In developed countries, endometrial cancer (EC) is the most common malignancy of the female genital tract and the fourth most common cancer in women. An estimated 40,070 new cases of EC were diagnosed and 7,470 deaths from EC occurred in the United States during 2008 [1]. Of major concern is the realization that, although the incidence of endometrial carcinoma has remained relatively stable over the past decade, the number of deaths annually from this disease has more than doubled since 1987 (2,900 deaths; [2]). Presumably the causes of these statistics are multifactorial. However, it is clear that a critical and objective reassessment of the screening, diagnostic, staging, and treatment processes that guide the overall management of this neoplasm is mandatory. Exemplary of the vulnerability of management is the variability in the staging and treatment algorithms that are generally predicated on institutional and/or individual physician philosophies [3].

Widely accepted management of endometrial cancer consists of total hysterectomy, removal of remaining adnexal structures, and appropriate surgical staging in patients considered at risk for extrauterine disease [4, 5, 6]. External pelvic radiotherapy has been for many years the traditional postoperative treatment for patients with tumor characteristics predicting a poor prognosis [5, 6]. The role of systemic chemotherapy in endometrial cancer is less well defined. Traditionally, it has been used in patients with advanced or recurrent disease [7]; only during the last decade has systemic cytotoxic chemotherapy been elevated to a more critical role in the treatment of advanced endometrial cancer [8, 9, 10], especially after the publication of a prospective Gynecologic Oncology Group study showing a possible survival benefit of adjuvant treatment with systemic chemotherapy when compared to external radiotherapy in stage III and IV disease [11].

Surgical staging has been recommended since 1988 in endometrial cancer [6]. In spite of this general recommendation, the incorporation of a systematic pelvic and para-aortic lymphadenectomy in all patients has not been universally accepted [12, 13, 14]. Moreover, two large, prospective randomized trials [15, 16] have recently negated the findings of previous retrospective studies that had suggested a survival benefit for patients receiving lymphadenectomy [17, 18, 19, 20]. These two prospective studies [15, 16], however, are flawed by several biases [21].

In the following article, we will review the possible indications for a disease-based individualized post-surgical therapy in patients with endometrial cancer, with particular attention to the Mayo Clinic publications of the last decade. Specifically, to accomplish this aim we will analyze the following topics:

1. The analysis of the patterns of lymphatic spread and surgical staging in endometrial cancer.
3. The introduction of the concept of disease-based postoperative therapy.
4. The development of guidelines for the post-operative treatment of endometrioid endometrial cancer based on observations for disease-based therapy and retrospective studies on advanced endometrial cancer.

<table>
<thead>
<tr>
<th>Pelvic lymph node metastases</th>
<th>Tumor diameter (cm)</th>
<th>Patients</th>
<th>Pelvic lymphadenectomy (%)</th>
<th>Positive pelvic lymph nodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤2</td>
<td>123</td>
<td>59 (48)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>169</td>
<td>107 (63)</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>
Patterns of lymphatic spread and surgical staging in endometrial cancer

Performing systematic pelvic and para-aortic lymphadenectomy is still regarded as one of the most important steps to assess the presence of extra-uterine spread of disease and, therefore, to guide targeted post-operative treatment. The GOG-33 study has shown that patients with no or superficial myometrial invasion have a low probability of lymphatic metastases [22]. More recently, we have shown that patients with endometrioid grade 1 or 2 disease and superficial myometrial invasion have a 0% probability of lymphatic metastases when tumor diameter is 2 cm or less (Tab. 1, [13]). Therefore, it is possible to identify a group of patients in whom lymphadenectomy is likely to increase the risk of surgical complications without producing any concrete benefit.

As a consequence, tumor diameter, along with myometrial invasion and histologic grade and subtype (all assessed at intraoperative frozen section), can be used to decide whether to perform lymphadenectomy. This intraoperative selection has led to design surgical guidelines that avoid unnecessary surgical procedures in low-risk patients (Tab. 2). The guidelines are in use at our institution since 2004 [23].

Another important issue in tailoring nodal dissection is the understanding of the routes of lymphatic spread to the pelvic and para-aortic areas. Overall, 67% of patients with lymphatic dissemination have para-aortic lymph node metastases, with 16% having isolated nodal disease confined to the para-aortic area (Tab. 3). Moreover, 60% of patients with nodal involvement above the inferior mesenteric artery have negative homolateral inframesenteric para-aortic nodes [24].

These findings clearly suggest that when para-aortic nodal dissection is considered necessary in the treatment of an EC patient, it should involve the para-aortic area up to the level of the renal vessels. On the other hand, the identification of a subgroup of patients with extremely low probability of node metastases (Tab. 1) allows the selection of those cases in which not only nodal dissection, but also post-operative radiation therapy could be spared.

Performing only pelvic node sampling in unselected cases leads to a low rate of patients with positive lymph nodes: for example, in the ASTEC trial, nodal metastases were found in only 9% of patients included in the lymphadenectomy arm [15]. Conversely, selection of at-risk patients using the criteria given in Tab. 2 and performance of systematic nodal dissection in both pelvic and para-aortic areas allow the identification of nodal metastases in 22% of cases, sparing unnecessary surgical procedures in 27% of all EC patients [24].

The analysis of patterns of lymphatic spread in endometrial cancer is also useful for defining the need and the extent of postoperative treatment in endometrial cancer. In the presence of pelvic node involvement, the rate of para-aortic lymph node invasion is 60% [24]. Therefore, in the absence of appropriate systematic surgical staging, the administration of pelvic radiotherapy in patients considered at risk for recurrence will lead to over-treatment of individuals who have negative pelvic lymph nodes, and to undertreatment of those patients with positive pelvic lymph nodes who have associated disease in the para-aortic area.

The role of lymphadenectomy in the overall management of EC is still a highly debated issue. Due to the recent publication of two large prospective randomized trials, which have recently showed that pelvic lymphadenectomy does not improve survival in endometrial cancer [15, 16], we need to spend a few words on
this topic. The two studies show some differences in their design: in the ASTEC trial all women with clinical stage I were included without exclusion criteria, whereas the Italian study excluded women with stage IA and IB grade 1 tumors, as well as non-endometrioid malignancies. Moreover, in the Italian study systematic nodal dissection was performed, as opposed to pelvic node sampling in the ASTEC trial (median number of lymph nodes harvested = 30 vs. 12, respectively). Yet, the studies share some characteristics that could lead to misinterpretation of their results. In fact, the percentage of nodal positivity is low in both studies (13% and 9%): this suggests that (regardless of the differences in the mentioned exclusion criteria) low-risk cases were included in both studies, thus, diluting the possible (if any) therapeutic benefit of lymphadenectomy. Another important limitation of these two studies is that nodal dissection was limited to the pelvis, without recommendation for para-aortic lymphadenectomy. It has already been demonstrated that radiotherapy limited to the pelvis does not improve survival. Therefore, it is not surprising that pelvic lymphadenectomy alone has no therapeutic impact, particularly if considering that 67% of patients with nodal involvement have para-aortic lymph node metastases and 16% of patients with documented lymphatic dissemination have isolated para-aortic metastases [24]. Finally, both studies did not use the information derived from lymphadenectomy to target postoperative treatment (i.e., to spare patients with negative nodes from radiotherapy or to target postoperative treatment to the metastatic areas), thus, eliminating one of the potential benefits of this surgical procedure.

Patterns of metastatic dissemination in endometrial cancer

Endometrial cancer is generally diagnosed early in its natural history: in fact approximately 80% of patients present with stage I disease. Nevertheless, approximately 1 in every 3 women who die of EC had been considered to have early locoregional disease at primary treatment. The majority of treatment failures and the accompanying compromised longevity are probably the result of the inability in recognizing sites of occult extrauterine dissemination at the time of primary treatment. Furthermore, adjuvant therapy has generally been dictated by traditional preferences (modality-based) rather than determined by patterns of recurrence (target-based algorithms).

Traditional therapy (modality-based) for high-risk endometrial cancer is external beam radiotherapy frequently supplemented with vaginal brachytherapy [25]. This type of approach has been demonstrated to improve local control but not survival in early stage disease [12, 26, 27].

Understanding the different pathways of metastatic dissemination of endometrial cancer and their predictive factors allows the development of an individualized model for possible target-based therapeutic approaches. The natural history of epithelial corpus cancer includes four potential routes of metastasis: (1) contiguous extension (mainly to the vagina), (2) hematogenous dissemination, (3) lymphatic embolization, and (4) exfoliation with intraperitoneal spread. On the basis of regression analysis, independent pathologic risk factors predictive of the four routes of metastatic spread were identified:

1. **Contiguity**: Histologic grade 3 and lymphovascular space invasion are proven predictors of vaginal relapse in stage I EC [28].
2. **Hematogenous**: Deep myometrial invasion is the strongest predictor of hematogenous recurrence (>50% for all stages and ≥66% for stage I) [29, 30].
3. **Lymphatic**: Lymphatic failure is more likely to occur when cervical stroma involvement and positive lymph nodes are present [31].
4. **Peritoneal**: Predictors of peritoneal relapse are the following: (a) Stage IV disease or (b) stage II–III disease with two or more of the following risk factors: cervical invasion, peritoneal cytologic results positive for EC, positive lymph nodes, and nonendometrioid histologic findings [32]. The above characteristics are summarized in Tab. 4.

In our analysis [33], we stratified recurrences, based on the different patterns of spread. More precisely, 18% of patients had isolated recurrence in the vagi-
na, 21% had an isolated hematogenous relapse, 16% had an isolated lymphatic relapse, and 18% had an isolated peritoneal relapse. However, 12.5% of patients had concomitant hematogenous and lymphatic recurrence, 11% had concomitant hematogenous and peritoneal recurrence, 0.5% had concomitant lymphatic and peritoneal recurrence, and 3% had concomitant recurrence in all three sites. Of all the recurrences, 27% had multiple sites of primary relapse (Fig. 2). The respective relapse rates at 5 years were 28% for patients who were at risk for hematogenous dissemination, 31% for lymphatic recurrence and 42% for peritoneal failure. This contrasted with less than a 5% recurrence rate in the corresponding subgroups not at risk for relapse (p<0.001).

The associated recurrences for each of the diverse routes of spread would presuppose different adjuvant treatment strategies. Such target-based therapies are predicated on the cataloging of specific pathologic or molecular factors that can identify patients at high risk for harboring occult disease disseminated via one or more of these routes [33].

The optimal treatment paradigm for patients with endometrial cancer should minimize overtreatment by identifying patients not requiring lymphadenectomy, radiotherapy or chemotherapy and minimize undertreatment by identifying those patients benefitting from lymphadenectomy or radiation or chemotherapy or a combination of these modalities. As noted above, 46% of the at-risk patients (which equates to 35% of the Mayo population) experienced treatment failure. Extrapolating these percentages to the 40,070 patients diagnosed with endometrial cancer in the US during 2008 [1], 14,425 patients (36%) would be at high risk for failure and 6,451 (46%) would be anticipated to fail. This estimate approaches the anticipated number of deaths (n=7,470) that have been attributed to this disease during 2008 [1]. Therefore, approximately one-third of the patients with endometrial cancer in the US would potentially benefit from enrollment in clinical trials addressing disease-based adjuvant therapy. Innovative disease-based algorithms should be incorporated in the development of future multimodality clinical trials predicated on the site or sites of recurrence.

The objective of defining risk factors for different potential routes of dissemination after systematic surgical staging was to provide practical treatment algorithms for the postoperative management of endometrial cancer.

In patients with adequate surgical staging, we suggest:

- using systemic chemotherapy (or any other experimental systemic treatment) in the presence of risk factors for hematogenous recurrences;
- external beam radiotherapy for preventing lymphatic recurrences in the pelvic and para-aortic areas.
- the administration of chemotherapy for the prevention of abdominal recurrences based on the results of the GOG 122 study [11] and on our finding of extra-abdominal recurrences in 43% of patients with abdominal failure [32].
- vaginal brachytherapy in patients at risk of vaginal recurrence.

Risk factors for all the different sites of metastatic dissemination are summarized in Tab. 1.

Sufficient data have been generated from which to draw conclusions for designing practical postoperative guidelines, employing the disease-based criteria [33] and the focused analysis of subgroups of patients with advanced stage endometrial cancer. We are currently testing the above guidelines in a prospective fashion. Results still need additional follow-up and more mature data.

**Conclusion**

In summary, there is an exigent need for a paradigm shift in the management of endometrial cancer. The continuing debate as to whether to perform lymphadenectomy versus radiotherapy (again
fueled by the two recent trials on the therapeutic role of pelvic lymphadenectomy) is indicative of an old, modality-based view of management of this malignancy. In our opinion, the traditional modality-based approach should be replaced with a disease-based paradigm implying innovative care pathways.

Corresponding author
A. Mariani M.D.
Department of Gynecologic Surgery
Mayo Clinic
200 First St. S.W, 55905 Rochester, MN USA
Mariani.andrea@mayo.edu

References

15. The writing committee on behalf of the ASTEC study group (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial); a randomised study. Lancet 373:125–136