# Nodal metastasis in endometrial cancer

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**Summary**

*Purpose:* Besides hysterectomy and bilateral salpingo-oophorectomy, the goal of surgery in early endometrial cancer is to identify extrauterine disease. The purpose of this study was to evaluate disease characteristics and survival of patients found to have nodal metastasis at staging for endometrial cancer. *Methods:* All patients presenting to our practice from January 1993 to July 2009 with a new diagnosis of early endometrial cancer underwent pelvic and paraaortic lymph node sampling at the time of surgery as permitted by the body mass index. Patient and disease characteristics of patients with nodal metastasis were abstracted by retrospective chart review. Factors contributing to disease-free and overall corrected survival were evaluated. *Results:* Forty-three patients with an early endometrial cancer were found to have pelvic and/or paraaortic nodal metastasis. Thirty-three percent of patients with nodal metastasis had papillary serous or clear cell cancers. Such tumors were often superficially invasive, yet were more likely to demonstrate lymphovascular space involvement as compared to endometrioid cancers. Furthermore, in a global model of disease-free and overall corrected survival, only tumor histology (endometrioid vs non-endometrioid) was a significant prognostic factor. Excluding clear cell and papillary serous tumors, only tumor grade was a significant prognostic factor in disease-free survival and overall corrected survival in patients with endometrioid adenocarcinomas and nodal involvement. Following adjuvant treatment after surgery, the recurrences were nearly evenly divided between pelvic, paraaortic nodal and distant sites. Only four of 33 (12%) patients treated with adjuvant pelvic radiation experienced a failure in the irradiated field. Furthermore, none of the patients experiencing a paraaortic nodal recurrence received adjuvant radiation to this site. *Conclusions:* The data suggest a benefit to the use of adjuvant radiation for local control of disease. Furthermore, the use of paclitaxel and carboplatinum chemotherapy also appears a promising adjunct in patients with endometrioid histologies and nodal spread. Papillary serous and clear cell cancers contributed disproportionately to the incidence of nodal metastasis and an adverse prognosis following further adjuvant therapy of patients with nodal disease. Despite taxol/carboplatinum chemotherapy, over half of the patients with non-endometrioid cancers recurred, as opposed to one of 19 endometrioid cancers so treated. The ideal form of adjuvant treatment for such patients remains problematic.

*Key words:* Endometrial cancer; Nodal metastasis; Non-endometrioid endometrial cancers.

## Introduction

Endometrial cancer is the most frequent malignancy arising in the female genital tract, accounting for approximately 42,000 cases on an annual basis [1]. Fortunately, 75% of endometrial cancers appear to be confined to the uterus at diagnosis and represent clinical Stage I disease. However, despite the use of adjuvant therapy, about 20% of patients with "early disease" will develop a recurrence [2].

The early studies of the Gynecologic Oncology Group identified prognostic factors contributing to adverse outcomes as determined by systematic surgical staging. In a study of 621 patients with clinical Stage I disease and comprehensive staging, malignant cells were identified in the peritoneal cytologies in 12% of the patients [3]. Five percent had adnexal metastases, and 11% of the patients had either pelvic or paraaortic nodal metastasis. Tumor grade and depth of myometrial invasion closely correlated with nodal metastasis. Only 3% of patients with well-differentiated cancers had nodal metastasis, as opposed to 18% of those with grade 3 disease. Furthermore, the frequency of pelvic lymph node metastasis increased from 5% in patients with superficial invasion, to 25% in those with deep myometrial invasion.

Data from early studies of the Gynecologic Oncology Group contributed much of the foundation for the current FIGO surgical staging of endometrial cancer. Comprehensive surgical staging defines the extent of disease and offers a rational basis for any further treatment. Lymphadenectomy contributes prognostic information and provides opportunities for tailored adjuvant therapy in patients with nodal metastasis.

The purpose of this study was to analyze disease characteristics and survival of patients with nodal metastasis at surgery for endometrial cancer. Disease features identified at surgery were evaluated as independent prognostic factors influencing disease-free and overall corrected survival in patients with either pelvic or paraaortic nodal disease. Finally, patterns of recurrence were analyzed according to the nature of the adjuvant therapy administered after surgery.

## Materials and Methods

This retrospective study was approved by the Institutional Review Board of the Pinnacle Health Hospitals. All patients felt to be surgical candidates presenting to the practice with a new diagnosis of endometrial cancer from January 1993 to July 2009 underwent pelvic and paraaortic lymph node sampling (in addition to hysterectomy and salpingo-oophorectomy) as permitted by the body mass index (BMI). Patients with pelvic and/or paraaortic lymph node metastasis were identified by review of the office electronic medical record or through the Tumor Registry Service of the Pinnacle Health System. All patients had clinical Stage I or II (occult) endometrial adenocar-

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cinomas and underwent hysterectomy, bilateral salpingo-oophorectomy and staging without preoperative radiotherapy. Definitive surgery was performed, on average, within 32 days following the pathologic diagnosis of an endometrial carcinoma. Surgery was performed as an open procedure in 32 patients (74%). Eleven patients had minimal access surgery with a robotic approach in four, LAVH in five and total laparoscopic hysterectomy in two patients. All but one of the patients underwent removal of pelvic lymph nodes and 35 of the 43 also underwent paraaortic lymph node sampling. Given adequate visualization, pelvic lymphadenectomy was performed with skeletonization of the obturator nerve, external iliac vein and external iliac artery, as opposed to selective node sampling. Enlarged, bulky lymph nodes were removed in an effort to reduce residual tumor burden. Both left and right paraaortic lymph nodes were obtained below the level of the inferior mesenteric artery given adequate exposure.

Charts of all identified individuals were abstracted for patient characteristics, surgical procedures and pathologic findings. Pathology reports were specifically reviewed as to tumor histology, tumor grade, depth of myometrial invasion, lymphovascular space involvement, cervical disease, adnexal metastasis, and peritoneal cytology. Lymph nodes excised were scored as to total number removed, number of positive nodes and location (pelvic vs paraaortic).

Following surgery, patients were encouraged to undergo both radiotherapy and paclitaxel/carboplatinum chemotherapy. Patients without paraaortic disease were treated with only pelvic radiotherapy. The pelvis was treated with approximately 45 Gy by AP/PA or four-field technique. In patients with paraaortic nodal disease, the treatment field was extended up to T12. The chemotherapy administered consisted of paclitaxel/platinum-based regimens using dosages and schedules identical to those used for ovarian epithelial cancers.

Three patients declined further treatment after surgery. Thirty-three patients received pelvic radiotherapy (with or without a paraaortic field). Twenty-four of the patients also received taxol/carboplatinum chemotherapy and the remaining nine received only radiation. Eight of the 33 patients were also given extended field radiation to the paraaortic area. Thirty-one patients received paclitaxel and carboplatinum chemotherapy; seven of the 31 were treated without radiotherapy.

Statistical analyses were performed using SYSTAT 11 (Chicago, IL) or Medicalc. Associations between categorical variables were evaluated by the Fisher exact test or chi-square. The Kaplan-Meier method was used to generate life-table survival curves and calculate disease-free and overall corrected survival. The Cox proportional hazards model was used to identify independent prognostic factors in disease-free and overall corrected survival. Variables entered into the stepwise Cox proportional hazards model were retained if the respective $p$ value was less than 0.05, and eliminated if the $p$ value exceeded 0.10. Differences in survival for patient subgroups were compared by the log-rank test.

## Results

In patients undergoing primary surgery and staging for clinical Stage I and Stage II occult endometrial adenocarcinoma from January 1, 1993 to July 1, 2009, 43 patients were found to have pelvic and/or paraaortic nodal metastasis. Thirty-eight patients presented with abnormal or postmenopausal bleeding. The remaining five had smears showing endometrial cells or atypical glandular cells. The diagnosis of endometrial cancer was made by outpatient sampling of the uterine cavity in 17 patients (40%). Twenty-five individuals required curettage to establish a diagnosis. One patient was found to have an endometrial cancer at intraoperative evaluation of the hysterectomy specimen.

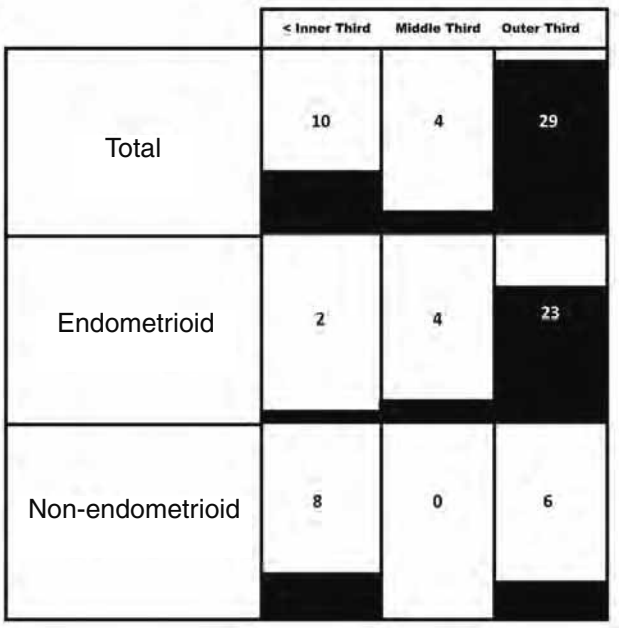


Figure 1. — Depth of myometrial invasion for all 43 patients with nodal metastasis, and those with endometrioid vs non-endometrioid tumor histology.

Of the 43 patients with nodal metastasis, ages ranged from 38.7 to 83.8, with an average of 63.8 years at the time of diagnosis. Two of the patients were African American and the remaining individuals were Caucasian. Hypertension was the most frequent medical problem with a prevalence rate of 49%. Seven of the 43 patients (16%) had a diagnosis of diabetes mellitus. BMI ranged from 19.7 to 60.9 with an average of 32.5. Seven patients (16%) had a BMI of < 25. Seven individuals had a BMI > 40 with three of the patients having a BMI in excess of 50.

Fourteen of the 43 patients (33%) had non-endometrioid (3 clear cell and 11 papillary serous) cancers with the remaining individuals having tumors of endometrioid histology. Patient age at diagnosis and BMI were not statistically different for the two tumor histologies. Furthermore, the frequency of cervical involvement, ovarian metastasis and positive cytologies was not statistically greater in patients with clear cell and papillary serous cancers as compared to endometrioid cancers. However, patients with non-endometrioid cancers were statistically more likely to show either no or superficial myometrial invasion ($p = 0.02$) and lymphovascular space involvement ($p < 0.01$) as compared to endometrioid adenocarcinomas giving rise to lymph node metastasis. Eight of 14 non-endometrioid cancers had either no invasion or superficial, inner third invasion, of the myometrium as compared to only two of 29 endometrioid cancers (Figure 1). All 14 hysterectomy specimens with clear cell or pap-

Fig. 2

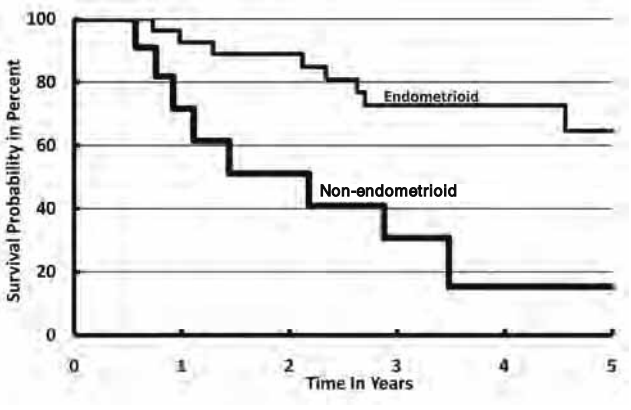


Fig. 3

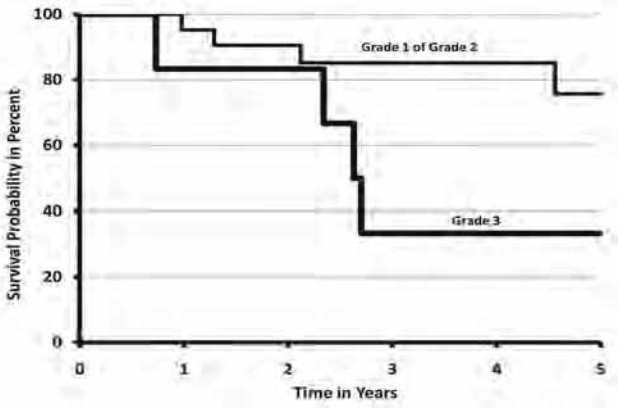


Figure 2. — Kaplan-Meier actuarial life-table estimates for disease-free survival in patients with endometrioid vs non-endometrioid (papillary serous and clear cell) cancers.
Figure 3. — Kaplan-Meier actuarial life-table estimates for disease-free survival in patients with endometrioid adenocarcinomas and nodal metastasis as grouped by tumor grade.

illary serous cancers demonstrated lymphovascular space involvement as compared to 52% of endometrioid cancers.

Forty-two of the 43 patients (98%) underwent pelvic lymph node sampling with documented nodal metastasis in 36 individuals. The number of lymph nodes removed ranged from one to 25 with an average of 8.6 nodes per patient. A total of 363 pelvic lymph nodes were removed, of which 76 (21%) contained metastasis. Thirty-five of the 43 patients (81%) underwent sampling of the lower paraaortic chain, removing from one to 18 (average of 3.9) lymph nodes. Thirty-three percent of the paraaortic lymph nodes removed (45/135) were positive for metastasis. Twelve patients had both positive pelvic and positive paraaortic lymph nodes at the time of staging. The distribution of regional lymph node metastasis is summarized in Table 1. Correlates of lymph node metastasis included six patients with positive peritoneal cytologies, seven with ovarian tumors, and 21 individuals with cervical involvement. Lymphovascular space involvement was demonstrated in 29 of the 43 hysterectomy specimens (67%). Depth of tumor invasion in the 43 hysterectomy specimens is shown in Figure 1.

With an average follow up of 3.3 years after surgery, the two- and five-year actuarial disease-free survivals for all patients were 81% and 48%, respectively. The type of nodal metastasis (pelvic vs paraaortic), total number of positive lymph nodes, tumor histology (endometrioid vs non-endometrioid), pelvic cytology, ovarian involvement, presence of peritoneal disease (e.g., positive cytology, ovarian involvement, or peritoneal tumor), cervical disease, depth of myometrial invasion and lymphovascular space involvement were used as covariates in a global model of disease-free survival and overall corrected survival. In a stepwise Cox proportional hazards regression of both disease-free and overall corrected survivals, the only variable retained in these models using a $p < 0.05$ was tumor histology. Two- and five-year actuarial disease-free survivals for patients with clear cell or papillary serous cancers were 51% and 15%, respectively, as compared to 89% and 65% for individuals with endometrioid histology. The Kaplan-Meier life-table for disease-free survival in patients with endometrioid and non-endometrioid cancers is shown in Figure 2. The subgroup of patients with endometrioid histology was also evaluated in terms of disease-free survival and overall corrected survival using similar covariates by the use of the log-rank test. Only tumor grade was a significant predictor of outcome in terms of disease-free ($p = 0.02$) and overall corrected survival ($p < 0.01$). The Kaplan-Meier life table plots for disease-free survival in patients with grade 3 and grade 1 to 2 tumors is shown in Figure 3.

There were 16 treatment failures contributed by eight of 14 non-endometrioid and eight of 29 endometrioid cancers. The recurrences were nearly evenly divided between pelvic, paraaortic nodal, and distant disease failures. Despite further therapy after documentation of recurrent disease, 14 of the 16 patients have succumbed to disease from 0.1 to 11 years after documentation of disease recurrence. Table 2 summarizes the location of the recurrent disease, tumor histology and the nature of the adjuvant treatment administered. Eight of the 16 recurrences were detected by CA 125 follow-up.

A total of 33 patients received pelvic radiotherapy (with or without a paraaortic field). Only four of the 33 patients (12%) treated with pelvic radiotherapy demonstrated a recurrence within the irradiated field. Furthermore, none of the five patients with a paraaortic recurrence received radiation to this area. Thirty-one patients received paclitaxel and carboplatinum chemotherapy with or without radiotherapy, accounting for eight recurrences. There were two pelvic treatment failures, three recurrences in the paraaortic chain, and three distant failures (one with local disease). Twelve of the 31 patients (39%) receiving chemotherapy had tumors of papillary serous or clear cell histology with recurrences in seven of

Table 1. — *Incidence of positive pelvic and paraaortic metastasis for the 43 patients with nodal metastasis.*

| Pelvic lymph nodes | Paraaortic lymph nodes | |
|---|---|---|
| | Positive | Negative |
| Positive | 12 | 24 |
| Negative | 7 | 0 |

Table 2. — *Location of disease recurrence, tumor histology, and nature of preceding adjuvant therapy for the 16 patients with recurrent disease.*

| Location of recurrence | Histology | Nature of adjuvant therapy |
|---|---|---|
| Pelvis | Non-endometrioid: 2 | Chemotherapy in 2 with radiation (pelvic & paraaortic fields) in 1 patient |
| | Endometrioid: 3 | Pelvic radiation in 3 patients |
| Paraaortic area | Non-endometrioid: 3 | Chemotherapy in 3 with RT in 1 patient |
| | Endometrioid: 2 | Pelvic radiotherapy in 2 patients |
| Local and distant disease | Non-endometrioid: 1 | Chemotherapy in 1 |
| Distant disease | Non-endometrioid: 2 | Pelvic radiation in 1 & chemotherapy in 1 |
| | Endometrioid: 3 | Pelvic radiation in 3 patients with chemotherapy in 1 |

the 12 patients. However, only one of 19 endometrioid adenocarcinomas recurred after adjuvant paclitaxel and carboplatinum.

## Discussion

Although two recent studies have questioned the therapeutic benefit of lymphadenectomy in "early"endometrial cancer [4, 5], the information obtained clearly provides prognostic information. The literature and data from the present study demonstrate that patients with nodal metastasis have an adverse prognosis. Hirahatake and colleagues observed cumulative five-year survival rates of 94% in patients without nodal metastasis, 75% in those with metastasis limited to the pelvic nodes, and 38% in patients with both pelvic and paraaortic nodal disease [6]. At a median follow-up of 37 months, McMeekin *et al*. observed a three-year survival estimate of 70% for patients with paraaortic nodal disease and 87% for those with isolated pelvic node metastasis [7]. More recent data has shown that patients with retroperitoneal lymph node metastasis had a five-year overall survival of 55% and a progression-free survival of 48% [8]. In the present series, two- and five-year disease free actuarial survivals were 81% and 48%, respectively, observations consistent with those previously reported in the literature. The present data also suggest that tumor histology is a significant factor in determining outcome for those patients with nodal disease. However, further stratification of prognostic factors, such as positive cytologies or adnexal metastasis was not observed as previously described by the Mayo group [9].

Radiation appears to be a useful adjuvant following surgery in endometrial cancer patients with nodal metastasis. Only four of 33 patients treated with pelvic radiation developed recurrences in the irradiated field. Furthermore, none of the five patients with paraaortic recurrences received radiation to the paraaortic chain. These observations are consistent with recent reports in the literature. Klopp and co-workers noted a high rate of locoregional recurrences in endometrial cancers with nodal involvement without the use of tailored radiotherapy [10]. Five-year relapse-free survival and overall survival were significantly better with the use of regional radiotherapy. Furthermore, in node-positive patients treated without regional radiotherapy, the most frequent site of relapse was the pelvis. Similarly, data from other institutions also suggest that adjuvant radiotherapy is associated with a significant survival benefit in women with node-positive endometrial cancers [11]. Adjuvant radiotherapy improved the survival from 54% to 74% in patients with a single positive node and from 52% to 60% in those with two to five positive nodes.

The role of chemotherapy, especially taxane and platinum-based regimens remains to be defined in patients with nodal metastasis. A randomized, prospective, Gynecologic Oncology Group study showed that doxorubicin and cisplatinum chemotherapy in patients with advanced (Stage III and IV) endometrial cancer and residual disease ≤ 2 cm resulted in improved survival as compared to those patients treated with whole abdominal radiotherapy [12]. In the present study, despite taxol and carboplatinum chemotherapy in 31 patients, there were two pelvic recurrences, three failures in the paraaortic chain and three distant recurrences (with local disease in one patient). The benefit of chemotherapy is unclear given the heterogeneity of tumor histologies and grades. However, any benefit appears to favor those patients with endometrioid histology. Twelve of the 31 patients (nearly 40%) receiving chemotherapy had tumors of papillary serous or clear cell histology accounting for seven recurrences. However, only one of 19 endometrioid adenocarcinomas recurred after adjuvant paclitaxel and carboplatinum.

More than 20 years have elapsed since the description of the clinicopathologic characteristics of papillary serous cancers of the uterus [13]. Although tumors of non-endometrioid histology comprise only about 10% of endometrial adenocarcinomas [14], papillary serous and clear cell cancers contribute disproportionately to pelvic and paraaortic nodal metastasis. In the present series, 33% of patients with regional lymph node metastasis had tumors of non-endometrioid histology. Tumors of papillary serous or clear cell histology with nodal metastasis were more likely to demonstrate lymphovascular space involvement, despite often limited myometrial invasion, as compared to endometrioid cancers. In terms of disease-free and corrected overall survival, tumor histology (endometrioid vs non-endometrioid) was the only statistically significant predictor of outcome in patients with lymph node metastasis. The more aggressive bio-

logic behavior of non-endometrioid histology is also demonstrated in a population of patients limited to those with nodal metastasis. Despite the use of paclitaxel and carboplatinum chemotherapy with or without additional radiation, seven of the 12 patients eventually developed recurrent disease. The ideal form of adjuvant therapy in patients with nodal metastasis as a result of non-endometrioid cancers remains problematic and will require randomized studies in patients with these uncommon, yet biologically aggressive cancers.

## Conclusions

Although lymphadenectomy may not provide a therapeutic benefit, it does identify prognostic information that provides for subsequent tailored adjuvant treatment of patients with nodal metastasis. The data suggest a benefit to the use of adjuvant radiation for local control of disease. The use of paclitaxel and carboplatinum chemotherapy also appears promising in patients with endometrioid histologies. Papillary serous and clear cell cancers contributed disproportionately to the incidence of nodal metastasis and an adverse prognosis in a population with nodal metastasis, despite subsequent adjuvant treatment. The optimal treatment of such patients with nodal involvement remains problematic.

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