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Review

Surgical *Versus* Conservative Treatment for Endometrial Cancer in Women of Reproductive Age: Incidence of Urinary Tract Symptoms

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Abstract. *Endometrial cancer is the most common gynecologic malignancy. The mainstay of treatment for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy. Radiation and chemotherapy accompanied with progestins can also play a significant role in treatment. Lower urinary tract symptoms (LUTS) following therapy for endometrial cancer are an extremely difficult and challenging condition that deteriorates patients' quality of life. Current literature remains rather scarce regarding LUTS after therapy for endometrial cancer. This review aimed to investigate the incidence of LUTS in endometrial cancer treatment.*

Endometrial cancer is a very commonly diagnosed malignancy of females even in women of reproductive age. It is the sixth most common malignancy worldwide with 61.880 new cases in 2019 in the United States and nearly 11,000 deaths from the disease, which primarily affects postmenopausal women (1, 2). Its incidence is increasing especially in socioeconomically developed countries including the United States where its rate reaches 19 cases in every 100,000 women (3). Similar rates are also observed in Eastern and Northern Europe. However, an extreme increase is observed in developing countries of South Africa and several countries in Asia (3).

The most frequent symptom is the post-menopausal bleeding. Other, not so rare symptoms include: irregular, unpredictable, heavy or prolonged (>7 days) periods, bleeding between periods, after sex and after menopause, pelvic pain and pressure, discharge, changes in bowel habits and urination frequency (4, 5).

The treatment of endometrial cancer may be surgical or conservative (6). The surgical treatment includes exploratory laparotomy, total hysterectomy with bilateral salpingo-oophorectomy, robotic total hysterectomy with pelvic and paraaortic lymphadenectomy, laparoscopic-assisted vaginal hysterectomy and total laparoscopic hysterectomy (7). Conservative treatment includes the use of progestins, radiation and/or chemotherapy based on staging of the disease (8). Concerning surgical treatment, the first choice is total hysterectomy with bilateral salpingo-oophorectomy.

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Three out of four women have early stage 1 cancer and they can be cured totally by surgery. The decision of whether the patient should undertake radiation and/or chemotherapy is mostly based on the histological results after the surgery (6). As for the conservative treatment, the use of progestins and more specifically medroxyprogesterone acetate (MPA), megestrol acetate (MA) and more recently levonorgestrel-release intrauterine devices (LNG-IUDs) is the most usual option for young women at reproductive age who wants to have children (8). According to American Cancer Society, chemotherapy and/or radiation therapy are also considered as a conservative option especially in women with endometrial cancer stage IV (IVA, IVB) (8).

Lower urinary tract symptoms (LUTS) are clinical symptoms that implicate the urethra, the urinary sphincter and the bladder. Recurrence is not a very unusual situation and one or more LUTS may coexist to a patient. According to the International Continence Society (ICS), LUTS can be divided into seven categories, from which the three main categories are the irritative, the obstructive and the postmicturition symptoms (9). The first one includes increased urgency/frequency of urination, nocturia, stress of incontinence, the second one comprises incomplete voiding, poor stream, retention and overflow incontinence (9). At last, the third category contains the feeling of incomplete emptying and postmicturition dribble (9). It appears that one third of patients with LUTS are improving, one third remains stable and one third is deteriorating. Their progress is variable and unpredictable, after the onset of the symptoms. Subjects with more severe urinary incontinence showed poorer scores on health-related quality of life and mental well-being assessments (10).

As for the quality of life and mental well-being, urinary incontinence is discriminated from all the other LUTS as it is one of the most important factors creating daily problems for women. It negatively impacts daily activities, social life, personal relationships, sleep and energy, and liquid consumption (11). Furthermore, it necessitates the use of protection and generates feelings of embarrassment (11).

This study aims to investigate and present the incidence of urinary tract symptoms in women who underwent a surgical procedure for endometrial cancer and those who had a conservative therapy with chemoradiotherapy or progestins.

Surgical Treatment and Urinary Tract Symptoms

Nowadays, it is essential to understand the long-term adverse effects of surgical interventions and in our review the urological adverse effects after hysterectomy, as women's life expectancy is increasing year by year (12). The surgical treatment is the most common and effective treatment for endometrial cancer and more specifically it is the first line treatment of dysfunctional uterine bleeding (DUB) (13). An excellent 5-year overall survival rate of 93% and 99% is achieved by the total hysterectomy with bilateral salpingoophorectomy with or without pelvic and/or para-aortic lymph node dissection (8, 14). Total abdominal hysterectomy affects the function of several pelvic organs such as the bladder due to the narrowness of pelvic anatomy affecting also the nerves (14). Brown *et al*. in a meta-analysis of 11 observational, controlled studies, concluded that the chances of developing urinary incontinence are 40% higher in women who have had a hysterectomy as compared with those who have had not (15).

Simple hysterectomy is the main cause of the development of symptoms of bladder dysfunction. Many women with simple hysterectomy are related with these symptoms. Parys BT *et al*. have reported in their review that there was an increase in the incidence of urinary symptoms from 58.3% pre-operatively to 75.0% post-operatively (16). Post-operative vesicourethral dysfunction and pelvic neuropathy are mainly associated with simple hysterectomy as several cross-sectional studies included in the previously referred review have indicated (16). The results of another prospective study, using questionnaires about hysterectomy-associated LUTS showed that there was no significant difference between women pre-operatively and after a 3-year post-operative follow-up, indicating that there is no risk for LUTS after surgery (17). Additionally, a prospective observational study that took place in the Netherlands, analyzed questionnaires of 430 women that had abdominal or vaginal hysterectomy and found out that after a 3-year follow-up, the participants who had a vaginal hysterectomy had significantly more urinary tract symptoms than the women who underwent an abdominal hysterectomy (18). Another meta-analysis in the Netherlands has shown that hysterectomy has an important role in the post-operative appearance of incontinence, without differentiating the type, as it increases the odds by approximately 30% (19). In Italy, case-control study in gynecological settings has shown that women with higher BMI and a history of total hysterectomy for endometrial cancer had increased risk of all types of urinary incontinence (20). A nationwide study in Taiwan comprised 2,410 women has shown that hysterectomy is indeed a risk factor for incontinence and that the prevalence of incontinence among women who underwent surgical procedure was about 42% and among women that did not, it was around 27% (21).

Non-surgical Treatment of Endometrial Cancer and Urinary Tract Symptoms

Radiotherapy is well established in the treatment algorithm of endometrial cancer, both as complementary therapy after surgical treatment or as definitive therapy for advanced

Table I. *Treatment strategies and urinary tract symptoms results*.

Authors	Treatment	Urinary tract symptoms-Results
Brown JS *et al*. (15)	Hysterectomy	40% higher urinary incontinence after surgery
Parys BT *et al*. (16)	Hysterectomy	16.7% increased LUTS after surgery
Gustafsson C *et al*. (17)	Hysterectomy	No increase in urinary tract symptoms after surgery
Lakeman MM *et al*. (18)	Hysterectomy	Increased risk for LUTS after vaginal hysterectomy compared to abdominal hysterectomy
van der Vaart CH *et al*. (19)	Hysterectomy	30% increased incontinence after surgery
Parazzini F *et al*. (20)	Hysterectomy	Increased risk of urinary incontinence
Hsieh CH *et al*. (21)	Hysterectomy	15% increased urinary incontinence
Herwig *et al*. (23)	Radiation therapy	53.7% urinary incontinence after adjuvant radiation therapy
Skjeldestad *et al*. (24)	Radiation therapy	Similar risk of urinary incontinence
Sorbe BG *et al*. (25)	Radiation therapy+hysterectomy	30.0% genitourinary adverse events
White AJ *et al*. (26)	Radiation +/– vaginal Brachytherapy	18% bladder problems After radiation and vaginal brachytherapy and 12.3% after vaginal brachytherapy only
Soisson S *et al*. (27)	Radiation +/– chemotherapy	37.4% urinary system disorders
Heliovaara-Peippo *et al*. (28)	LNG-IUS or hysterectomy	Increased stress urinary incontinence after surgery comparing to LNG-IUS, increased day-time frequency and sensation of incomplete emptying after hysterectomy
Robinson D *et al*. (29)	Progestins	No significant relationship between urinary incontinence and progestin use
Champaneria R *et al*. (30)	Progestins	Increased risk of interstitial cystitis

endometrial cancer (stage IV). It is known that the bladder is at risk during radiation therapy for the treatment gynecologic malignancies. Most of the published literature reports that bladder symptoms result from pelvic radiation; these symptoms are mostly reported without validated measures (22). Many factors can determine whether a woman is at risk for urinary tract symptoms following radiation therapy including the pretreatment status of the bladder, bladder tolerance to the radiation, the fractionation of the radiation, the size of the field, and the total dose of radiation to the bladder (22).

Early urinary complications such as irritative bladder symptoms, stress of incontinence, abnormal voiding function, and radiation-induced cystitis can develop from the start of therapy to weeks after completion of treatment. Late complications of pelvic radiation therapy such as urinary incontinence, irritative symptoms, fibrosis, necrosis, late radiation cystitis, hemorrhagic cystitis, bladder ulceration, and vesicovaginal fistula, have been reported from 6 months to 30 years after completing treatment (22).

The prevalence of urinary symptoms following radiation therapy for endometrial cancer is inconsistent. Herwig *et al*. have reported urinary incontinence in 53.7% of women with stage I endometrial cancer treated with adjuvant radiation therapy (23). Skjeldestad and Hagen have reported on urinary symptoms of 160 women treated for gynecologic cancer in Norway and compared them to 432 age-matched controls. Twenty-one percent of cases were survivors of endometrial cancer and 82.3% of them received adjuvant radiation therapy. These cases were not associated with higher incidence of urinary incontinence compared to controls (24). A randomized trial has reported genitourinary adverse events in 30.0% of early stage endometrial cancer patients treated with radiation and surgery, and in 7.9% of patients with surgery only (25). In another randomized trial, bladder problems were reported in 18% of endometrial cancer patients who had external beam radiation and vaginal brachytherapy, and in 12.3% of patients with vaginal brachytherapy only (26). Soisson *et al*. have reported that endometrial cancer survivors after radiation and/or chemotherapy had elevated risk for urinary system disorders between 1-5 and >5-10 years after diagnosis. Within 5 years of cancer diagnosis, 37.4% of endometrial cancer patients may be diagnosed with urinary diseases. Their results provide evidence that those treated with RT and/or chemotherapy compared to those treated with surgery alone are at higher risk for urinary system disorders within 5 years of diagnosis (27).

Regarding progestins, Heliovaara-Peippo *et al*. have found that women treated with LNG-IUS were more likely to experience dysuria at 6 and 12 months compared to those having a hysterectomy. Also, at 12 months, more patients who underwent hysterectomy experienced increased day-time frequency and sensation of incomplete emptying than those who received LNG-IUS. Finally, more women who had undergone hysterectomy reported stress of urinary incontinence compared with those who had LNG-IUS (28). Robinson *et al*. have found that there was no significant relationship between urinary incontinence and progestin use

(29). Finally, interstitial cystitis seems to have a higher prevalence amongst women that have previously used or currently use progestins than those who had no prior use (30).

The different treatment strategies and possible results on urinary tract symptoms are summarized in Table I.

Conclusion

In conclusion, LUTS are an extremely difficult and challenging condition amongst endometrial cancer patients that deteriorate their quality of life. It seems that patients with endometrial cancer receiving surgery and radiotherapy with or without chemotherapy are at higher risk for presenting urinary system disorders than patients receiving surgery or radiotherapy alone. Progestin use seems to have lower risk for LUTS, but, dysuria and interstitial cystitis remain a serious side effect. Additional studies with a large number of patients are needed to fully understand these results, as current literature remains rather scarce on this topic.

Conflicts of Interest

The Authors declare no potential conflicts of interest regarding this study.

Authors' Contributions

Antonios Koutras: interpretation of data, drafting of the manuscript, study conception and design; Angelis Peteinaris: analysis and interpretation of data, drafting of the manuscript; Spyridon Davakis: drafting of themanuscript and analysis and interpretation of data; Georgios Kalinterakis: acquisition of data, drafting of the manuscript; Ioannis Tsilikis: acquisition of data and drafting of the manuscript; Nikolaos Garmpis: drafting of the manuscript and analysis and interpretation of data; Prokopis-Andreas Zotos: drafting of the manuscript and analysis and interpretation of data; Athanasios Chionis: analysis and interpretation of data, drafting of manuscript; Dimitrios Schizas: acquisition of data, drafting of the manuscript, critical revision of the manuscript; Ioannis Karavokyros: acquisition of data, drafting of the manuscript, critical revision of manuscript; Nikolaos Thomakos: acquisition of data, drafting of the manuscript, critical revision of the manuscript; Emmanuel Kontomanolis: acquisition of data, drafting of the manuscript, critical revision of the manuscript; Athanasios Syllaios: analysis and interpretation of data, drafting of the manuscript, study conception and design.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69(1)*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

2 Constantine GD, Kessler G, Graham S and Goldstein SR: Increased incidence of endometrial cancer following the Women's Health Initiative: An assessment of risk factors. J Womens Health (Larchmt) *28(2)*: 237-243, 2019. PMID: 30484734. DOI: 10.1089/jwh.2018.6956

3 Lortet-Tieulent J, Ferlay J, Bray F and Jemal A: International patterns and trends in endometrial cancer incidence, 1978–2013. J Natl Cancer Inst *110(4)*: 354-361, 2017. PMID: 29045681. DOI: 10.1093/jnci/djx214

4 Braun MM, Overbeek-Wager EA and Grumbo RJ: Diagnosis and management of endometrial cancer. Am Fam Physician *93(6)*: 468-474, 2016. PMID: 26977831.

5 Pakish JB, Lu KH, Sun CC, Burzawa JK, Greisinger A, Smith FA, Fellman B, Urbauer DL and Soliman PT: Endometrial cancer associated symptoms: a case-control study. J Womens Health (Larchmt) *25(11)*: 1187-1192, 2016. PMID: 27254529. DOI: 10.1089/jwh.2015.5657

6 Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR and Sessa C; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group: ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol *27(1)*: 16-41, 2016. PMID: 26634381. DOI: 10.1093/annonc/mdv484

7 Homesley HD, Boike G and Spiegel GW: Feasibility of laparoscopic management of presumed stage I endometrial carcinoma and assessment of accuracy of myoinvasion estimates by frozen section: a gynecologic oncology group study. Int J Gynecol Cancer *14*: 341-347, 2014. PMID: 23546545. DOI: 10.1007/s10147-013-0551-8

8 Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V and Denschlag D: European Society of Gynecological Oncology Task Force for Fertility Preservation. Int J Gynecol Cancer 25(7): 1258-1265, 2015. PMID: 26186070. DOI: 10.1097/IGC.0000000000000493

9 Bradway C, Coyne KS, Irwin D and Kopp Z: Lower urinary tract symptoms in women – A common but neglected problem. Journal of the American Academy of Nurse Practitioners *20(6)*: 311-318, 2008. PMID: 18588658. DOI: 10.1111/j.1745-7599.2008.00329.x

10 Cox L and Rovner ES: Lower urinary tract symptoms in women: epidemiology, diagnosis, and management. Curr Opin Urol *6(4)*: 328-33, 2016. PMID: 26999076. DOI: 10.1097/MOU.0000000000000283

11 Abrams P, Smith AP and Cotterill N: The impact of urinary incontinence on health-related quality of life (HRQoL) in a real-world population of women aged 45-60 years: results from a survey in France, Germany, the UK and the USA. BJU International *115(1)*: 143-152, 2014. PMID: 24958472. DOI: 10.1111/bju.12852

12 Skorupska KA, Miotła P, Kubik-Komar A, Rechberger E, Adamiak-Godlewska A and Rechberger T: Urinary incontinence after hysterectomy- does type of surgery matter? Ginekol Pol 87(2): 94-97, 2016. PMID: 27306284. DOI: 10.17772/gp/61551

13 Whitaker L and Critchley HO: Abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol *34*: 54-65, 2016. PMID: 26803558. DOI: 10.1016/j.bpobgyn.2015.11.012

14 Abdel Fattah M, Barrington J, Yousef M and Mostafa A: Effect of total abdominal hysterectomy in pelvic floor function. Obstet Gynecol Surv *59*: 299-304, 2004. PMID: 15024230. DOI: 10.1097/01.ogx.0000120166.84206.dd

15 Brown JS, Sawaya G, Thom DH and Grady D: Hysterectomy and urinary incontinence: a systemic review. Lancet *356(9229)*: 535-539, 2000. PMID: 10950229. DOI: 10.1016/S0140-6736(00)02577-0

16 Parys BT, Woolfenden KA and Parsons KF: Bladder dysfunction after simple hysterectomy: urodynamic and neurological

evaluation. Eur Urol *17*: 129-133, 1990. PMID: 2311638. DOI: 10.1159/000464020

17 Gustafsson C, Ekström A, Brismar S and Altman D: Urinary incontinence after hysterectomy – three-year observational study. Urology *68(4)*: 769-774, 2006. PMID: 17070350. DOI: 10.1016/j.urology.2006.04.001

18 Lakeman MM, van der Vaart CH and Roovers JP; HysVA study group: Hysterectomy and lower urinary tract symptoms: a nonrandomized comparison of vaginal and abdominal hysterectomy. Gynecol Obstet Invest *70(2)*: 100-106, 2010. PMID: 20299800. DOI: 10.1159/000297507

19 van der Vaart CH, van der Bom JG, de Leeuw JR, Roovers JP and Heintz AP: The contribution of hysterectomy to the occurrence of urge and stress urinary incontinence symptoms. BJOG *109(2)*: 149-154, 2002. PMID: 11911100. DOI: 10.1016/s1470-0328(02)01332-0

20 Parazzini F, Chiaffarino F, Lavezzari M and Giambanco V; VIVA Study Group: Risk factors for stress, urge or mixed urinary incontinence in Italy. BJOG *110(10)*: 927-933, 2003. PMID: 14550363.

21 Hsieh CH, Chang WC, Lin TY, Su TH, Li YT, Kuo TC, Lee MC, Lee MS and Chang ST: Long-term effect of hysterectomy on urinary incontinence in Taiwan. Taiwan J Obstet Gynecol *50(3)*: 326-330, 2011. PMID: 22030048. DOI: 10.1016/j.tjog.2011.07.008

22 Erekson EA, Sung VW, DiSilvestro PA and Myers DL: Urinary symptoms and impact on quality of life in women after treatment for endometrial cancer. Int Urogynecol J Pelvic Floor Dysfunct *20(2)*: 159-163, 2009. PMID: 18985266. DOI: 10.1007/s00192-008-0755-z

23 Herwig R, Bruns F, Strasser H, Pinggera GM, Micke O, Rehder P, Gozzi C, Willich N and Hertle L: Late urologic effects after adjuvant irradiation in stage I endometrial carcinoma. Urology *63*: 354-358, 2004. PMID: 14972490. DOI: 10.1016/j.urology.2003.09.040.

24 Skjeldestad FE and Hagen B: Long-term consequences of gynecological cancer treatment on urinary incontinence: a population-based cross-sectional study. Acta Obstet Gynecol Scand *87*: 469-475, 2008. PMID: 18382876. DOI: 10.1080/00016340801948326

25 Sorbe BG, Horvath G, Andersson H, Boman K, Lundgren C and Pettersson B: External pelvic and vaginal irradiation *versus* vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma: a prospective, randomized study–quality-of-life analysis. Int J Gynecol Cancer *22(7)*: 1281-1288, 2012. PMID: 22864336. DOI: 10.1097/IGC.0b013e3182643ba0

26 White AJ, Reeve BB, Chen RC, Stover AM and Irwin DE: Urinary incontinence and health-related quality of life among older Americans with and without cancer: a cross-sectional study. BMC Cancer *13*: 377, 2013. PMID: 23924272. DOI: 10.1186/1471-2407-13-377

27 Soisson S, Ganz PA, Gaffney D, Rowe K, Snyder J, Wan Y, Deshmukh V, Newman M, Fraser A, Smith K, Herget K, Hanson HA, Wu YP, Stanford J, Werner TL, Setiawan VW and Hashibe M: Long-term, adverse genitourinary outcomes among endometrial cancer survivors in a large, population-based cohort study. Gynecol Oncol *148(3)*: 499-506, 2018. PMID: 29289418. DOI: 10.1016/j.ygyno.2017.12.025

28 Heliövaara-Peippo S, Halmesmäki K, Hurskainen R, Teperi J, Grenman S, Kivelä A, Tomas E, Tuppurainen M and Paavonen J: The effect of hysterectomy or levonorgestrel-releasing intrauterine system on lower urinary tract symptoms: a 10-year follow-up study of a randomised trial. BJOG *117(5)*: 602-609, 2010. PMID: 20156209. DOI: 10.1111/j.1471-0528.2010.02505.x

29 Robinson D, Toozs-Hobson P and Cardozo L: The effect of hormones on the lower urinary tract. Menopause Int 9(4): 155-162, 2013. PMID: 24336244. DOI: 10.1177/1754045313511398

30 Champaneria R, D'Andrea RM and Latthe PM: Hormonal contraception and pelvic floor function: a systematic review. Int Urogynecol J *27(5)*: 709-722, 2016. DOI: 10.1007/s00192-015-2833-3

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