Editorial

Pushing the envelope: expanding fertility sparing treatment of endometrial cancer

Katherine Ikard Stewart , Melinda S. Yates , Shannon N. Westin

Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA

OPEN ACCESS

Received: Jun 26, 2020
Accepted: Jun 26, 2020

Correspondence to Shannon N. Westin

Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, University of Texas MD Anderson Cancer Center, 1155 Herman Pressler, Unit 1362, Houston, TX 77030, USA.
E-mail: swestin@mdanderson.org

Copyright © 2020. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology, and Japan Society of Gynecologic Oncology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Katherine Ikard Stewart
<https://orcid.org/0000-0001-6922-5433>
Melinda S. Yates
<https://orcid.org/0000-0001-9450-5517>
Shannon N. Westin
<https://orcid.org/0000-0002-1922-0156>

Funding

NIH SPOR in Uterine Cancer (NIH 5P50CA098258-13) (SW, MY), MD Anderson Cancer Center Support Grant (NIH CA016672).

► See the article “Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GIG) study” in volume 31, e74.

Fertility-sparing management of apparent early stage, low grade endometrial cancer is becoming more prevalent as growing evidence reveals acceptable oncologic and reproductive outcomes. Expansion of who can receive conservative therapy is especially relevant as more women delay childbearing and the incidence of endometrial cancer continues to rise, including rates among premenopausal women [1]. Current society guidelines recommend consideration of fertility-sparing management for only complex atypical endometrial hyperplasia and grade 1 (well differentiated) endometrioid endometrial cancers that meet very specific criteria [2,3].

The oncologic safety of a fertility-sparing treatment approach in grade 2 endometrioid endometrial cancers is largely unknown. To date, small retrospective case series have comprised the bulk of the literature including this important patient population. Prior to the current manuscript by Falcone and colleagues, the largest series included 17 patients with grade 2–3 endometrial cancer without myometrial invasion treated with oral medroxyprogesterone. This agent achieved a complete response rate of 76.5% and recurrence rate of 23.1% [4]. Another series included 8 patients with grade 2 endometrial cancer treated with levonorgestrel-releasing intrauterine device (LNG-IUD) alone and demonstrated an overall response rate of 75% [5]. Importantly, these responses are quite similar to outcomes for grade 1 endometrioid tumors [5,6]. Despite reports of reassuring response rates, in one study, grade 2 endometrial cancer treated with medroxyprogesterone and LNG-IUD was associated with a lower live birth rate when compared to grade 1 endometrial cancer [7]. Conversely, a recent study from China included 11 grade 2 endometrial cancer patients treated with oral progestin therapy and reported equivalent response, recurrence, and pregnancy rates compared to grade 1 endometrial cancer [8]. Given the substantial differences in median body mass index across these studies, the impact of obesity on underlying tumor biology, progestin response, and fertility outcomes remains unknown. There is a clear paucity of evidence in the management of these patients.

In this issue of the *Journal of Gynecologic Oncology*, Falcone and colleagues [9] report on the oncologic and reproductive outcomes in 23 patients with grade 2 endometrial cancer from multiple centers. Patients were treated with a combination of hysteroscopic resection plus

NIH T32 Training Grant 5 T32 CA101642 02 (KS). The funding sources had no involvement in the creation of this manuscript.

Conflict of Interest

Shannon N. Westin reports personal fees for consulting from AstraZeneca, Circulogene, Clovis Oncology, Merck, Novartis, Pfizer, Roche/Genentech, GSK/Tesaro, Zentalis, Eisai, and research funding to her institution from ArQule, AstraZeneca, Bayer, Clovis Oncology, Cotinga Pharmaceuticals, Novartis, Roche/Genentech, and GSK/Tesaro. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: S.K.I., Y.M.S., W.S.N.; Data curation: S.K.I., Y.M.S., W.S.N.; Formal analysis: S.K.I., Y.M.S., W.S.N.; Funding acquisition: S.K.I., Y.M.S., W.S.N.; Investigation: S.K.I., Y.M.S., W.S.N.; Methodology: S.K.I., Y.M.S., W.S.N.; Project administration: S.K.I., Y.M.S., W.S.N.; Resources: S.K.I., Y.M.S., W.S.N.; Writing - original draft: S.K.I., Y.M.S., W.S.N.; Writing - review & editing: S.K.I., Y.M.S., W.S.N.

progestin therapy with LNG-IUD, megestrol acetate or norethisterone acetate. One of the clear strengths of this study is sample size. With a total of 23 patients, it is now the largest reported case series of grade 2 endometrial cancers receiving fertility-sparing management. The reported complete response rate (73.9%) was consistent with previous studies. It is notable, however, that time to complete response was slightly longer (6 v 4.5 months) and duration of response was shorter (21 vs. 58 months) when compared to the largest reported series of conservatively treated grade 1 endometrial cancer patients [6]. The fact that only 58.5% of the complete responders attempted to conceive in this study coupled with refusal of definitive surgery in some patients, highlights the need for a comprehensive counseling approach prior to considering a treatment that strays from standard of care.

The authors mention the potential application of biomarkers, which could prove essential in predicting response to treatment and reducing risk of unfavorable outcomes. However, with very limited data on conservatively treated grade 2 endometrial cancers, biomarker analyses have not yet been reported. Histopathologic evaluation demonstrating absence of exogenous progesterone effect at early time points after progestin therapy initiation has been associated with lack of progestin response [5]. Given the known discordance in grade and histotype between pathologists, analysis of ProMisE classification using p53, MSH6, PMS2, and POLE could be implemented to improve reproducibility in identifying at-risk groups [10]. A preliminary report of this application in 48 patients with endometrial intraepithelial neoplasia or endometrial cancer (two of which were grade 2), revealed that presence of the copy number high/p53 aberrant molecular phenotype was associated with shorter time to progression after treatment with the levonorgestrel IUD [11]. This is certainly interesting but requires validation in larger prospective studies. Prediction of progestin response using other biomarkers in grade 1 endometrioid endometrial cancers has produced conflicting results, but could be used to guide selection of candidate markers for evaluation in grade 2 cancers [12]. Proliferation rate (Ki67) and progesterone receptor (including specific isoforms and glandular or stromal expression patterns) may be candidates for evaluation.

We commend the authors for their contribution to an area in desperate need of evidence-based guidance and we strongly agree with their conclusion that the numbers must be interpreted with caution. While these are encouraging data, in the absence of larger prospective studies, patients should be counseled with a shared decision-making approach. One must clearly understand the lack of high-quality evidence available, potential oncologic perils including risk of a missed underlying histologic diagnosis and/or undetected spread of disease, which could ultimately have a detrimental effect on overall survival. In addition, it is of paramount importance to consider overall health and fertility potential of an individual patient prior to recommending oncologic treatment that deviates from the standard of care. Early evaluation with oncofertility colleagues should be strongly considered. Given the relative rarity of this intervention, all providers should systematically follow these patients and contribute to the literature by reporting oncologic and reproductive outcomes in order to maximize care of this growing patient population.

REFERENCES

1. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer [Internet]. Bethesda, MD: National Cancer Institute; c2020 [cited 2020 Jun 21]. Available from: <https://seer.cancer.gov/statfacts/html/corp.html>.

2. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:170-99.
[PUBMED](#) | [CROSSREF](#)
3. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Radiother Oncol* 2015;117:559-81.
[PUBMED](#) | [CROSSREF](#)
4. Park JY, Kim DY, Kim TJ, Kim JW, Kim JH, Kim YM, et al. Hormonal therapy for women with stage IA endometrial cancer of all grades. *Obstet Gynecol* 2013;122:7-14.
[PUBMED](#) | [CROSSREF](#)
5. Pal N, Broaddus RR, Urbauer DL, Balakrishnan N, Milbourne A, Schmeler KM, et al. Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device. *Obstet Gynecol* 2018;131:109-16.
[PUBMED](#) | [CROSSREF](#)
6. Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *Eur J Cancer* 2013;49:868-74.
[PUBMED](#) | [CROSSREF](#)
7. Chae SH, Shim SH, Lee SJ, Lee JY, Kim SN, Kang SB. Pregnancy and oncologic outcomes after fertility-sparing management for early stage endometrioid endometrial cancer. *Int J Gynecol Cancer* 2019;29:77-85.
[PUBMED](#) | [CROSSREF](#)
8. Wang YQ, Zhou R, Xu LJ, Xia M, Lu Q, Liu GL, et al. Analysis of prognosis and pregnancy outcomes of fertility-preserving treatment for patients with stage Ia, grade 2 endometrial cancer. *Zhonghua Fu Chan Ke Za Zhi* 2020;55:327-32.
[PUBMED](#) | [CROSSREF](#)
9. Falcone F, Leone Roberti Maggiore U, Di Donato V, Perrone AM, Frigerio L, Bifulco G, et al. Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIg) study. *J Gynecol Oncol* 2020;31:e74.
[CROSSREF](#)
10. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol* 2018;29:1180-8.
[PUBMED](#) | [CROSSREF](#)
11. Puechl AM, Spinosa D, Berchuck A, Drury KE, Whitaker RS, Strickland KC. 29 - Turning ProMisE into practice: predicting response in medically managed endometrial cancers via molecular classification. In: Abstract presentation at Society of Gynecologic Oncology 2020 Annual Meeting on Women's Cancer; 2020 Mar 27-31; Duke University Medical Center, Durham, NC, USA. Chicago, IL: Society of Gynecologic Oncology; 2020.
12. Baxter E, Brennan DJ, McAlpine JN, Mueller JJ, Amant F, van Gent MD, et al. Improving response to progestin treatment of low-grade endometrial cancer. *Int J Gynecol Cancer* 2020;ijgc-2020-001309.
[PUBMED](#) | [CROSSREF](#)