Fertility-sparing treatment of endometrial cancer: options, outcomes and pitfalls

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Endometrial cancer is the most common gynecologic malignancy in the United States, with over 40,000 cases diagnosed each year. While a majority of cases are diagnosed in post-menopausal women, up to 14% of cases will be in pre-menopausal women, including 4% diagnosed in women less than 40 years of age. While hysterectomy with bilateral salpingo-oophorectomy with assessment of the retroperitoneal lymph nodes is standard initial treatment for endometrial cancer, younger women may desire fertility sparing options. The decision to proceed with conservative management in this younger patient population is associated with multiple complexities, including the inherent oncologic risks of an inadequately staged and treated endometrial cancer, the risk of a synchronous or meta-synchronous cancer, the increased risk of an inherited genetic predisposition to malignancy and the lack of uniformity in the medical management and surveillance. In this review we will discuss the conservative management of endometrial cancer, specifically the role of progestin hormonal therapy, including the risks associated with non-standard care, appropriate candidate selection and work up, expected outcomes, various progestin agents and recommended follow-up.

Keywords: Endometrial neoplasms, Fertility preservation, Progestins

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 40,000 cases diagnosed each year [1]. While a majority of cases are diagnosed in post-menopausal women, up to 14% of cases will be in pre-menopausal women, including 4% diagnosed in women less than 40 years of age [2-5]. A majority of cases in younger women are early stage and low grade, thus associated with an excellent outcome [2]. While hysterectomy, bilateral salpingo-oophorectomy and assessment of the retroperitoneal lymph nodes is standard initial treatment for endometrial cancer, younger women may desire fertility sparing options. The decision to proceed with conservative management in this younger patient population is associated with multiple complexities, including the inherent oncologic risks of an inadequately staged and treated endometrial cancer, the risk of a synchronous or meta-synchronous cancer, the increased risk of an inherited genetic predisposition to malignancy and the lack of uniformity in the medical management and surveillance. In this review we will discuss the conservative management of endometrial cancer, specifically the role of progestin hormonal therapy, including the risks associated with non-standard care, appropriate candidate selection and work up, expected outcomes, various progestin agents and recommended follow-up.

WHAT ARE THE ONCOLOGIC RISKS?

While most young women with endometrial cancer have low grade tumors confined to the uterus [2], any decision to

deviate from the standard approach of hysterectomy with oophorectomy and staging should be done so with the acknowledgement of the risk of an undiagnosed, and therefore subsequently untreated, synchronous or metastatic cancer. In Duska et al's review [2] of women less than 40 years of age, a majority of women had stage I and grade I disease, however 19 of 95 patients (20%) had disease beyond the uterus, including 10 with advanced disease. Four women died as a result of their disease. In a study from Australia of premenopausal women with endometrial cancer, there was a higher incidence of coexistent ovarian malignancies when compared to women greater than 45 years old [3]. Five of 17 women less than 45 had stage III or IV disease. In a review of over 2,000 women aged 40 years or younger collected from the National Cancer Institute database, although a majority of patients had disease confined to the uterus (75%), approximately 17% had stage III or IV disease [4]. These younger patients are also at increased risk of other gynecologic pathologies, including ovarian tumors. In a review of young women with endometrial cancer by Walsh et al. [6], 26 of 102 women (25%) were found to have coexisting epithelial ovarian tumors (23 synchronous primaries and 3 metastases). These studies confirm the need for thorough examination and careful patient selection, while highlighting the risks inherent in conservative management of an unstaged cancer.

The pathogenesis of endometrial cancer in a young woman is usually a resultant of a hyperestrogenic state that arises in the setting of endometrial hyperplasia. A tissue biopsy consistent with endometrial hyperplasia should be considered a potential harbinger of endometrial cancer. This relation was initially definitively established in the seminal paper by Kurman et al. [7] in which they reported a 29% risk of progression of endometrial hyperplasia with atypia to endometrial cancer. More recently, Trimble al. [8] reported a 43% incidence of endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia. This high rate of concurrent carcinoma warrants consideration in management decisions.

WHO ARE APPROPRIATE CANDIDATES?

Considering that a majority of women with endometrial cancer have early stage disease which will be cured with surgery alone, every effort should be taken to ensure that the endometrial cancer is confined to the endometrium and low grade, therefore likely to respond to hormonal therapy without compromising their ultimate curability. Pretreatment evaluation should consist of a full evaluation including a complete history and physical with attention toward and signs or symptoms suspicious for advanced/metastatic disease. If not already done, a dilation and endometrial curettage should be performed, as it has been shown to be more accurate in correlating with final pathology in grade I endometrial cancer when compared to office endometrial biopsy [9]. Additionally, the endometrial cancer is more likely to be removed with a D&C than an endometrial biopsy [10].

After confirming the low grade nature of the tumor, attempts should then be undertaken to rule out myometrial invasion and lymph node metastasis. MRI has proven to be a superior means to determine myometrial invasion when compared to transvaginal ultrasound and CT. When comparing histologic findings to MRI, Sironi et al. [11] reported a sensitivity and specificity of 74% for assessing superficial myometrial invasion. The sensitivity and specificity for tumor confined to the endometrium was 57% and 96%, respectively. In a similar study, the reported accuracy of detecting deep myometrial invasion and cervical invasion was 95% and 88%, respectively [12]. MRI can also be used to assess loco-regional disease spread [13]. Enlarged lymph nodes and those with central necrosis should be considered suspicious for metastatic disease.

WHAT PERCENTAGE OF PATIENTS WILL RESPOND TO HORMONAL THERAPY?

A majority of patients with well differentiated endometrial cancer respond to treatment with progestational agents. In a meta-analysis of 27 articles, including 81 patients, Ramirez et al. [14] reported that 76% of patients responded to treatment. Twenty-four percent of patients who initially responded ultimately recurred at a median of 19 months. Consideration must be given to the publication bias inherent in the studies analyzed, whereby studies of successful treatment are more likely to be reported and published, thus overestimating the success rate. In the only prospective trial, 55% of cases of endometrial cancer were successfully treated with MPA [15].

WHAT HORMONAL THERAPY TO USE?

The initial data regarding hormonal therapy for endometrial hyperplasia and cancer was from small case series and retrospective reports. For this reason there is no consensus regarding the ideal progestin agent. In a review of available studies, the most commonly used agents were modroxyprogesterone acetate (MPA; 44%) and megesterol acetate (35%) [14]. In the first multicenter prospective trial of fertility-sparing treatment with progestins, investigators from Japan used a MPA 600 mg

oral dose given daily [15]. Additionally, other small series have reported treatment with levonorgestrel intrauterine devices (IUD) [16], in addition to hysteroscopic resection [17] and medroxyprogesterone [18].

The choice of progestin and its method of delivery should be dictated by its expected efficacy as well as expected side effects and patient tolerability. Orally administered progestins are not without side-effects, including thrombus formation, mood alterations, headaches, weight gain and breast pain and/or tenderness. In their prospective trial using 600 mg MPA, Ushijima et al. [15] reported the most common side effects were weight gain and liver dysfunction. There were no cases of thromboembolism. Progesterone therapy is contraindicated in those with a thromboembolism history, breast cancer or hepatic dysfunction. The progesterone-releasing IUD is a means to generate a localized effect within the endometrium while avoiding the adverse systemic toxicity. The levonorgestrel-releasing intrauterine system (Mirena) releases 20 mcg of levonorgestrel per day [19].

WHAT IS THE APPROPRIATE SURVEILLANCE OF THESE PATIENTS?

The importance of close surveillance cannot be overemphasized as the consequences of the lack of recognition of a non-hormonally responsive endometrial cancer could ultimately prove fatal. Although a majority of these carefully selected patients will respond to progestin therapy, there is no way to accurately predict who will be a responder versus a non-responder. A thinning of the endometrium as seen on transvaginal ultrasound is associated with an increased chance of responding to progestin therapy [15]. However, the predictive value is not sufficient enough to obviate endometrial sampling. BMI and polycystic ovarian syndrome also do not predict likelihood of response.

Among patients who do respond, a majority will do so by 16 weeks [15]. We would recommend that assessment of response should be in the form of endometrial sampling at four to six months after initiating progestin therapy. Those with persistence or progression of the endometrial cancer should be counseled to pursue more definitive therapy as those who have not responded by at 16 weeks are unlikely to do so. Those who have a documented histologic response and wish to pursue childbearing should follow-up with a reproductive endocrinologist with due haste. Responders who do not wish to pursue fertility immediately should be continued on hormonal therapy. The duration with which the hormonal therapy will be successful is unknown. Even initial responders

are at risk of recurrence, including extrauterine disease [20-22].

WHAT ARE THE EXPECTED REPRODUCTIVE OUTCOMES?

It is impossible to calculate the rate of successful conceptions as the denominator of the number of women pursuing fertility is unknown. Most patients who do conceive after conservative therapy require assisted reproductive technologies, including in vitro fertilization [15,23-25]. These patients face difficulty conceiving secondary to obesity, polycystic ovarian syndrome and chronic anovulation. Secondary to these issues we recommend an initial consultation with a reproductive endocrinologist in order to assess the patient's reproductive options and likelihood of conception. This ensures appropriately informed expectations regarding reproductive potential and thus the patient's desire to proceed with fertility-preserving therapy.

WHAT ADDITIONAL COUNSELING SHOULD THESE WOMEN RECEIVE?

In addition to an extensive conversation regarding the non-standard nature of progestin therapy for endometrial cancer and the risks intrinsic to an unstaged cancer, these women warrant additional counseling. As young women with endometrial cancer are often obese, they should be encouraged to institute dietary and healthy lifestyle modifications, including exercise, with subsequent referrals made to ensure their implementation. Additionally it should be appreciated that women diagnosed with endometrial cancer at a young age are at increased risk for a mismatch repair gene mutation associated with Lynch syndrome and should be referred for genetic counseling [26]. Identification of those with this inherited genetic predisposition will allow the patient and her relatives to undertake additional cancer prevention strategies.

CONCLUSION

The care of the premenopausal endometrial cancer patient desirous of maintaining her reproductive potential poses several challenges. While hormonal therapy with progestin agents are effective in a majority of treated cases, it is not without risks. Risks include an unrecognized and untreated advanced endometrial cancer or synchronous tumor. Patients should be carefully selected and extensively counseled regarding the deviation from the standard of care, the oncologic

risks, and the subsequent likely need for reproductive technologies to ensure conception. These young women may harbor a genetic predisposition for endometrial and colon cancer.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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