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Review

Improving oncologic outcomes for women with endometrial cancer: Realigning our sights

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HIGHLIGHTS

- Existing and planned trials in high risk and advanced stage endometrial cancer have included heterogeneous cohorts.
- Preliminary evidence exists that response to chemotherapy may be correlated with both stage and grade.
- Consideration should be given to enrolling stage IV patients into phase I trials at diagnosis given their poor prognosis.

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ABSTRACT

This review will examine existing results on the postoperative treatment of women with high-risk and advanced stage endometrial cancer. Preliminary data suggests that response to treatment is highly dependent on both grade and stage. It is hoped that this discussion will highlight deficiencies in our collective knowledge base to be addressed in future clinical trials for the benefit of women with endometrial cancer.

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Introduction

Controversy surrounding surgical staging and the role of lymphadenectomy in patients with endometrial cancer has occupied center stage at clinical congresses nationally and internationally. While we remain in need of a surgical standard of care, this decades-old preoccupation has in some ways distracted us from crucial considerations necessary to improve oncologic outcomes: namely, which patients are most likely to die of disease as opposed to co-morbid conditions, and how are they most effectively treated? This review will explore these fundamental questions by assessing investigations of patients who received postoperative treatment for high-risk or advanced stage disease. It is hoped that this discussion will highlight deficiencies in our collective knowledge base that will be addressed in future clinical trials for the benefit of women with endometrial cancer.

As a starting point for discussion, Fig. 1 is a graphic representation of 1303 consecutive patients surgically treated for endometrial cancer at a single institution. To account for inconsistencies in staging techniques around the world, in this figure patients are stratified by uterine risk

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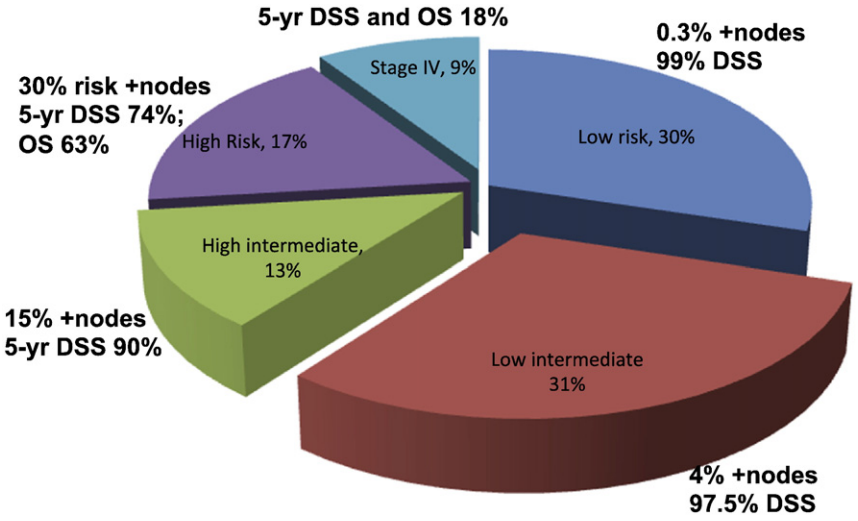

Fig. 1. Representation of 1303 consecutive patients with endometrial cancer treated surgically at Mayo Clinic, Rochester, with accompanying risk of lymphatic metastases and survival. Note that in the Mayo risk classification system patients are stratified by uterine risk factors alone, not stage. Low risk: endometrioid grade 1 or 2, ≤50% myometrial invasion (MI), and primary tumor diameter (PTD) ≤2 cm; endometrioid without MI; Low intermediate risk: low risk grade 1 or 2 cases, but PTD >2 cm or PTD unknown; High intermediate risk: endometrioid grade 1 or 2 and >50% MI; endometrioid grade 3 and ≤50% MI; High risk: non-endometrioid; endometrioid grade 3 and >50% MI; adnexal, vaginal, or parametrial involvement; Stage IV: FIGO stage IV.

factors alone. Considering the potential for trial enrollment, the low and low intermediate risk groups are a tempting cohort to study given they represent 60% of all women with endometrial cancer and 70% of women with endometrioid lesions. However, overall survival (OS) was 93% and disease specific survival (DSS) 99%, indicating that these women are far more likely to die of comorbidities than of endometrial cancer itself (only 16% of deaths in low-risk patients are cancer-related) [1]. In other words, in the United States, endometrial cancer is most commonly not an oncologic threat, but a public health dilemma most effectively addressed with interventions aimed at promoting an active lifestyle and healthy diet. In stark contrast, the 40% of patients with high-risk and stage IV disease have an appreciable risk of treatment failure and death. While this represents a smaller cohort, the need to improve their oncologic outcomes is more urgent. In fact, only 8% of endometrial cancer-related deaths are in low and low intermediate risk patients, while 86% of recurrences and 92% of cancer-related deaths occur in the remaining risk groups.

High risk endometrial cancer

Considering the high risk group, a substantial proportion will have positive lymph nodes (Fig. 1). However, irrespective of lymph node status, 30% will develop hematogenous recurrences with accompanying 5-year survival of less than 70% [2,3]. A number of investigators have therefore attempted to improve outcomes through the use of adjuvant therapies. ASTEC/EN.5 randomized 905 women with high grade and any MI = myometrial invasion or low grade and >50% MI to external beam irradiation therapy vs. observation [4]. While not a pure cohort, 72% of patients were of endometrioid histology with >50% MI, providing useful information on the high-risk group. Given their high underlying risk of hematogenous dissemination, it is not surprising that regional radiation did not improve outcomes, even when stratified by intermediate or high risk of recurrence. To address this problem of distant metastases, JGOG randomized patients with stage I–III endometrial cancer, all with MI >50%, to either pelvic radiation therapy or cyclophosphamide–doxorubicin–cisplatin (CAP) chemotherapy [5]. No difference in outcomes was found for the entire cohort. However, significant improvements were seen for specific risk categories. Notably, the 5-year progression free survival (PFS) (84% vs. 66%, HR 0.44; $p = 0.02$) and overall survival (OS) (90% vs. 74%, HR 0.24; $p < 0.01$) favored CAP for high intermediate risk patients (HIR, $n = 120$). The investigators defined HIR as follows (all with >50% MI): patients over the age of 70 years, grade 3 of any age, stage II, or IIIA (positive cytology). The observed difference in OS is convincing, with a few caveats. First, type II histologies were excluded in this trial (*note: for the purposes of this review, type I is defined as endometrioid histology irrespective of grade; type II refers to serous or clear cell carcinomas*). Second, only 14% of patients were grade 3. We can therefore conclude from these two trials that 1) radiation therapy does not appear to appreciably impact disease specific, recurrence free, or overall survival in patients with high risk endometrial cancer; and 2) chemotherapy may improve OS in a subset of patients with deep MI, recognizing that little data exists for high grade and serous lesions. The nuance that heterogeneous carcinomas require tailored therapies should not be lost and is purposely repeated throughout this review.

At first read, the second caveat appears unnecessarily conservative given that poorly differentiated lesions are generally thought to have better initial responses to cytotoxic therapy than their well-differentiated counterparts. But histologic subtype, and more precisely grade (discussed later), appears to be a critical consideration when predicting response to therapy, as further supported by trials in advanced stage patients. Hogberg et al. pooled 540 patients with high-risk stage I/II and stage III endometrial cancer randomly assigned to pelvic radiotherapy with or without sequential chemotherapy from NSGO and MaNGO [6]. Half of the patients were grade 3, 70% were type I, and 56% were stage IB or IC (FIGO 2009 stage IB). The combination resulted in a 37% reduction in the risk for relapse or death ($p < 0.01$), a 45% reduction in DSS ($p = 0.01$) and a 31% reduction in OS that approached statistical significance ($p = 0.07$). However, there was no difference in PFS for patients with serous or clear cell carcinomas (HR for PFS and OS was 0.83 ($p = 0.59$) and 0.94 ($p = 0.88$), respectively). GOG 122 randomized 396 patients with stage III/IV endometrial cancer to whole abdominal irradiation therapy vs. doxorubicin and cisplatin [7]. Grade 3 patients accounted for 53%, and 26% were type II. Distinct from previously reviewed investigations, this was not a pure adjuvant trial as 16% harbored gross residual disease at the time of treatment. The use of chemotherapy was associated with improved 5-year PFS and OS (HR 0.68; $p < 0.01$). However, an infrequently quoted finding from this trial was that while chemotherapy appeared to be efficacious for endometrioid patients, PFS and OS were not statistically different for patients with type II histologies (HR 0.91 and 1.03, respectively). A third investigation pooled over 1200 patients from 4 randomized GOG trials [8].