Gynecologic Oncology 153 (2019) 49–54

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Unexpected malignant uterine pathology: Incidence, characteristics and outcome in a large single-center series of hysterectomies for presumed benign uterine disease

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HIGHLIGHTS

- Unexpected uterine malignancies after hysterectomy were rare with an incidence of 44/10.765 (0.42%).
- Most unexpected uterine malignancies were endometrial carcinomas (0.31%), with only few uterine sarcomas (0.11%).
- Outcome of patients with unexpected uterine malignancies is favorable, particularly for unexpected endometrial carcinomas.
- So far no patient treated with intraoperative power morcellation has had an locoregional relapse.
- Thorough preoperative workup and expert pathology are important for optimal patient treatment.

ARTICLE INFO

Article history:
Received 18 October 2018
Received in revised form 23 December 2018
Accepted 28 December 2018
Available online 8 January 2019

Keywords:
Hysterectomy
Uterine cancer
Unexpected
Uterine malignancy
Uterine sarcoma
Endometrial cancer

ABSTRACT

Objective. Hysterectomy is a frequently used therapeutic option for benign gynecological conditions. The purpose of this study was to investigate the incidence and characteristics of unforeseen malignant pathologies of the uterine corpus in a large population-based, single center cohort.

Methods. Patients who underwent hysterectomy for presumed benign conditions between 2003 and 2016 were identified. In cases of unexpected malignancies of the uterine corpus (UUM), available tissue samples were collected and a specialized gynecopathological review was performed.

Results. A total of 10,756 patients underwent hysterectomy for benign indications. After chart and gynecopathological review, 45/10,756 (0.42%) cases of unexpected uterine malignancies were confirmed. 33/45 (73.3%) were endometrial carcinomas (UEC) and 12/45 (26.7%) were uterine sarcomas (UUS). 27/33 (81.8%) UEC were FIGO IA, 5/33 (15.2%) FIGO IB and 1/33 (3%) FIGO stage II disease. Endometrioid and serous histotype were present in 31/33 (93.9%) and in 2/33 (6.1%) cases, respectively. 8/12 (66.7%) USS were early stage (FIGO IA or IB); only 3/12 (25.0%) were diagnosed at an advanced stage (≥FIGO II). Fatal outcome was observed in 1 patient diagnosed with UEC and 3 patients diagnosed with UUS.

Conclusion. Our study shows that diagnosis of UUM is rare (0.42%). The majority of UUM tend to be early stage, making preoperative diagnosis difficult. In case of UEC, patient outcome is generally favorable. Nevertheless, the appropriate surgical approach for hysterectomy for a benign indication should be chosen carefully, taking all preoperative findings into account. Patients should always be informed about the residual risk of UUM.

1. Introduction

Hysterectomy is a frequently used therapeutic procedure in women with benign gynecological conditions, such as symptomatic leiomyomas, abnormal uterine bleeding and uterovaginal prolapse [1].

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https://doi.org/10.1016/j.ygyno.2018.12.026
0090-8258/

Over the last decade, advances in technology and surgical technique have led to a paradigm shift in surgical uterus removal. Open abdominal procedures are increasingly replaced by minimal invasive approaches, decreasing operation time, complications and patient's recovery time [2,3]. Routine examination prior to hysterectomy includes gathering information about family history of cancer, gynecological examination (speculum and bimanual examination) and transvaginal ultrasound to exclude a potential uterine malignancy [4,5]. Transvaginal ultrasound has proven to be a valid tool in identifying patients with a high-risk of endometrial carcinoma (EC) preoperatively [6]. Additional invasive procedures such as dilation and curettage (D&C) are used for confirmation of diagnosis in these cases. However, studies have shown the use of D&C in identifying focal malignant lesions to be less precise than previously thought, making false negative results inevitable [7–9]. Therefore, potential malignancies such as uterine sarcoma (US) or endometrial carcinoma (EC) cannot be fully ruled out in a preoperative setting [10]. US only account for 5% of malignancies within the corpus uteri, but leiomyosarcoma and high-grade endometrial stroma sarcoma are especially known for their aggressive nature and poor patient outcome [11]. If malignancies such as US are missed at preoperative evaluation, abdominal tumor cell spread during surgery may lead to an upstaging of disease and thus, increase the risk of tumor recurrence and worse overall outcome [12]. Early EC on the other hand has a rather favorable prognosis with 5-year survival-rates exceeding 90% [13]. Tumor characteristics such as advanced FIGO stage disease, poor tumor cell differentiation, expression of mutant p53 protein, lymphovascular space invasion (LVSI) and aberrant L1 cell-adhesion molecule (L1CAM/CD171) expression are known to be associated with a higher risk of recurrence and adverse outcome in EC [14–19]. In most cases, timely diagnosis and treatment of EC is necessary to ensure a favorable outcome [20]. Previous studies evaluating the incidence of unexpected uterine malignancies (UUM) in women who underwent hysterectomy for benign conditions have recorded frequencies of 0.12–3% for unexpected endometrial carcinoma (UEC) and 0.09–0.49% for unexpected uterine sarcoma (UUS) [10,21–24]. The aim of our study was to evaluate the incidence of unforeseen uterine malignancies in a large population-based, single center cohort. Furthermore, we aimed to assess the characteristics of unexpected malignancies and to discuss implications for clinical routine.

2. Methods

All patients treated with benign hysterectomy at the Department of Gynecology and Obstetrics, University of Tuebingen, Germany between 2003 and 2016 were identified. Patients with an unexpected diagnosis of EC or US within the corpus uteri were selected from the chart review. While reviewing clinical data, special attention was given to the indication for benign hysterectomy, course of preoperative workup (D&C), surgical approach and type of adjuvant treatment. Patients with the diagnosis of primary gynecological cancer or endometrial hyperplasia with atypia in D&C prior to benign hysterectomy were excluded from this cohort. Also, patients with an unexpected diagnosis of cervical carcinoma were not included in this study. Thereafter, all available tumor tissue and corresponding preoperative D&C samples were collected, and specialized pathology review was performed. Special attention was given to tumor grade and stage, and the presence of LVSI. Aberrant L1CAM expression in UEC was tested for with immunohistochemistry (IHC), as previously reported [19]. Carcinomas were considered L1CAM positive if ≥10% of tumor cells showed a membranous L1CAM expression. If pathology review did not confirm the diagnosis of a uterine malignancy, cases were also excluded from the study. The Tuebingen University Independent Ethics Committee issued study approval. Follow-up data was received from the Tuebingen University Hospital Clinical Cancer Registry. Binominal 95% confidence intervals (CI) were calculated using the Wilson interval, significance levels were calculated using the Fisher's-exact test (JMP 13.2 (SAS)).

3. Results

3.1. Study cohort

We identified 10,756 patients who were treated for benign gynecological conditions with hysterectomy in the specified period of time. Indications for elective surgery were: symptomatic uterine leiomyomas, family history of cancer, endometrial hyperplasia without atypia, pelvic organ prolapse, symptomatic endometriosis, pelvic pain and abnormal uterine bleeding. 4419/10,756 (41.1%) of procedures performed were laparoscopic supracervical hysterectomies (LASH), 828/10,756 (7.7%) were total laparoscopic hysterectomies (TLH), 4237/10,756 (39.4%) were vaginal hysterectomies (VH) and 1272/10,756 (11.8%) were abdominal hysterectomies (TAH). After specialized gynecopathological review, a total of 45/10,756 (0.42%; 95% CI 0.31–0.56) UUM were recorded, of which 33/10,756 (0.31%; 95% CI 0.22–0.43) were UEC and 12/10,756 (0.11%; 95% CI 0.06–0.19) were UUS (Fig. 1). Subgroup analysis depending on surgical approach showed UEC and UUS to be most frequently diagnosed within the TLH subgroup, with incidence rates of 1.21% and 0.36% respectively. Associations between type of procedure and uterine pathology are summarized in Table 1.

3.2. Unexpected endometrial carcinomas

In total, 27/33 (81.8%) tumors were FIGO stage IA, 5/33 (15.2%) were FIGO stage IB and 1/33 (3%) was FIGO stage II disease. 30/33 (90.9%) carcinomas were G1, 1/33 (3%) was G2 and 2/33 (6.1%) were G3. LVSI was present in 1/33 (3%) case, L1CAM expression in ≥10% of epithelial tumor cells was noted in 2/33 (6.1%) cases. Endometrioid histotype (Type I) was present in 31/33 (93.9%) tumors, 2/33 (6.1%) tumors were of serous histotype (Type II). When current classification guidelines (ESMO-ESGO-ESTRO 2016 consensus conference [25]) were applied, 24/33 (72.7%) cases were classified as low, 5/33 (15.2%) as intermediate, 1/33 (3%) as high-intermediate and 3/33 (9.1%) as high-risk disease. According to current treatment guidelines, adjuvant radiotherapy was recommended in 13/33 (39.4%) cases. During preoperative workup 19/33 (57.6%) patients with UEC received D&C, of which 8/19 (42.1%) showed endometrioid hyperplasia without atypia. Indication for preoperative D&C included genital postmenopausal bleeding in 9/19 (47.4%) cases, suspect endometrium upon ultrasound in 7/19 (36.8%) cases, and suspected uterine fibroids in 3/19 (15.8%) cases. Again, cases with the diagnosis of hyperplasia with atypia prior to hysterectomy were excluded from this study.

Disease specific adverse outcome was observed in 1/33 (3%) patient with UEC, 23 months after initial diagnosis. In this case, high expression of L1CAM (10–40% of tumor cells) and serous type histology was present. Initially this patient was diagnosed with FIGO stage 1A disease after primary VH, classified as ESMO 2016 high-risk, and subsequently treated with adjuvant radiotherapy. Median follow up for UEC patients was 68 months (4–148 months). Details of clinicopathological data of UEC are given in Table 2A.

A total of 3 UEC patients were primarily treated with LASH, including intra-abdominal power morcellation. None of these patients were upstaged after surgery and no relapse of disease has been noted in these patients so far (Table 3).

3.3. Unexpected uterine sarcomas

After specialized pathology review of all unexpected US, 8/12 (66.7%) were confirmed to be leiomyosarcomas and 4/12 (33.3%) were confirmed as low-grade endometrial stromal sarcoma (LGESS). Most UUS were early stage, with 3/12 (25.0%) and 5/12 (41.7%) being stage IA (<5 cm) and stage IB (>5 cm) respectively. Poor differentiation (grade 3) was present in 5/12 (41.7%) tumors. Further adjuvant treatment regiments were decided upon after complete surgical tumor staging. A total of 2/12 (16.7%) patients received adjuvant chemotherapy.

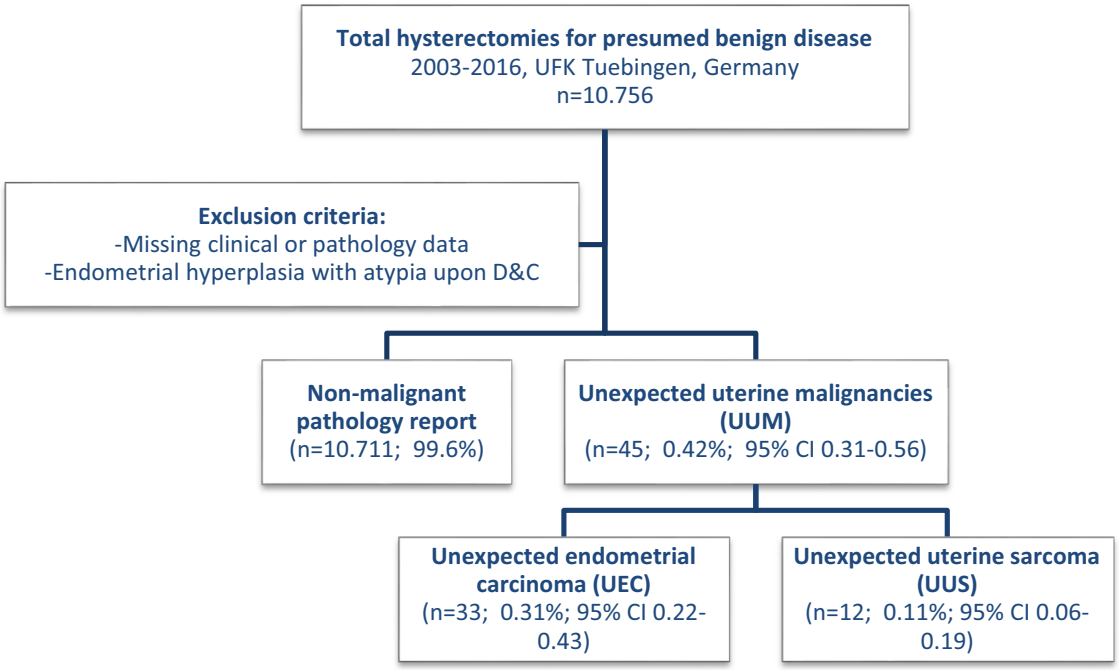

Fig. 1. Incidence of unexpected gynecologic malignancy after presumed benign hysterectomy.

Disease recurrence occurred in 4/12 (33.3%) of patients diagnosed with UUS. These patients presented with pulmonary and skeletal metastasis, in two cases additional peritoneal recurrence was noted. In all cases, recurrence of disease was treated with palliative chemotherapy and additional radiotherapy of skeletal metastatic lesions in 2 cases. So far, only 3 patients with recurrent disease have had a fatal outcome. Median follow up for UUS patients was 44 months (12–120 months). Details of clinicopathological data of UUS are given in Table 2B.

Six patients with UUS were primarily treated with intra-abdominal power morcellation without knowledge of uterine malignancy. None of these patients have been diagnosed with loco-regional recurrence so far (Table 3).

4. Discussion

With around 250,000 procedures every year in Germany alone, benign hysterectomy is a frequently performed surgical procedure in gynecology [26]. Advances in minimal invasive surgery allow for the safe and fast treatment of benign gynecological conditions. However, despite great efforts in preoperative examination, postoperative diagnosis of unexpected uterine malignancy cannot be ruled out completely [5,10]. We aimed to investigate the incidence of unexpected uterine malignancies and their characteristics after benign hysterectomy.

In our study, 45/10,756 (0.42%) patients were diagnosed with UUM after hysterectomy for presumed benign disease. In other words, less than one in every 200 patients treated with hysterectomy for a benign condition was diagnosed with an unexpected malignant uterine pathology. 33/10,756 (0.31%) were UEC, 12/10,756 (0.11%) were UUS (Table 1). These results are similar to those of Ouldamer et al. and Frick et al. who reported an incidence of 0.4% and 0.3% for UEC, respectively [22,27]. A large population-based study from South Korea reports only an incidence of 0.12% for UEC and 0.06% for UUS [28]. Lower incidence rates of UUC in the study by Yuk et al. are probably due to lower crude incidence rate of endometrial cancer in South Korea (8.7/100,000 in South Korea compared to 26.6/100,000 in Germany) [29,30]. A recent study by Mahnert et al. reports a noticeably higher frequency with 1.02% and 0.22% for UEC and UUS after benign hysterectomy, respectively [10]. Upon subgroup analysis depending on surgical approach, incidence of unexpected EC was highest in the group of patients treated with TLH [10/828 (1.21%), $p < 0.01$; Table 1], and lowest in the group treated with LASH [3/4419 (0.07%), $p < 0.01$; Table 1]. These results are in line with Theben et al. and Bojahr et al., who report a cumulative incidence of 0.125% and 0.07% for UEC in cohorts of 1584 and 10,731 patients treated with LASH, respectively [23,31] (Table 4). These results could be explained by specific preoperative workflows in patients with hysterectomy for benign reasons. Patients treated with LASH tend to be younger and premenopausal and are therefore at a lower risk for diagnosis of UEC. Also, preoperative examination influences the decision on operative approach and TLH is often chosen if preoperative examination is inconclusive and indicates a high-risk situation for UUM, possibly explaining high numbers of UEC and UUS within the TLH subgroup of our cohort. TLH is the appropriate approach for treatment of early endometrial cancer and does not include morcellation, which should be generally avoided if a woman is considered to have a high risk of uterine malignancy [32,33].

Preoperative D&C was performed in 57.6% of unexpected EC cases, 42.1% of which were diagnosed with endometrioid hyperplasia without atypia prior to surgery. Although our study is limited to cases with

Table 1
Incidence of unexpected endometrial carcinoma (UEC) and unexpected uterine sarcoma (UUS) depending on surgical procedures [laparoscopic supracervical hysterectomies (LASH), total laparoscopic hysterectomies (TLH), transvaginal hysterectomies (VH) and abdominal hysterectomies (TAH)].

	Total	LASH	TLH	VH	TAH
# of patients	10,756 (100%)	4419 (41.08%)	828 (7.70%)	4237 (39.39%)	1272 (11.83%)
Benign pathology reports	10,711 (99.58%)	4410 (99.79%)	815 (98.43%)	4219 (99.58%)	1268 (99.68%)
UEC	33 (0.31%)	3 (0.07%)	10 (1.21%)	17 (0.40%)	2 (0.16%)
UUS	12 (0.11%)	6 (0.14%)	3 (0.36%)	1 (0.02%)	2 (0.16%)

Table 2
Clinicopathological characteristics of patients with unexpected malignant uterus pathology (UEC and UUS).

	#/Number of patients
A	
Unexpected endometrial carcinoma (UEC)	33 (100%)
Histology	
Endometrioid	31 (93.9%)
Non-endometrioid	2 (6.1%)
FIGO stage	
IA	27 (81.8%)
IB	5 (15.2%)
II	1 (3%)
Tumor grade	
Grade 1	30 (90.9%)
Grade 2	1 (3%)
Grade 3	2 (6.1%)
Preoperative D&C	
History of hyperplasia	8 (24.2%)
No history of hyperplasia	11 (33.3%)
n.a.	14 (42.5%)
LVSI	
Negative	32 (97%)
Positive	1 (3%)
L1CAM	
Negative	30 (90.9%)
Positive	2 (6.1%)
n.a.	1 (3%)
Adjuvant therapy	
Radiotherapy	13 (39.4%)
None	20 (60.6%)
ESMO 2016 risk	
Low	24 (72.7%)
Intermediate	5 (15.3%)
Intermediate-high	1 (3%)
High	3 (9%)
Follow-up	
Relapse of disease	1 (3%)
Disease specific death	1 (3%)
B	
Unexpected uterine sarcoma (UUS)	12 (100%)
Type	
Leiomyosarcoma	8 (66.6%)
Endometrial stromal sarcoma (low-grade)	4 (33.3%)
Adjuvant therapy (primary treatment)	
Chemotherapy	2 (16.7%)
None	10 (83.3%)
FIGO stage	
IA	3 (25%)
IB	5 (41.7%)
IIB	1 (8.3%)
IVB	2 (16.7%)
Missing	1 (8.3%)
Follow-up	
Relapse of disease	4 (33.3%)
Disease specific deaths	3 (25%)

unexpected diagnosis of uterine malignancies, the authors hypothesize that if hyperplasia without atypia is diagnosed at preoperative evaluation (D&C), the risk of unexpected EC could be elevated and procedure options should be chosen carefully. Further studies are warranted to investigate the frequency of unexpected EC upon diagnosis of hyperplasia without atypia compared to a non-hyperplastic endometrium.

In our study, one patient with UEC experienced relapse and eventually died. In this case, advanced FIGO stage disease, serous histology, L1CAM positivity and LVSI were noted. However, most cases of unexpected EC did not present with high-risk features, were early FIGO stage and therefore classified as low risk disease (72.7%) (Table 2). In some cases, early endometrial cancer cannot be safely predicted in a preoperative setting, even if preoperative D&C is inconspicuous [7,8]. Despite recent efforts, preoperative diagnosis of US also remains extremely difficult [34]. Even optimal preoperative diagnostic protocols do not diminish the very slight risk of patients being diagnosed with an UEC or UUS after hysterectomy for presumed benign uterine disease.

Given the very low incidence of US in general, our frequency of 0.13% of UUS is in line with previously reported data, ranging from 0.09–0.49% [10,21–24]. One patient from the present study was diagnosed with UUS and underwent power morcellation. However, as the postoperative imaging revealed, the patient had primary systematic metastatic disease. In all other patients with US that underwent power morcellation, no loco regional relapse was observed during follow-up. This finding does not support the assumption that power morcellation may affect the outcome of patients diagnosed with US, current data on this issue are still equivocal [33]. Additionally, our data support the current preoperative assessment for hysterectomy as being safe and practical. Nevertheless, if a patient is considered to be at high risk of US, surgical approaches which include any type of morcellation should be completely avoided.

This study is strengthened by a specialized pathological review. After reevaluation of all specimens from unexpected malignancies, two cases were excluded from our study cohort due to pathology review diagnosis of endometrial hyperplasia, with an initial diagnosis of EC (data not shown). Misdiagnosis of EC or US could also contribute to variable frequency of unexpected uterine malignancies in other patient cohorts. This finding further supports previous studies implying the importance of a specialized pathological review not only in a research, but also in routine diagnostics [35,36].

4.1. Final conclusion

To our knowledge, this is the largest single center, population-based study to determine the incidence and outcome of unexpected malignant uterine pathology after benign hysterectomy. Unexpected diagnosis of UUM upon primarily benign hysterectomy was relatively uncommon (0.44%) in this study. In cases of UEC diagnosis, tumors were early stage disease and displayed low-risk features, making preoperative diagnosis difficult. Therefore, preoperative examination in the context of benign hysterectomy must be undertaken with care, and patients should be educated about the very slight possibility of a malignant diagnosis. If endometrial hyperplasia without atypia is present in preoperative D&C and therefore alludes towards a higher risk situation, adequate surgical techniques such as TLH should be discussed.

Table 3
Unexpected endometrial carcinoma (UEC) and unexpected uterine sarcoma (UUS) primarily treated with intraabdominal power morcellation.

Case ID	Initial stage (FIGO 2009)	Type	Adjuvant therapy	Upstaging after completing surgery	Relapse of disease	Death of disease	Follow-up (months)
UEC 1	IA	Endometrioid	None	No	None	No	29
UEC 2	IA	Endometrioid	None	No	None	No	5
UEC 3	IA	Endometrioid	Radiotherapy	No	None	No	4
UUS 1	IA	LGESS	None	No	None	No	12
UUS 2	IA	LMS	None	No	None	No	12
UUS 3	IA	LGESS	None	No	None	No	96
UUS 4	IB	LMS	None	No	None	No	12
UUS 5	IIB	LMS	None	No	None	No	48
UUS 6	IVB	LMS	Chemotherapy	No	Pulmonal metastasis	Yes	36

Table 4
Summary of recent studies investigating the frequency of unexpected uterine malignancies (UUM). Type of surgery: laparoscopic supracervical hysterectomies (LASH), total laparoscopic hysterectomies (TLH), transvaginal hysterectomies (VH) and abdominal hysterectomies (TAH).

Study	Type of surgery	UUM	UEC	UUS
This study	LASH, TLH, VH, TAH	45/10.756 (0.42%; 95% CI 0.31–0.56%)	33/10.756 (0.31%; 95% CI 0.22–0.43%)	12/10.756 (0.11%; 95% 0.06–0.19%)
Parsons et al. (2018) [36]	Laparotomic, laparoscopic	n.a.	13/6981 (0.19%; 95% CI 0.03–1.05%)	n.a.
Kho et al. (2016) [37]	Abdominal, laparoscopic, robotic-assisted, VH	n.a.	n.a.	9/10.119 (0.089; 95% CI 0.02–0.5%)
Mahnert et al. [10]	Laparotomic, laparoscopic	172/6.360 (2.7%; 95% CI 2.33–3.13%)	65/6.360 (1.02%; 95% CI 0.8–1.3%)	14/6.360 (0.22%; 95% CI 0.13–0.37%)
Yuk et al. [28]	Laparotomic, laparoscopic	24/12.850 (0.11%; 95% CI 0.11–0.26%)	16/12.850 (0.12%; 95% CI 0.06–0.19%)	8/12.850 (0.06%; 95% CI 0.02–0.11%)
Bojahr et al. [31]	LASH	14/10.731 (0.13%)	8/10.731 (0.07%)	6/10.731 (0.06%)

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors would like to thank Dr. Elizabeth Kramer for proofreading and constructive criticism of the manuscript.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical approval study approval was obtained from the independent

Ethics Committee of the University of Tuebingen. All procedures were performed in accordance with the ethical standards of the institutional research committee.

Author contribution

Wagner P	clinical data, data analysis, manuscript writing, visualization
Kommoss F	data analysis, manuscript writing, visualization
Kommoss S	conceptualization, editing of the manuscript, supervision
Hartkopf AD	clinical data, editing of the manuscript
Pasternak J	clinical data, manuscript writing
Oberlechner E	data analysis, manuscript writing
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Neis F	clinical data, data analysis
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Krämer B	data analysis, editing of the manuscript
Reisenauer C	clinical data, data analysis
Staebler A	clinical data, data analysis, resources
Wallwiener D	conceptualization, resources
Brucker S	editing of the manuscript, clinical data, resources
Taran FA	conceptualization, data analysis, manuscript writing, clinical data, supervision

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References

[1] R. Garry, Health economics of hysterectomy, Best Pract. Res. Clin. Obstet. Gynaecol. 19 (3) (2005) 451–465.
[2] N.K. Billfeldt, C. Borgfeldt, H. Lindkvist, J.H. Stjerndahl, M. Ankardal, A Swedish population-based evaluation of benign hysterectomy, comparing minimally invasive and abdominal surgery, Eur. J. Obstet. Gynecol. Reprod. Biol. 222 (2018) 113–118.
[3] M. Wallwiener, F.A. Taran, R. Rothmund, A. Kasperkowiak, G. Auwarter, A. Ganz, et al., Laparoscopic supracervical hysterectomy (LSH) versus total laparoscopic hysterectomy (TLH): an implementation study in 1,952 patients with an analysis of risk factors for conversion to laparotomy and complications, and of procedure-specific re-operations, Arch. Gynecol. Obstet. 288 (6) (2013) 1329–1339.
[4] E.M. Sandberg, W.J.K. Hehenkamp, P.M. Geomini, P.F. Janssen, F.W. Jansen, A.R.H. Twijnstra, Laparoscopic hysterectomy for benign indications: clinical practice guideline, Arch. Gynecol. Obstet. 296 (3) (2017 Sep) 597–606.
[5] Indication and technics of hysterectomy for benign diseases, Guideline of the German Society of Gynecology and Obstetrics (AWMF REgistry No. 015/077), March 2015http://www.awmf.org/leitlinien/detail/ll/015-070.html.
[6] M. Dueholm, I. Hjorth, K. Dahl, E. Hansen, G. Ortoft, Ultrasound scoring of endometrial pattern for fast-track identification or exclusion of endometrial cancer in women with postmenopausal bleeding, J. Minim. Invasive Gynecol. (2018 Jun 23) (Article in Press).
[7] E. Epstein, A. Ramirez, L. Skoog, L. Valentin, Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding, Acta Obstet. Gynecol. Scand. 80 (2001) 1131–1136.
[8] N. van Hanegem, M.M. Prins, M.Y. Bongers, B.C. Opmeer, D.S. Sahota, B.W. Mol, et al., The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis, Eur. J. Obstet. Gynecol. Reprod. Biol. 197 (2016) 147–155.
[9] T.J. Clark, C.H. Mann, N. Shah, K.S. Khan, F. Song, J.K. Gupta, Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review, BJOG 109 (2002) 313–321.
[10] N. Mahnert, D. Morgan, D. Campbell, C. Johnston, S. As-Sanie, Unexpected gynecologic malignancy diagnosed after hysterectomy performed for benign indications, Obstet. Gynecol. 125 (2) (2015) 397–405.
[11] K. Galaal, F.M. Kew, K.F. Tam, A. Lopes, M. Meirovitz, R. Naik, et al., Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma, Eur. J. Obstet. Gynecol. Reprod. Biol. 143 (2) (2009) 88–92.
[12] M.H. Einstein, R.R. Barakat, D.S. Chi, Y. Sonoda, K.M. Alektiar, M.L. Hensley, et al., Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease, Int. J. Gynecol. Cancer 18 (5) (2008) 1065–1070.
[13] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, CA Cancer J. Clin. 65 (1) (2015) 5–29.
[14] F. Amant, P. Moerman, P. Neven, D. Timmerman, E. Van Limbergen, I. Vergote, Endometrial cancer, Lancet 366 (9484) (2005) 491–505.
[15] P. Morice, A. Leary, C. Creutzberg, N. Abu-Rustum, E. Darai, Endometrial cancer, Lancet 387 (10023) (2016) 1094–1108.
[16] J.D. Wright, N.I.B. Medel, J. Sehouli, K. Fujiwara, T.J. Herzog, Contemporary management of endometrial cancer, Lancet 379 (9823) (2012) 1352–1360.
[17] Y.P. Geels, J.M. Pijnenborg, B.B. Gordon, M. Fogel, P. Altevogt, R. Masadah, et al., L1CAM expression is related to non-endometrioid histology, and prognostic for poor outcome in Endometrioid endometrial carcinoma, Pathol. Oncol. Res. 22 (4) (2016 Oct) 863–868.
[18] T. Bosse, R.A. Nout, E. Stelloo, E. Dreef, H.W. Nijman, I.M. Jurgenliemk-Schulz, et al., L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results, Eur. J. Cancer 50 (15) (2014) 2602–2610.
[19] F. Kommoss, F. Kommoss, F. Grevenkamp, A.K. Bunz, F.A. Taran, F. Fend, et al., L1CAM: amending the "low-risk" category in endometrial carcinoma, J. Cancer Res. Clin. Oncol. 143 (2) (2016) 255–262.
[20] L.M. Elit, E.M. O'Leary, G.R. Pond, H.Y. Seow, Impact of wait times on survival for women with uterine cancer, J. Clin. Oncol. 32 (1) (2014) 27–33.
[21] S. Takamizawa, H. Minakami, R. Usui, S. Noguchi, M. Ohwada, M. Suzuki, et al., Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas, Gynecol. Obstet. Investig. 48 (1999) 193–196.
[22] A.C. Frick, M.D. Walters, K.S. Larkin, M.D. Barber, Risk of unanticipated abnormal gynecologic pathology at the time of hysterectomy for uterovaginal prolapse, Am. J. Obstet. Gynecol. 202 (5) (2010) 507.
[23] J.U. Theben, A.R. Schellong, C. Altgassen, K. Kelling, S. Schneider, D. Grosse-Drieling, Unexpected malignancies after laparoscopic-assisted supracervical hysterectomies (LASH): an analysis of 1,584 LASH cases, Arch. Gynecol. Obstet. 287 (3) (2013) 455–462.

[24] M.J. Mingels, Y.P. Geels, J.M. Pijnenborg, A.A. van der Wurff, A.A. van Tilborg, M.A. van Ham, et al., Histopathologic assessment of the entire endometrium in asymptomatic women, Hum. Pathol. 44 (10) (2013) 2293–2301.
[25] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, A. Gonzalez-Martin, J. Ledermann, et al., ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up, Int. J. Gynecol. Cancer 26 (1) (2016) 2–30.
[26] A. Stang, R.M. Merrill, O. Kuss, Hysterectomy in Germany: a DRG-based nationwide analysis, 2005–2006, Dtsch. Arztebl. Int. 108 (30) (2011) 508–514.
[27] L. Ouldamer, L. Rossard, F. Arbion, H. Marret, G. Body, Risk of incidental finding of endometrial cancer at the time of hysterectomy for benign condition, J. Minim. Invasive Gynecol. 21 (1) (2014) 131–135.
[28] J.S. Yuk, L.Y. Kim, S.H. Kim, J.H. Lee, The incidence of unexpected uterine malignancy in women undergoing hysterectomy for a benign condition: a national population-based study, Ann. Surg. Oncol. 23 (12) (2016) 4029–4034.
[29] K.W. Jung, Y.J. Won, C.M. Oh, H.J. Kong, D.H. Lee, K.H. Lee, et al., Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014, Cancer Res. Treat. 49 (2) (2017) 292–305.
[30] Germany AjpotRKIatAoP-bCRi, Cancer in Germany 2011/2012. Contributions to Federal Health Reporting, 2012 10.
[31] B. Bojahr, R.L. De Wilde, G. Tchartchian, Malignancy rate of 10,731 uteri morcellated during laparoscopic supracervical hysterectomy (LASH), Arch. Gynecol. Obstet. 292 (3) (2015) 665–672.
[32] M. Janda, V. Gebski, L.C. Davies, P. Forder, A. Brand, R. Hogg, et al., Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial, JAMA 317 (12) (2017) 1224–1233.
[33] AAGL, Morcellation during uterine tissue extraction: an update, J. Minim. Invasive Gynecol. 25 (4) (2018) 543–550.
[34] T. Nagai, Y. Takai, T. Akahori, Highly improved accuracy of the revised PREoperative sarcoma score (rPRESS) in the decision of performing surgery for patients presenting with a uterine mass, Springerplus 4 (1) (2015) 520.
[35] F. Grevenkamp, F. Kommoss, F. Kommoss, S. Lax, F. Fend, D. Wallwiener, et al., Second opinion expert pathology in endometrial cancer: potential clinical implications, Int. J. Gynecol. Cancer 27 (2) (2017) 289–296.
[36] L.H.P. Parsons, R. Pedersen, D.L. Richardson, K.A. Kho, The prevalence of occult endometrial cancer in women undergoing hysterectomy for benign indications, Eur. J. Obstet. Gynecol. Reprod. Biol. 223 (2018) 108–112.
[37] K.A. Kho, K. Lin, M. Hechanova, D.L. Richardson, Risk of occult uterine sarcoma in women undergoing hysterectomy for benign indications, Obstet. Gynecol. 127 (3) (2016) 468–473.