



Survey article

Current practice patterns in nodal evaluation and adjuvant treatment of advanced stage endometrioid endometrial cancer: An SGO survey

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ABSTRACT

The use of sentinel lymph node (SLN) mapping over full lymphadenectomy for endometrioid endometrial cancer (EC) has had varying uptake. Adjuvant therapy for advanced stage EC is also a debated topic globally. Two recent randomized controlled trials have attempted to clarify which treatment approach should be recommended. Our aims were to identify common practice patterns in the intraoperative lymph node evaluation as well as the practice patterns in the treatment of advanced stage (stage III-IV) endometrioid EC among gynecologic oncologists.

A 16-question survey was distributed via email to all Society of Gynecologic Oncology members. Study data were collected anonymously and managed using REDCap electronic data tools. Respondents were asked questions regarding demographics, assessing nodal status, and choice of adjuvant treatment for each stage. Descriptive statistics, student's t-tests, and chi-squared analyses were performed.

A total of 1531 surveys were distributed and 187 (12%) members responded. The majority (70%) of respondents identified nodal metastases by performing SLN mapping prior to nodal evaluation in grade 1–2 disease, however only half perform SLN mapping in grade 3 EC. Adjuvant chemotherapy was recommended by 90% of practitioners for advanced EC. However, external beam radiation or brachytherapy was combined with chemotherapy in 74% of stage III EC and 35% of stage IV EC.

While 90% of practitioners recommend chemotherapy-based adjuvant treatment for women with stage IIIA–IVA endometrioid EC, decreasing local recurrence appears to be a factor in treatment planning as radiation combined with chemotherapy is used in 63% of cases.

1. Introduction

Approximately one-third of women with endometrial cancer are diagnosed at an advanced stage (Siegel et al., 2017) where five-year survival is only between 20 and 60% (Lewin et al., 2010). Conversely, five-year survival for stage I disease is approximately 80–90% (Lewin et al., 2010). Therefore, it is important to identify adjuvant treatments to improve survival in advanced stage (III-IV) patients.

Prior to the 1988 International Federation of Gynecology and Obstetrics (FIGO) revised staging system, endometrial cancer was staged clinically (Creasman, 2009). Recognition of nodal disease as a prognostic factor in part led to the determination that endometrial cancer should be staged surgically, and in 2009, FIGO stratified patients with nodal metastasis into pelvic (IIIC1) and para-aortic (IIIC2) nodal involvement (Creasman, 2009). Studies have shown a difference in survival for stage IIIC1 (57%) vs stage IIIC2 (49%) disease (Lewin et al.,

2010) and a benefit of chemotherapy over those who do not receive chemotherapy in node positive patients (Hogberg, 2010). However, complete lymphadenectomy can be associated with major complications, including lymphedema and lymphocele (Volpi et al., 2019). Sentinel lymph node (SLN) mapping can be performed to minimize these complications, particularly in low-grade endometrioid tumors, however this has been controversial in patients with high risk tumor characteristics due to a higher false-negative detection rate (Rossi et al., 2017; Soliman et al., 2017).

Advanced stage EC comprises a heterogeneous group of diseases ranging from direct extension of disease to nodal metastasis to distant metastasis (Randall et al., 2006; Matei et al., 2019; De Boer et al., 2018). Recent randomized controlled trials have evaluated adjuvant combined chemotherapy and radiation therapy versus radiation or chemotherapy alone and have not found improvements in overall survival with one treatment over another, leading to difficulties in clinical

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decision-making (Matei et al., 2019; De Boer et al., 2018). The use of radiation decreases local recurrence rates without improving distant failures, however the use of chemotherapy alone decreases distant failure rates without improving local control (Matei et al., 2019; De Boer et al., 2018). The adequacy of intraoperative nodal evaluation in choice of adjuvant treatment appears to be important as well, as one study showed that there were no para-aortic failures in node positive patients who received extended-field RT, however recurrences in the para-aortic nodes were found in 14% of those patients who received pelvic-only RT or chemotherapy alone (Chapman et al., 2019).

Currently available practice guidelines allow for a wide range of intraoperative nodal evaluation techniques as well as adjuvant treatment options without a clear standard of care. Given these controversies, we sought to identify common practice patterns among gynecologic oncologists in intraoperative nodal evaluation methods and utilization of adjuvant treatments in patients with advanced stage (stage III-IV) endometrioid EC.

2. Methods

After receiving approval from the Institutional Review Board and permission from the Society of Gynecologic Oncology to obtain and distribute surveys via email to its members, a 16-question survey was developed and distributed to gynecologic oncologists and fellows-in-training (Table 1). The questions were designed based on current treatment paradigms used for stage IIIA-IVB endometrioid EC. Along with demographics, these questions included preferences of respondents for assessment of intraoperative nodal status based on grade as well as adjuvant treatment of endometrioid EC based on stage. Adjuvant treatment options included chemotherapy alone (CT), combined chemotherapy and external beam radiation (CT + RT), external beam radiation alone (RT), chemotherapy with brachytherapy (C + B), or “other”, which prompted a free text box in which the respondent could type their alternative preference. Study data were collected and managed using REDCap electronic data capture tools hosted at our institution (Pa et al., 2009). The initial survey was distributed in February 2019 with a second survey sent one week later to those members who did not respond to the first survey request. Descriptive statistics were performed. Associations between answers to questions and practice length, type, and location were investigated using student’s *t*-test and

Table 1
Survey questions distributed to members of the Society of Gynecologic Oncology.

What is your gender?
How long have you been a practicing gynecologic oncologist?
What type of practice are you currently in?
Do you train fellows?
Do you train residents?
Where is your practice located?
Approximately how many endometrial cancer cases do you manage per year?
In patients with presumed grade 1–2 endometrioid endometrial cancer, how are you assessing nodal status?
In patients with presumed grade 3 endometrioid endometrial cancer, how are you assessing nodal status?
In patients with stage IIIA endometrioid endometrial adenocarcinoma with positive adnexa only, what adjuvant treatment do you prefer?
In patients with stage IIIA endometrioid endometrial adenocarcinoma with positive serosal involvement only, what adjuvant treatment do you prefer?
In patients with stage IIIB endometrioid endometrial adenocarcinoma, what adjuvant treatment do you prefer?
In patients with stage IIIC1 endometrioid endometrial adenocarcinoma, what adjuvant treatment do you prefer?
In patients with stage IIIC2 endometrioid endometrial adenocarcinoma, what adjuvant treatment do you prefer?
In patients with stage IVA endometrioid endometrial adenocarcinoma, what adjuvant treatment do you prefer?
In patients with stage IVB endometrioid endometrial adenocarcinoma, what adjuvant treatment do you prefer?

Table 2
Demographics of Respondents (n = 187).

Variable	Number (%)
Gender	
Male	93 (49.7%)
Female	93 (49.7%)
Practice Length	
Fellow	10 (5.3%)
0–5 years	55 (29.4%)
5–10 years	31 (16.6%)
10–15 years	19 (10.2%)
15–20 years	15 (8.0%)
20–25 years	19 (10.2%)
> 25 years	38 (20.3%)
Practice Type	
Academic	105 (56.1%)
Private	37 (19.8%)
Combined	42 (22.5%)
Military	3 (1.6%)
Train Fellows	
Yes	58 (31.0%)
No	127 (67.9%)
Train Residents	
Yes	152 (81.3%)
No	32 (17.1%)
Practice Location	
Northeast	48 (25.7%)
Southeast	35 (18.7%)
Southwest	21 (11.2%)
Northwest	4 (2.1%)
West	18 (9.6%)
Midwest	41 (21.9%)
International	20 (10.7%)
Number of Cases/Year	
< 25	12 (6.4%)
25–50	53 (28.3%)
50–100	77 (41.2%)
100–150	22 (11.8%)
150–200	12 (6.4%)
> 200	9 (4.8%)

Pearson’s Chi-squared test. Statistics were performed using Graphpad Prism version 8.3.1.

3. Results

1,531 surveys were distributed and 187 (12%) members responded. Demographics of the respondents to the survey are listed in Table 2. There were an equal number of male and female respondents. 51% of respondents were in practice for under 10 years. 79% practiced in an academic or combined academic/private practice with 81% training residents and 31% training fellows. 20% of respondents were in a private practice and 2% were in military practice. 93% of respondents treated > 25 EC patients yearly. 11% of respondents practiced outside of the United States.

3.1. Intraoperative lymph node evaluation

The majority (70%) of respondents identified nodal metastases by performing SLN mapping in those patients with grade 1–2 disease, with an additional 20% following the “Mayo criteria” (Mariana et al., 2008) by performing frozen evaluation prior to nodal evaluation (Table 3). Length in practice was a significant factor in preference, with SLN mapping being performed more frequently in respondents in practice for 0–10 years and 15–20 years and pelvic and para-aortic lymphadenectomy being performed more frequently in respondents in practice for 20–25 years (*p* < 0.001). Practice location also influenced preference for nodal evaluation (*p* = 0.016). Pelvic lymphadenectomy only was more frequently performed by international respondents and SLN mapping was more frequently used by those practicing in the

Table 3
Assessment of Nodal Status (n = 187).

Variable	Number (%)
Grade 1–2	
Frozen Evaluation	36 (19.3%)
SLN Biopsy	132 (70.5%)
Pelvic Lymphadenectomy	14 (7.5%)
Pelvic and Para-aortic Lymphadenectomy	3 (1.6%)
Grade 3	
Frozen Evaluation	3 (1.6%)
SLN Biopsy	90 (48.1%)
Pelvic Lymphadenectomy	17 (9.1%)
Pelvic and Para-aortic Lymphadenectomy	76 (40.6%)

Key: SLN: sentinel lymph node

United States.

Conversely, type of nodal evaluation for grade 3 EC patients was variable, with 48% of the respondents performing SLN mapping and 50% either pelvic only or both pelvic and para-aortic lymphadenectomy (Table 3). This preference did not correlate with practice length, type, or location. However, the majority of those who performed lymphadenectomy (110 respondents) perform both pelvic and para-aortic lymphadenectomy over pelvic lymphadenectomy alone (84% vs 16%, respectively, Table 3).

3.2. Adjuvant treatment

We separated stage IIIA patients into those with adnexa positive disease and those with serosa only disease to assess for differences in treatment. In patients with stage IIIA adnexa positive disease, the most commonly used adjuvant treatment was combined chemotherapy and external beam radiation (CT + RT) (47.0%, Table 4). Practice length, type, or location did not correlate with choice of adjuvant treatment for patients with adnexal metastasis (data not shown). However, there were differences in treatment based on practice location in patients with stage IIIA serosa positive only disease (Table 4). Respondents based in the northwest were more likely to choose C + B than those respondents in other locations (p = 0.036).

In patients with stage IIIB disease, most respondents favored treatment with CT + RT (58.8%) and less treated with CT alone (10%, Table 4). There were no differences in preference based on practice length, type, or location.

In patients with stage IIIC1 disease, the majority of respondents give CT + RT (73%), with less giving CT + B (8%) and even fewer RT alone (3%, Table 4). The same trend was seen in stage IIIC2 disease (79%, 5%, and 1%, respectively, Table 4). For stage IVA disease, around half of respondents (49%) give CT + RT, but more respondents than with prior stages (39%) give CT alone (Table 4). In stage IVB disease, the majority of respondents gave chemotherapy with carboplatin and paclitaxel (70%) or with carboplatin, paclitaxel, and bevacizumab (8%) with many fewer respondents giving CT + RT (13%, Table 4). There were no significant correlations based on demographics in any of these stages.

Overall, a regimen that included chemotherapy was used in 91% of advanced EC treatment. The use of adjuvant radiation therapy (RT or brachytherapy) along with chemotherapy was used in 74% of stage III EC and 35% of stage IV EC. Grade and type of nodal evaluation did not influence adjuvant treatment.

4. Discussion

Current controversies in surgical staging and adjuvant treatment for endometrioid EC are reflected in the practice patterns among gynecologic oncologists in this study, though common themes arose. First, we observed a difference in practice patterns followed for nodal evaluation in endometrioid EC. There was a statistically significant difference

Table 4
Adjuvant Treatment (n = 187).

Variable	Number (%)
Stage IIIA Adnexa Positive	
RT alone	13 (7.0%)
C alone	47 (25.1%)
C + RT	88 (47.0%)
C+B	33 (17.6%)
Other	5 (2.7%)
Stage IIIA Serosa Positive	
RT alone	19 (10.2%)
C alone	39 (20.8%)
C+RT	92 (49.2%)
C+B	29 (15.5%)
Other	6 (3.2%)
Stage IIIB	
RT alone	12 (6.4%)
C alone	19 (10.2%)
C+RT	110 (58.8%)
C+B	32 (17.1%)
Other	11 (5.9%)
Stage IIIC1	
RT alone	6 (3.2%)
C alone	19 (10.2%)
C+RT	137 (73.3%)
C+B	15 (8.0%)
Other	7 (3.7%)
Stage IIIC2	
RT alone	1 (0.6%)
C alone	21 (11.2%)
C+RT	147 (78.6%)
C + B	9 (4.8%)
Other	7 (3.7%)
Stage IVA	
RT alone	1 (0.6%)
C alone	73 (39.0%)
C+RT	91 (48.7%)
C+B	9 (4.8%)
Other	8 (4.3%)
Stage IVB	
RT alone	0 (0.0%)
Chemotherapy with carboplatin/paclitaxel	132 (70.5%)
Chemotherapy with carboplatin/paclitaxel/bevacizumab	15 (8.0%)
C+RT	25 (13.4%)
C+B	5 (2.7%)
Other	8 (4.3%)

Key: EBRT: radiation therapy.

between length of practice and preference for nodal evaluation in grade 1–2 disease, with respondents in practice for 0–10 and 15–20 years favoring SLN mapping and those in practice 20–25 years favoring full lymphadenectomy. While lymphadenectomy was previously recommended as the gold standard, recent studies have suggested that SLN mapping can replace lymphadenectomy, and survival advantage of full lymphadenectomy is debated (Kitchener et al., 2009). The FIRES trial in 2017 evaluated SLN mapping compared with complete lymphadenectomy in clinical stage I disease of all grades and histologies. This showed that 3% of node positive patients would not be identified by SLN mapping. However, only 29% of the patients in the study had a high-risk histology with 11% of the total having grade 3 endometrioid EC, and the one false-negative identified was in a high-risk pathologic subtype (high grade serous) (Rossi et al., 2017). Another prospective study of patients with high risk EC (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) demonstrated a false negative rate of 5% with SLN mapping in these patients (Soliman et al., 2017). Our study shows that gynecologic oncologists are concerned about these false negative rates, as only 48% of respondents use SLN biopsy for grade 3 disease.

Adjuvant therapy for advanced stage EC is also a debated topic globally, and studies have often combined all advanced endometrial cancer stages in their design. GOG122 demonstrated superior progression-free survival (PFS) and overall survival (OS) with chemotherapy versus whole abdomen radiation in patients with stage III/IV EC,

however failure rates were still high (Randall et al., 2006). The recently published results of GOG258 showed that the relapse free survival was the same between advanced endometrial cancer patients treated with combination chemotherapy and radiation as compared to chemotherapy alone. There were fewer vaginal and nodal recurrences with combination chemotherapy and radiation with increased distant recurrence rates (Matei et al., 2019). The results of PORTEC-3 showed an improvement in failure free as well as OS with C + RT as opposed to RT alone, with the greatest benefit seen in patients with stage III EC (De Boer et al., 2018). The NCCN recommends systemic therapy and/or RT with or without brachytherapy for stage IIIA-IVB endometrioid adenocarcinoma of the uterus. Prognostic factors and clinical scenarios in which patients should or should not receive RT are not specified (Network and Neoplasms, 2019). In our study, we found that chemotherapy-based treatment is most commonly used, but the use of adjuvant radiation therapy (RT or brachytherapy) with chemotherapy is used in 74% of stage III EC and 35.0% of stage IV EC. The use of RT increased with increasing sub-stage in stage III EC. As expected, the use of brachytherapy decreased with increasing stage. More respondents use CT alone with stage IVA and IVB disease than stage III disease. Interestingly, there was no association between respondent preference for lymph node evaluation and choice of adjuvant therapy.

These results suggest that choice of adjuvant treatment by current practitioners is individualized in advanced stage EC. Practitioners are choosing combined chemotherapy and external beam radiation therapy in the majority of instances for stage III disease, emphasizing the desire for the improved local control benefit of the addition of radiation therapy. A recently published article evaluating the optimal adjuvant treatment regimen for node-positive EC patients revealed that in grade 3 endometrioid EC patients, disease specific survival (DSS) was significantly improved with CT + RT over CT alone, however there was no difference in DSS between the two groups in grade 1–2 endometrioid EC (Chapman et al., 2019). This suggests that grade, rather than stage, may be the more important factor in adjuvant treatment decision.

One limitation of our study is that the preferential sequence of adjuvant CT + RT was not elucidated. However, there were no instances in which sequence of CT + RT was specified in the free text option if a respondent chose “other”. High-risk histologies other than grade 3 endometrioid EC were not evaluated via this survey. This study is also limited by the 12% response rate, which leads to difficulty in generalizing these results in to the entire population of gynecologic oncologists. In our study, the majority of respondents practice in an academic setting and just over half of respondents were in practice for under 10 years which may have influenced results. However, there were no significant differences in nodal evaluation or treatment based on practice type. The differences in preference for SLN biopsy over full lymphadenectomy in those respondents with fewer years in practice may reflect the comfort in performing this newer technique. Despite these limitations, this was a pertinent survey addressing two important and controversial topics in the treatment of advanced endometrial cancer.

5. Conclusions

SLN mapping or frozen section evaluation is performed for grade 1–2 in 91% of respondents. Despite recent evidence showing a high degree of diagnostic accuracy in detecting endometrial cancer metastasis in all tumor grades, only 48% of respondents perform SLN mapping for grade 3 endometrioid EC.

Chemotherapy-based adjuvant treatment is performed by 90% of practitioners in advanced EC. Although adjuvant radiation in addition to chemotherapy has not been shown to be superior to chemotherapy alone, RT or brachytherapy is combined with chemotherapy in 74% of stage III EC and 35% of stage IV EC, likely due to the concern for loco-regional recurrence. We postulate that future practice patterns will be driven by adjuvant therapy that can minimize both loco-regional and distant recurrences. Practitioner preference for adjuvant therapy should be taken into consideration when designing future trials in endometrioid endometrial cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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