Obstet Gynecol 2010;116(5):1141–9. [PubMed: 20966700]
4. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY and Pecorelli S: Carcinoma of the corpus uteri. FIGO 26th Annual Report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006;95:S105–43.
5. Creasman W Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009;105:109. [PubMed: 19345353]

6. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev 2017;10:CD007585. [PubMed: 28968482]
7. Soliman PT, Frumovitz M, Spannuth W, Greer MJ, Sharma S, Schmeler KM, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. Gynecol Oncol 2010;119:291–4. [PubMed: 20708226]
8. AlHilli MM, Mariani A. The role of para-aortic lymphadenectomy in endometrial cancer. Int J Clin Oncol 2013;18:193–9. [PubMed: 23412768]
9. Denschlag D, Ulrich U, Emons G. The Diagnosis and Treatment of Endometrial Cancer. Progress and Controversies. Dtsch Arztebl Int 2011;108:571–7.
10. Kim CH, Soslow RA, Park KJ, Barber EL, Khoury-Collado F, Barlin JN, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 2013;23:964–70. [PubMed: 23694985]
11. Gadducci A, Guerrieri ME, Cosio S, Fabrini MG, Laliscia C, Attianese D, et al. Rates, Sites and Times of Recurrence and Clinical Outcome of Endometrial Cancer Patients with Histologically-positive Nodes: An Italian Two-center Retrospective Study. Anticancer Res 2018;38:1695–1703 [PubMed: 29491104]
12. Watari H, Todo Y, Takeda M, Ebina Y, Yamamoto R, Sakuragi N. Lymph-vascular space invasion and number of positive paraaortic node groups predict survival in nodepositive patients with endometrial cancer. Gynecol Oncol 2005;96:651–7. [PubMed: 15721407]
13. Fujimoto T, Nanjyo H, Nakamura A, Yokoyama Y, Takano T, Shoji T, et al. Paraaortic lymphadenectomy may improve disease-related survival in patients with multipositive pelvic lymph node stage IIIc endometrial cancer. Gynecol Oncol 2007;107:253–9. [PubMed: 17640720]
14. Lee LJ, Viswanathan AN. Combined chemotherapy and radiation improves survival for node-positive endometrial cancer. Gynecol Oncol 2012;127:32–7. [PubMed: 22735786]
15. Rajasooriyar C, Bernshaw D, Kondalsamy-Chennakesavan S, Mileshkin L, Narayan K. The survival outcome and patterns of failure in node positive endometrial cancer patients treated with surgery and adjuvant radiotherapy with curative intent. J Gynecol Oncol 2014;25:313–9. [PubMed: 25142629]
16. Sueoka K, Umayahara K, Abe A, Usami T, Yamamoto A, Nomura H, et al. Prognosis for endometrial cancer patients treated with systematic pelvic and para-aortic lymphadenectomy followed by platinum-based chemotherapy. Int J Gynecol Cancer 2015;25:818–26.
17. Bogani G, Cromi A, Serati M, Di Naro E, Donadello N, Casarin J, et al. Chemotherapy reduces para-aortic node recurrences in endometrial cancer with positive pelvic and unknown para-aortic nodes. Int J Gynecol Cancer 2015;25:263–8. [PubMed: 25486102]
18. Chen JR, Chang TC, Fu HC, Lau HY, Chen IH, Ke YM, et al. Outcomes of patients with surgically and pathologically staged IIIA-IVB pure endometrioid type endometrial cancer: a Taiwanese Gynecology Oncology Group (TGOG-2005) retrospective cohort study (A STROBECompliant Article). Medicine (Baltimore) 2016;95:e3330. doi: 10.1097/MD.0000000000003330. [PubMed: 27082583]
19. Young MR, Higgins SA, Ratner E, Yu JB, Mani S, Silasi DA, et al. Adjuvant carboplatin, paclitaxel, and vaginal cuff brachytherapy for stage III endometrial cancer: analysis of outcomes and patterns of recurrence based on pathologic characteristics. Int J Gynecol Cancer 2015;25:431–9. [PubMed: 25621409]
20. Lupe K, D'Souza DP, Kwon JS, Radwan JS, Harle IA, Hammond JA, et al. Adjuvant carboplatin and paclitaxel chemotherapy interposed with involved field radiation for advanced endometrial cancer. Gynecol Oncol 2009;114:94–8. [PubMed: 19406459]
21. Shaikh T, Churilla TM, Mantia-Smaldone GM, Chu C, Rubin SC, Anderson PR. The role of adjuvant radiation in lymph node positive endometrial adenocarcinoma. Gynecol Oncol 2016;141:434–9. [PubMed: 27090796]
22. Holloway RW, Gupta S, Stavitzski NM, Zhu X, Takimoto EL, Gubbi A, et al. Sentinel lymph node mapping with staging lymphadenectomy for patients with endometrial cancer increases the detection of metastasis. Gynecol Oncol 2016;141:206–10. [PubMed: 26905211]

23. Plante M, Stanleigh J, Renaud MC, Sebastianelli A, Grondin K, Grégoire J. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter? Gynecol Oncol 2017;146:240–6. [PubMed: 28577885]

24. St Clair CM, Eriksson AG, Ducie JA, Jewell EL, Alektiar KM, Hensley ML, et al. Low-Volume Lymph Node Metastasis Discovered During Sentinel Lymph Node Mapping for Endometrial Carcinoma. Ann Surg Oncol 2016;23:1653–9. [PubMed: 26714954]

25. Touhami O, Grégoire J, Renaud MC, Sebastianelli A, Plante M. Performance of sentinel lymph node (SLN) mapping in high-risk endometrial cancer. Gynecol Oncol 2017;147:549–53. [PubMed: 28942993]

26. Mariani A, Webb MJ, Keeney GL, Podratz KC. Routes of lymphatic spread: a study of 112 consecutive patients with endometrial cancer. Gynecol Oncol 2001;81:100–4. [PubMed: 11277658]

27. Altay A, Toptas T, Dogan S, Simsek T, Pestereli E. Analysis of Metastatic Regional Lymph Node Locations and Predictors of Para-aortic Lymph Node Involvement in Endometrial Cancer Patients at Risk for Lymphatic Dissemination. Int J Gynecol Cancer 2015;25:657–64. [PubMed: 25647255]

28. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 2017;18:384–92. [PubMed: 28159465]

29. Hirahatake K, Hareyama H, Sakuragi N, Nishiya M, Makinoda S, Fujimoto S. A clinical and pathologic study on para-aortic lymph node metastasis in endometrial carcinoma. J Surg Oncol 1997;65:82–7. [PubMed: 9209518]

30. Klopp AH, Jhingran A, Ramondetta L, Lu K, Gershenson DM, Eifel PJ. Nodepositive adenocarcinoma of the endometrium: outcome and patterns of recurrence with and without external beam irradiation. Gynecol Oncol 2009;115:6–11. [PubMed: 19632709]

HIGHLIGHTS

- Isolated paraaortic recurrence is uncommon in stage IIIC1 endometrial cancer patients not undergoing paraaortic dissection.
- Non-endometrioid histology is associated with risk of recurrence.
- The identification of positive pelvic lymph nodes can guide decisions about adjuvant treatment.

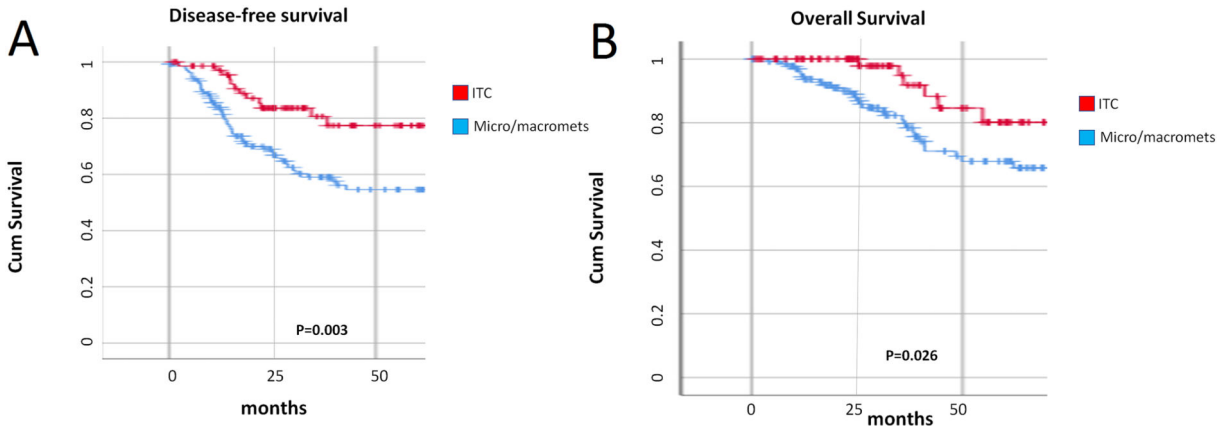

Figure 1.

A) Disease-free survival (in months) in ITC vs. micro-/macrometastasis; **B)** Overall survival (in months) in ITC vs. micro-/macrometastasis

Table 1:

Patients' characteristics (n=207)

Variable	N (%)	
Age (years) Median (range)	66 (31–89)	
Body mass index (kg/m2) Median (range)	30.2 (15.1–61.7)	
Race		
Asian	9	4.3%
Black	19	9.2%
White	163	78.7%
Unknown	16	7.7%
Procedure		
Laparoscopic	34	16.4%
Open	58	28%
Robotic	115	55.6%
Uterine size (gr) Median (range)	137.7 (5–1243)	
Histology		
Endometroid	133	64.2%
Serous	37	17.9%
Carcinosarcoma	21	10.1%
Clear Cell	5	2.4%
Mixed epithelial	5	2.4%
Mucinous	3	1.4%
Other	3	1.4%
Grade *(reported only for endometrioid and mucinous histology)*		
1	72	51.8%
2	47	33.8%
3	20	14.4%
Pelvic Washing		
Negative	148	71.5%
Positive/ suspicious	44	21.3%
Unknown	15	7.2%
LVI *		
No	36	17.4%
Suspicious	1	0.5%
Yes	170	82.1%

Variable	N (%)	
Depth of Invasion		
<50%	97	46.9%
>50%	110	53.1%
Total Positive Pelvic LNs[¥] Median (range)	1 (1–11)	
Total LNs Removed Median (range)	5 (1–34)	
Volume of LN Metastasis		
ITC-only[§]	71	34.3%
Micro-/macrometastasis	136	65.7%

[*] LVI: Lymphovascular invasion

[¥] LN: Lymph node

[§] ITC-only: Isolated tumor cells only

Table 2:

Types of adjuvant treatment (N=206)

TYPE OF ADJUVANT THERAPY	N (%)
Chemotherapy (CT) + /Radiotherapy (RT)	**141[¥] (68.4%)**
CT+ intravaginal RT	55 (26.7%)
CT + EBRT[*]	85 (41.3%)
Chemotherapy alone	**29 (14.1%)**
Radiotherapy alone	**25 (12.1%)**
Intravaginal RT	8 (3.9%)
EBRT[*]	17 (8.3%)
Hormone therapy	**3 (1.5%)**
Hormone alone	1 (0.5%)
Hormone +CT	1 (0.5%)
Hormone+ EBRT	1 (0.5%)
None	**8 (3.9%)**

[*] EBRT: External beam radiotherapy

[¥] In one patient we have no information regarding type of RT

Table 3:

Comparison of groups: Recurrence vs. No recurrence (n=206)

Variable	Group1 (recurrence) N=62 (30%)		Group 2 (no recurrence) N= 144 (70%)		P value
Age (years) Median (range)	67 (43–89)		66 (31–89)		0.3
Body mass index (kg/m2) Median (range)	30 (19.8–52.5)		30.2 (15-61.7)		0.36
Race					
White	44	70.9	118	81.9	
Black	11	17.7	8	5.6	0.005
Asian	0	0	9	6.2	
Hyspanic	0	0	0	0	
Unknown	7	11.3	9	6.2	
Procedure					
Robotic	32	51.6	82	56.9	0.27
Laparoscopic	8	12.9	26	18.1	
Open	22	35.5	36	25	
Uterine size (gr) Median (range)	162 (5–1243)		132 (35-700)		0.21
Histology					
Endometroid	24	38.7	109	75.7	
Serous	20	32.3	17	11.8	<0.001
Clear Cell	1	1.6	3	2.1	
Carcinosarcoma	12	19.3	9	6.2	
Mucinous	1	1.6	2	1.4	
Mixed Epithelial	2	3.2	3	2.1	
Other	2	3.2	1	0.7	
Grade[¥]					
1	9	33.3	63	56.3	
2	10	37.1	37	33	0.02
3	8	29.6	12	10.7	
Positive Washing					
Negative	35	56.4	112	81.2	
Positive/suspicious	18	29	26	18.8	0.03
LVI[*]					
No	6	9.7	30	20.8	0.053
Yes/Suspicious	56	90.3	114	79.2	
Depth of Invasion					

Variable	Group1 (recurrence) N=62 (30%)		Group 2 (no recurrence) N= 144 (70%)		P value
<50%	22	35.5	74	51.4	0.04
>50%	40	64.5	70	48.6	
Total Positive LNs[#] Median (range)	1 (1–11)		1 (1–8)		0.3
Total LNs Median (range)	5 (1–33)		5 (1–34)		0.64
Volume of LN mets					
ITC[£] only	12	19.4	59	40.9	
Micro-/macrometastasis	50	80.6	85	59.1	0.003

[¥] Only endometrioid, mucinous histotypes were graded

[*] LVI: Lymphovascular invasion

[#] LN: Lymph node

[£] ITC: Isolated tumor cells

Table 4.

Multivariable analysis of factors associated with recurrence

Variable	Univariate		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age	1.02 (0.99–1.05)	0.23		
BMI (kg/m^2)	1.01 (0.97–1.05)	0.48		
Histology				
endometrioid	Reference	--	Reference	
non-endometrioid	4.9 (2.61–9.33)	<0.001	5.99 (2.75–13.06)	<0.001
Procedure				
Robotic	Reference	--		
laparoscopy	0.79 (0.32–1.92)	0.6		
laparotomy	1.57 (0.8–3.06)	0.19		
Number of total nodes	0.99 (0.95–1.04)	0.84		
Number of positive nodes	1.11 (0.91–1.35)	0.29		
Volume of LN* mets	1.11 (0.91–1.35)	0.29		
ITC¥ only	Reference		Reference	
micro-/macrometastasis	0.35 (0.17–0.7)	0.003	0.49 (0.21–1.11)	0.09
Myometrial Invasion				
<50%	Reference		Reference	
>50%	1.92 (1.04–3.55)	0.04	1.44 (0.65–3.22)	0.37
Pelvic Washing				
Negative	Reference		Reference	
Positive/suspicious	2.21 (1.1–4.51)	0.03	1.51 (0.65–3.53)	0.34
LVI£				
No	Reference		Reference	
Yes/suspicious	2.46 (0.97–6.2)		3.31 (0.93–11.77)	0.06
Adjuvant treatment	3.12 (0.38–25.89)	0.29		
Type of adjuvant treatment				
Chemo	Reference		Reference	
RT	0.6 (0.2–1.78)	0.36	1.65 (0.4–6.83)	0.49
CT/RT	0.42 (0.19–0.95)	0.04	0.69 (0.25–1.91)	0.47
Hormone	N/A	N/A	N/A	N/A

All variables were tested for multicollinearity. Clinically significant variables and variables with p <0.2 on univariable analysis were included in the multivariable analysis.

*LN: Lymph node

¥ITC: Isolated tumor cell

£LVI: Lymphovascular invasion

Table 5:

Patterns of recurrence, Stage IIIC1: overall and by lymph node status (79 sites in 62 patients)

Recurrence Sites	Total 62/206 (30%)		ITC* 12/71 (17%)		Micro-/macrometastasis 50/135 (37%)	
	N	%	N	%	N	%
Nodal	17	8.3	2	2.8	15	11.1
Multisites	17	8.3	1	1.4	16	11.8
Lung	12	5.8	4	5.6	8	5.9
Abdomen	7	3.4	2	2.8	5	3.7
Pelvis	4	1.9	2	2.8	2	1.5
Vagina	4	1.9	0	0	4	2.9
Liver	1	0.5	1	1.4	0	0

* ITC: Isolated tumor cells