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# COMPARATIVE STUDY OF PREVALENCE IN UTERINE CANCER: KYRGYZSTAN AND INDIA

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## ABSTRACT:

Endometrial cancer is the most common gynecological malignancy in high- and middle-income countries. Although the overall prognosis is relatively good, high-grade endometrial cancers have a tendency to recur. Recurrence needs to be prevented since the prognosis for recurrent endometrial cancer is dismal. Treatment tailored to tumor biology is the optimal strategy to balance treatment efficacy against toxicity. Since The Cancer Genome Atlas defined four molecular subgroups of endometrial cancers, the molecular factors are increasingly used to define prognosis and treatment. Standard treatment consists of hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy (and increasingly sentinel node biopsy) enables identification of lymph node-positive patients who need adjuvant treatment, including radiotherapy and chemotherapy. Adjuvant therapy is used for Stage I–II patients with high-risk factors and Stage III patients; chemotherapy is especially used in non-endometrioid cancers and those in the copy-number high molecular group characterized by *TP53* mutation. In advanced disease, a combination of surgery to no residual disease and chemotherapy with or without radiotherapy results in the best outcome. Surgery for recurrent disease is only advocated in patients with a good performance status with a relatively long disease-free interval.

# INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the West, but in India, the incidence rates are low. Most of these cancers present at an early stage and are associated with a good prognosis. The treatment comprises surgical staging and adjuvant radiotherapy and/or chemotherapy depending on the final surgico-pathological stage.

### Background

Prognosis in advanced or recurrent endometrial cancer (AEC) is poor (5-year overall survival [OS] 15%-17%). Paclitaxel plus carboplatin (PC) is standard of care (SOC) first-line (1L) chemotherapy (CT), and no 2L SOC is established. We conducted a systematic literature review to assess the real-world effectiveness and safety of CTs in AEC

# UTERINE SARCOMAS

Uterine leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated uterine sarcoma are the three main types of uterine mesenchymal tumors (sarcomas). Leiomyosarcoma is the most common, with an incidence of 0.36 per 100,000 female life-years. Leiomyosarcoma make up 1% of all uterine cancers and 70% of uterine sarcomas. They are twice as common in Black women than White women.[23]Uterine leiomyosarcoma is an aggressive uterine malignancy. Patients with uterine leiomyosarcoma usually present at older than age 40 years, and the incidence increases significantly after age 50 years.[23-10] Leiomyosarcoma typically spreads hematogenously, and metastatic disease is frequently present at the time of initial resection.[23]The 5-year survival rate for stage I disease is only 55% and falls to 21.7% for stage IV disease.29 Other rare stromal malignancies include adenosarcoma, rhabdomyosarcoma, and malignant perivascular epithelioid tumors.[21]Additional risk factors for endometrial cancer before age 50 years include not using combined hormonal contraceptives and first birth after age 30 years. [17,27] Uterine sarcomas occur most commonly during perimenopause and early menopause. Leiomyosarcoma have the highest incidence between ages 45 and 59 years. Endometrial stromal sarcoma incidence rates are steady starting at age 45 years.[12]Two large meta-analyses have shown progressively increasing endometrial cancer risk with increasing BMI. Women who are overweight (BMI 25–29) have a relative risk (RR) of about 1.3, and women who are obese (BMI 30 or higher) have an RR of about 2.5 compared with normal-weight women.[28,11]In a meta-analysis of 19 studies, a 5-unit increase in BMI was associated with a 1.59 (95% CI 1.50–1.68) increase in RR of endometrial cancer.[20]Obesity increases risk for uterine sarcoma as well (odds ratio [OR] 1.73, 95% CI 1.22–2.46).[8]Physical activity is associated with a decreased risk of endometrial cancer. [13]Multiple prospective studies and meta-analyses have confirmed this protective role, regardless of BMI (most vs least physical activity: pooled RR 0.78, 95% CI 0.63–0.95).

### REVIEW OF RELATED LITERATURE

Mahantshetty *et al*. reported the clinical outcomes of early-stage endometroid adenocarcinoma at the Tata Memorial Centre, Mumbai.[14] With a median age of 54 years (26–72 years), 136 patients (55%) had undergone surgery elsewhere while 118 (47.3%) underwent a complete surgical staging. There were 60 (24.1%), 124 (49.8%), and 65 (26.1%) patients in the LR, IR, and HR groups, respectively. Adjuvant radiation was given in 160 patients (LR: 18; IR: 85; and HR: 57). With a median follow-up of 36 months (mean, 40 months), ten patients had vault

recurrences, (LR: 3; IR: 4; and HR: 3), 11 had nodal recurrences (five also had local recurrence; LR: 2; IR: 4; and HR: 5), and 16 had distant recurrences (three also had nodal; LR: 4; IR: 5; HR: 7). The 5-year DFS and OS rates were 80% and 95%, respectively. The DFS and OS rates at 5 years were 84% and 97%, 85% and 98%, and 60% and 85% for the LR, IR, and HR groups, respectively. On multivariate analysis, grade ($P$ = 0.002) and type of radiation ($P$ = 0.027) had a significant impact on DFS and OS. Late toxicities (Grade 3/4) were vaginal stenosis in four (1%) and radiation proctitis in three (1%) patients.

Rathod *et al*. reported that following complete surgical staging, 32.7% of the patients with IR and HR endometrial cancers were found to have retroperitoneal node metastasis; 52.9% in this group had both pelvic and para-aortic lymph nodal metastasis, and 5.9% had isolated para-aortic lymph nodal metastasis. The high-grade tumors (Grade 3) revealed 41.4% pelvic and 20.7% para-aortic lymph nodes metastasis, and there was statistically significant higher nodal metastasis in both pelvic and para-aortic lymph nodes with increasing depth of myometrial invasion ($P$ = 0.0119 and $P$ = 0.0001) and increasing size of the lesion ($P$ = 0.04 and $P$ = 0.0501).[19] Gholkar *et al*. reported that for the detection of pelvic nodes in HR endometrial cancers, $^{18}$F-FDG PET-CT had a sensitivity of 100%, specificity of 61.11%, PPV of 22.22%, NPV of 100%, and accuracy of 65%. For the detection of para-aortic nodes, $^{18}$F-FDG PET-CT had a sensitivity of 100%, specificity of 66.67%, PPV of 20%, NPV of 100%, and accuracy of 69.23%.[9] In the detection of recurrent endometrial cancer, the sensitivity, specificity, positive and negative predictive values, and accuracy of $^{18}$F-FDG PET-CT were 88.9%, 93.6%, 94.1%, 88%, and 91%, respectively, significantly higher than conventional imaging (CT and magnetic resonance imaging).[25]

Minimal access surgery including laparoscopic and robotic hysterectomies and lymphadenectomies are increasingly being used in surgical staging of endometrial cancers. In a prospective randomized study comparing robotic-assisted hysterectomy and regional lymphadenectomy with traditional laparotomy for the staging of endometrial carcinoma, estimated blood loss (81.28 ml), hospital stay (1.94 days), and perioperative complications were significantly less in robotic-assisted group in comparison to open method. Mean number of lymph nodes removed were 30.56 in robotic group versus 27.6 in open surgery.[26]

While endometrioid adenocarcinomas have been extensively studied in literature, uterine sarcomas are a group of rare uterine tumors characterized by less favorable outcomes. A study from a regional cancer center in North India in patients of uterine sarcomas found that the median OS was 7.67 months (mean 30.19 months), and 1- and 2-year actuarial survival rates were 45.45% and 36.36%, respectively.[3] Stratified by histology, median survival in patients with carcinosarcoma, endometrial stromal sarcoma, leiomyosarcoma, and undifferentiated endometrial sarcoma were, respectively, 6.57, 18.7, 6.8, and 9.38 months. On univariate analysis, response to therapy ($P$ = 0.0003), disease stage ($P$ = 0.00001), tumor size ($P$ = 0.02), and performance status ($P$ = 0.03) were the significant predictors of OS. Disease stage ($P$ = 0.005) and response to therapy ($P$ = 0.01) retained significance on multivariate analysis. A retrospective analysis of twenty patients of carcinosarcoma of uterus reported that 75% of the patients belonged to Stages I and II. Ninety-five percent of the patients underwent hysterectomy with bilateral

salpingo-oophorectomy and 60% had lymphadenectomy along with hysterectomy. Eight patients had disease recurrence. In patients who had gross extrauterine disease at the time of surgery, the survival was only 9 months whereas in patients who had complete staging with disease confined to the uterus, the survival was 36 months. [2] Uterine smooth muscle tumors of uncertain malignant potential and atypical leiomyoma are rare uterine tumors, and in a study of 21 cases, the mean age was 45 years (range 24–67 years). Coagulative tumor cell necrosis was seen in two cases on examination of additional material, wherein a revised diagnosis of leiomyosarcoma had been given. Infarction type necrosis and individual cell necrosis were seen in two and three cases, respectively. Mitoses were <5/10 hpf in all the cases. On follow-up (median 15 months), from the available 11 patients, nine patients were alive and disease-free, one patient had metastatic liver disease, and one had died due to an unknown cause.[6]

## SUMMARY

Since 2015, Kyrgyzstan's cancer registry has been providing crucial information on cancer cases in 3 of the country's regions, including the largest, Chüy Region. "The registry acts as a monitoring instrument and as a data hub, allowing us to collect and analyse information on all cancer cases in adults and children in one electronic database. We capture information on the disease stages, numbers and types of treatment in each case, from diagnosis to death or survival," explains Dr Ten.

The next major challenge for the National Cancer Control Programme will be to increase access to essential diagnostics and treatment for cancer patients, so that people can fully believe in life after cancer. 8% survival benefit than those who had diabetes and the difference was not significant (p=0.06). Similarly, for those with hypertension history, the survival rates was 91% while it was 93% for those who didn't have hypertension history and the difference was not significant (p=0.27). It is seen that survival by clinical extent of disease was poorer for non-localized disease patients. The five-year survival rates were 93% and 85% for localized and non-localized disease respectively A large number of patients had some treatment before attending TMH but the survival rate was similar to those with localized disease seen at TMH, and the differences were significant (p=0.07).

Surgically-treated patients, treated either as a single or in combination with other treatment modalities, showed a 95% five-year survival, compared to those who were treated with other modalities of treatment like radiotherapy or chemotherapy or in combination (91%) but the difference in rates was not statistically significant (p=0.26).

Carcinoma (HGSC) with near ubiquitous TP53 mutations can provide insight into another possible etiology of endometrial high-grade endometrioid carcinomas. Arising in the fallopian tube, the evolution of adnexal HGSC from serous tubal in situ carcinoma (STIC) associated with p53 signatures in tubal endothelium has been established by evidence through molecular, transitional, and epidemiological research. From this, the developmental similarities between adnexal HGSC and ESC are evident for their mutual associations with p53 signatures in morphologically normal epithelium through the apparently in situ phases of STIC transitioning to HGSC and,

likewise serous EIN transitioning to ESC with the potential intra-abdominal dissemination of very small, early cancerous lesions. High-grade adnexal carcinomas with aberrant p53 but non-papillary serous, endometrioid and transitional cell (SET) morphology and aggressive behavior are now classified as HGSC-SET carcinomas. In contrast to IHC demonstrating aberrant p53 staining in greater than or equal to 50% of high-grade, non-endometrioid adnexal tumors with associated poor prognosis, a study found that none of the adnexal tumors ultimately classified as endometrioid carcinomas showed aberrant p53 staining, and these patients had no recurrences and better survival.[15] On the basis of translational and pathological research, endometrial high-grade endometrioid carcinomas with aberrant p53 should be classed as type 2 endometrial cancers with expected guarded prognosis.

## CONCLUSION

We searched PubMed and Embase for studies on body mass index and the risk of endometrial cancer, published from 2013 to 2017. Data were independently extracted and analyzed using random or fixed effects meta-analysis depending on the degree of heterogeneity. The findings from this meta-analysis strongly support that the conditions of EBW (excess body weight), overweight, and obesity are all associated with an increased risk of endometrial cancer. Also, the strength of the association increases with increasing BMI (body mass index - ≥30kg $m^2$). The findings from this meta-analysis strongly support that the conditions of EBW, overweight, and obesity are all associated with an increased risk of endometrial cancer. Also, the strength of the association increases with increasing BMI.

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