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Cervical Villoglandular Papillary Adenocarcinoma: A Report of an Uncommon Case with Review of Literature

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Abstract**—** *Villoglandular papillary adenocarcinoma (VGA) is a rare variant of endocervical adenocarcinoma. It accounts for 3.7-4.8% of cervical adenocarcinomas and mainly affects women in their child bearing age. Prognosis is favourable, but depends on the disease staging, the status of the margins and lymph node involvement, which also affect its management modality. We report a case of a 32-year-old female diagnosed with villoglandular endocervical adenocarcinoma with review of literature.*

Keywords**—** *Adenocarcinoma, Papillary; Uterine Cervical Neoplasms; Lymphatic Metastasis; Neoplasm metastasis.*

I. INTRODUCTION

Cervical carcinoma is one of the most common malignancies in the world with a considerable mortality rate(1). As per the GLOBOCAN 2020, there are an estimated 6,04,127 (13.3%) new cervical cancers cases and 3,41,831 (7.8%) deaths associated with cervical carcinomas in the world, while India has reported 1,23,907 new cases and 77,348 deaths caused by this malignancy in 2020. Cervical cancer comprises 9.1% of all cancer related deaths, ranking it the second most common cause of malignancy induced death in the country, after breast carcinoma. (2,3) However, it is the squamous cell carcinoma of the cervix that is the major responsible culprit for the high prevalence and mortality associated with cervical cancers. Endocervical adenocarcinoma is a relatively uncommon type of cancer of the cervix and accounts for 15-20% of all cervical carcinomas. The villoglandular adenocarcinoma of the cervix is a rare variant of a well-differentiated adenocarcinoma. It accounts for 3.4 - 4.8% of cervical adenocarcinomas (4). It commonly affects young women, and is observed to have a good prognosis.

We report a case of a 32-year-old female who was diagnosed with cervical villoglandular adenocarcinoma.

II. CASE REPORT

A 32-year-old female, P2L1A1 presented to this tertiary care hospital with chief complaints of post coital bleeding for 06 months and vaginal bleeding over the last 03 months. She also gave a history of foul-smelling discharge from the vagina for the last 02 months.

She had previously undergone a biopsy in a primary health care centre, where a diagnosis of cervical villous papilloma was provided. However, radiological evaluation at the same centre revealed a well-defined exophytic growth along the posterior lip of the cervix measuring 1.9 cm x1 .7cm, confined to the cervix, seen on MRI. No extension to the vagina or parametrium was noted. CT scan of the abdomen failed to evidence an extension to the uterus or metastatic deposits in the bilateral ovaries and fallopian tubes.

The colposcopic examination at this centre revealed a growth of 1.5 cm on the posterior lip of the cervix, which bled on touch. A biopsy was taken from the growth and sent for histopathological evaluation. Microscopy revealed a non-encapsulated tumor composed of papillae lined by stratified columnar cells showing minimal to mild atypia. The lining cells showed nuclear atypia characterized by hyperchromatic cigar shaped nuclei and mild atypical mitosis. Nuclear stratification was also noted. No psammoma bodies or areas of necrosis were seen. No features of high-grade carcinoma were noted. The cervical architecture was distorted (Figure 1).

Immunohistochemistry revealed reactivity for p16, which is considered to be a reliable surrogate marker for Human Papilloma Virus (HPV) infection (5) (Figure 2a) while the tumor cells were negative for Vimentin, CK20, ER and PR (Figure 2b-2d).

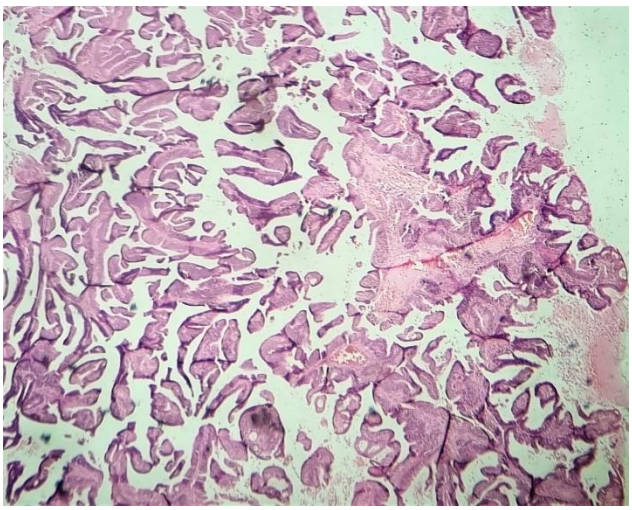

Figure 1(a): H&E-stained microscopic sections of the cervical growth reveal a non-encapsulated tumour composed of papillae lined by stratified columnar cells showing mild to moderate atypia, with no normal cervical architecture being seen (100x).

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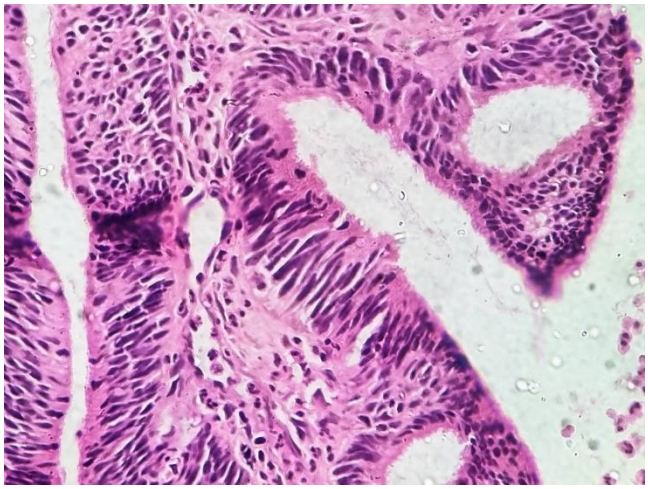

Figure 1(b): High power image (400x) from the cervical growth shows a papilla with nuclear atypia of the lining cells with characteristic hyperchromatic cigar shaped nuclei surrounding a central pedicle. This central pedicle contains a variable number of inflammatory cells.

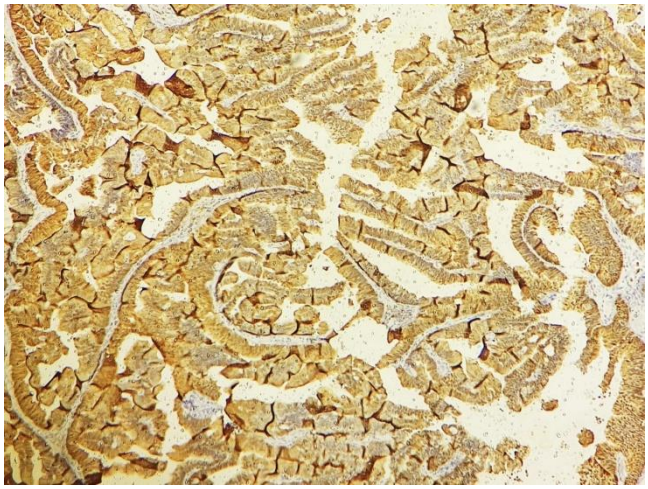

Figure 2: IHC features of VGA: The tumour cells show diffuse block positivity for p16 (100x).

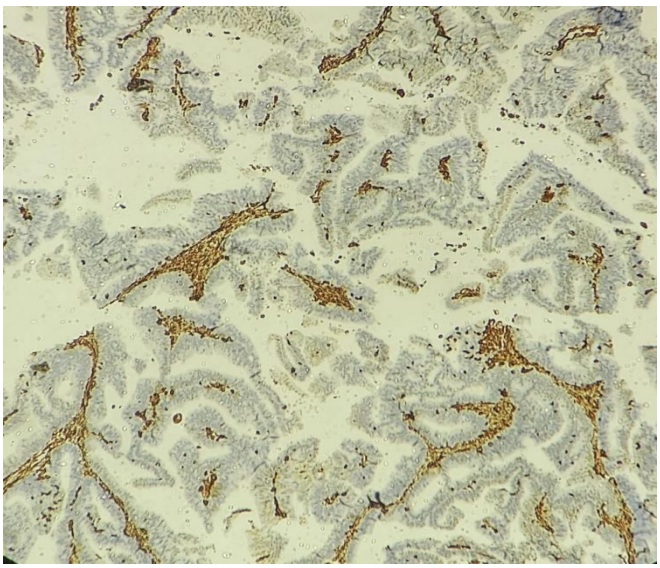

Figure 3(a): IHC features of VGA: Tumour cells are negative for Vimentin.

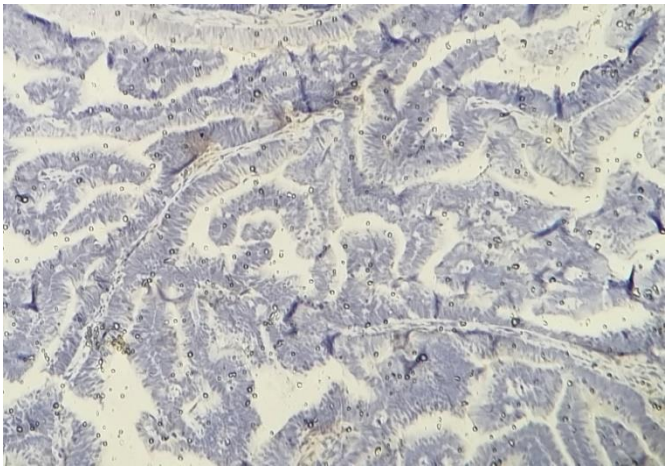

Figure 3(b): IHC features of VGA: Tumour cells are negative for CK20

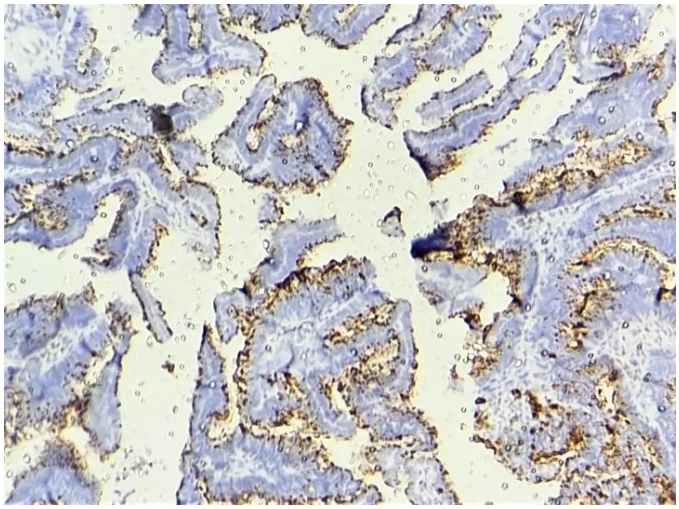

Figure 3(c): IHC features of VGA: Tumour cells are negative for ER.

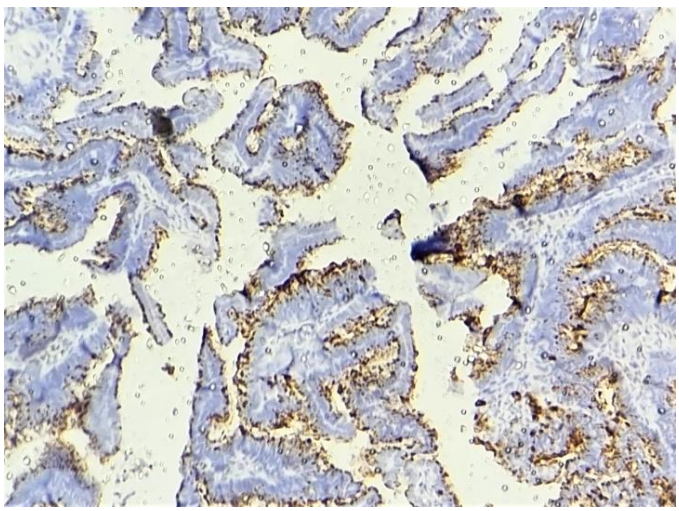

Figure 3(d): IHC features of VGA: Tumour cells are negative for PR

Based upon the above findings, a diagnosis of Papillary adenocarcinoma of the cervix, favouring villoglandular variant was connoted and she was referred to an oncocentre for further management.

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At the oncocentre, the patient underwent Wertheim's hysterectomy based upon the clinico-radio-pathological findings. The histopathological examination of the resected tumour from that centre was consistent with villoglandular variant of cervical papillary adenocarcinoma – Stage IB1. She did not undergo chemo or radiotherapy, and is currently undergoing follow up evaluation since past 02 years with no evidence of recurrence of disease. Her last follow - up visit at this hospital was approximately 05 months ago.

III. Discussion

The incidence of endocervical adenocarcinoma is on a rise since the past decade with a subtle fall in the cases of the cervical squamous cell carcinoma. Villoglandular carcinoma constitutes a rare well differentiated histological subtype of invasive adenocarcinoma of the uterine cervix. Its incidence has been quoted as 3.7– 4.8% of all adenocarcinomas of the cervix. (6) It was first reported by Young and Scully in 1989 and was recognized as a histopathological entity of cervical cancer by the World Health Organization (WHO) in 1994 (7–10). VGA is said to have a favourable prognosis as compared to its other counterparts.

It primarily affects women in the reproductive age group. The age at presentation is usually between 33 and 37 years. However, cases in peri and post-menopausal females have also been reported (7,10). The eldest reported female to develop VGA was 70 years old.(11)

VGA is characterized by three main histological features: (i) Exophytic proliferation, (ii) Papillary architecture and (iii) Mild to moderate cellular atypia (9). However, the classical microscopic feature of this malignancy is a surface papillary component of variable thickness with tall and thin papillae with a fibrous stromal core. Occasionally, short and broad papillae can be present. These papillae are characterized by a central pedicle ranging in size and shape from short and thick to long and thin forms. They may also contain a number of inflammatory cells.

Villoglandular papillary adenocarcinoma should be distinguished from endocervical adenocarcinoma with a minor villoglandular component. The predominant papillary component and mild cytological atypia of the villoglandular papillary adenocarcinoma compared with the marked cytological atypia of adenocarcinoma should help in their differentiation (6). Other tumours that must be differentiated include the rare adenosarcoma and minimal deviation adenocarcinoma, also called as adenoma malignum. Table 1 differentiates these entities.

The etiology of cervical adenocarcinoma remains unclear. However, studies (12,13) suggest a possible role of HPV infection in its pathogenesis and have also proven that HPV infection is more prevalent in VGA than other variants of cervical adenocarcinoma. Jones et al. (14), showed a significant association of HPV 16 and 18 with VGA. Our case also showed reactivity to p16, which indicates consistency with the role of HPV in its pathogenesis. Recent studies have also associated the use of contraceptive pills to the development of VGA (15–17).

The clinical presentation of VGA is similar to other forms of cervical carcinoma, which includes abnormal vaginal bleeding, contact bleeding and abnormal vaginal secretion. (16) It generally presents as a friable exophytic mass arising from the endocervix, which may or may not have an ulcerated surface. (18) Clinical features of VGA help in the early diagnosis and hence, helps in better prognosis as compared to other forms of cervical adenocarcinoma. Our patient also presented with the classical symptoms of abnormal vaginal bleeding and vaginal discharge.

The usually good prognosis associated with this tumor is reflected by the early stage at diagnosis, with over 94% of patients having stage 1 disease. Chen et al. (19) compared cases diagnosed with cervical villoglandular and conventional adenocarcinoma. Their study comprised 60 cases of VGA, of which 65% cases were diagnosed at stage I disease, and 5.4% patients reported with lymph node involvement. Most of these patients underwent primary surgical management, with no recurrence of the disease reported. They had a median survival of 60±36 months, which was significantly better than the survival of patients with conventional cervical adenocarcinoma. Lataifeh et al. (20) in their study have also acknowledged the role of clinical stage and histological subtype of the malignancy in determining the prognosis of the disease.

There is no specified standard treatment modality for management of VGA. However, surgical treatment is associated with excellent prognosis. Surgical management for this tumor includes cone biopsy, simple hysterectomy and radical hysterectomy. Disease-free periods have ranged from 13 months to 7 years (6). Park et al. (21), in their study have concluded that radical hysterectomy has excellent prognosis when combined with systemic adjuvant therapy.

Table 2 summarizes the cases of VGA reported in literature.

IV. Conclusion

Villoglandular variant of endocervical adenocarcinoma is an uncommon subtype of endocervical adenocarcinoma affecting younger women and is associated with good prognosis. Due to its less aggressive behaviour as compared to other forms of cervical malignancies, surgical management is sufficient.

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TABLE 1: Comparison of tumours with histopathological resemblance to VGA

Feature	VGA	Adenosarcoma	Adenoma malignum
Origin(13,22,23)	Epithelial	Malignant mesenchymal and benign glandular component	Epithelial
Incidence(13,23,24)	3.4-4.8%	5.5-7% of uterocervical sarcomas	1.3% of all cervical adenocarcinomas
Age group affected(7,10,25)	Reproductive age (33-37 years)	Predominantly reproductive age (Age range -11-67 years)	42 years (Age range - 25-72 years)
Clinical features(16,25,26)	Abnormal vaginal bleeding, contact bleeding and abnormal vaginal secretion	Abnormal vaginal bleeding	Menometrorrhagia, mucoid or watery vaginal discharge, abdominal pain, postmenopausal bleeding, or may be asymptomatic
Gross(18,22,23)	Friable exophytic mass arising from the endocervix, with or without an ulcerated surface	Broad based or sessile polypoid mass with cut surface composed of a solid tumour with numerous cysts	Multilocular cystic masses in the uterine cervix
Microscopy(9,22,24)	Exophytic proliferation, papillary architecture and mild to moderate cellular atypia	Peri-glandular cuffing and intraglandular protrusions of cellular stroma; non-invasive glands lined by benign appearing mullerian epithelium of various types showing mild to marked nuclear atypia; an average of ≥2 mitotic figures per 10 high-power fields in the stromal component; and more than mild nuclear atypia of the stromal cells	Well-spaced, deeply invasive branching glands lined with uniform columnar mucin-distended cells and infrequent foci of less well-differentiated neoplastic cells
Management(21,22,27)	Surgical excision combined with systemic adjuvant chemotherapy	Localised disease: Complete surgical removal Advanced/Recurrent/Metastatic disease: Cytotoxic chemotherapy with doxorubicin-based regimens, gemcitabine/docetaxel, trabectedin or platinum-based r	Surgical excision combined with radiation ± chemotherapy
Prognosis(19,20,22,25)	Good	Poor	Poor

TABLE 2: Cases of VGA reported in literature till date (total cases=332)

Author	Year	No of patients	Average age at presentation (years)	FIGO stage	Management	Outcome (follow up/months)
Young and Scully(7)	1989	13	33 (23-54)	Inos	4 RH+LNE	NED (24 – 168)[a]
Hopson et al(10)	1990	03	36 (28-42)	Ib	3 RH + LNE	NED (1 uneventful hospital course, 2: 8mths)
Jones at al(14)	1993	24	37 (27-54)	Inos	4 CONS 4 SH + RAD 15 RH	NED (7-77)[a]
Reed et al(28)	1993	04	34 (25-43)	Ib	1 SH + CT 3 RH + LNE + CT	NED (18-28)
Hurteau et al(29)	1995	01	22	Ib	CRH + LNE 32 weeks gestation	NED (14)
Skopelitou and Hadjiyannakis(30)	1996	01	21	Ib1	CONS	NED (12)
Novotny and Ferlisi(31)	1997	03	35 (25-48)	Inos	2 CONS 1 SH	NED (9-32)
Kaku et al(32)	1997	07	45 (33-54)	Ib	7 RH + LNE + BSO (2 LN +) + 1 RAD	NED (9-169) 1 DOD (Vaginal recurrence at 46 months post primary treatment)
Stanley-Christian et al(33)	1997	03	34 (37-41)	Ib1	RH + LNE + BSO	NED (publication date)
Borgo et al(34)	1998	01	26	Ib1	CONS	NED (40)
Lu et al(35)	1998	01	47	Ib1	RH + LNE	NED (9)
Bouman et al(36)	1999	03	34 (29-38)	Ib	1 CONS 1 RH + LNE 1 SH + RAD	NED (15) delivery 15 months after CON at 36 weeks NED (recovery uneventful)
Chang et al(37)	1999	03	40 (35-44)	2 Inos 1 Ib	CONS SH + RAD	NED (8–11) NED (13)
Lakhtakia et al(38)	2000	01	30	Ib	RH + LNE + CT	NED (9)
Lellé et al(39)	2000	01	45	Inos	RH + LNE	NED (9)
Hoffman et al(40)	2001	01	28	Ib1	CON (amputation of the cervical portio)	NED (40) delivery at 36 weeks
Khunamornpong et al(41)	2001	14	38 (22-49)	Ib	12 RH + LNE 02 RH + LNE + RAD (2 LN +)	NED (21-144)
Reale et al(42)	2001	01	69	Inos	RH + LNE	NED (60)
Polat et al(43)	2002	01	38	Inos	RH + LNE	NED (28)
Garcea et al(6)	2003	01	29	Ib1	RH + LNE + RAD (LN +)	NED (34)
Dede et al(44)	2004	01	28	Ib1	After termination of the pregnancy at 8 weeks RH	ROD (42), DOD (“on the fifth year of first diagnosis”)
Utsugi et al(45)	2004	10	45 (36-64)	Ib1	9 RH + LNE 1 RH + LNE + CT	NED (36-228)
Fadare and Zheng(46)	2005	01	47	Ib1	RH + LNE + BSO	NED (4)
Heron et al(47)	2005	01	32	Ib1	Delivery 38 weeks, VGA (Cervical polyp), 1 month PP: RH + LNE	ROD (44) (episiotomy scar) NED (96)
Falcon et al(48)	2006	01	34	Ib1	CONS	NED (96) delivery 60 months after CON
Macdonald et al(49)	2006	01	32	Ib1	CONS	ROD 3 months after CON recurrence (cervix), underwent RAD/ CT, DOD (tumor progression, UAC, second opinion)
Lavie et al(50)	2008	01	31	Ib1	CONS (14th week of gestation) CRH (37th week)	NED (18)
Gonzalez-Bosquet et al(51)	2009	01	28	Ib	RH + LNE	NED (18)
Korach et al(52)	2009	08	39 (33-65)	5 Ib1 3 Ia1	2 CONS 2 SH 3 RH + LNE + BSO	5 NED (72–120) 1 term delivery 2 NED (78-180) 1 ROD (24), DOD (“few months later”)
Takai et al(53)	2010	01	28	Ib1	CONS (16 weeks of gestation)	NED (44) delivery at 38 weeks
Rubeša-Mihaljević et al(54)	2010	01	22	IIIB	RH + LNE	DOD 02 years after diagnosis

Lai et al(12)	2011	12	42 (32-52)	10 Ib1 2 Ia2	9 RH + LNE + BSO 2 RH + LNE (1 LN +) 1 LNE + RAD/CT	11 NED (34-162) 1 ROD (alive 153 mths)
Choi et al(55)	2012	03	52 (48-55)	Ib1	1RH	NED (13–23)
Sethi et al(56)	2012	01	47	Ib	TAH+BSO	NED (60)
Hagiwara et al(57)	2013	06	37 (30-41)	Ib1	1 SH + LN-biopsy 4 RH + LNE ± BSO 1 RH + LNE + RAD (1 LN +)	NED (42–154)
He(58)	2013	01	31	Ib1	Biopsy at 28 weeks (cervical papilloma), CRH + LNE (36 weeks)	NED (84)
Lataifeh et al(20)	2013	28	37 (29-49)	Ib1	2 CS and CONS, trachelectomy and LNE 4 trachelectomy and LNE 12 RH + LNE + Brachy 4 RH + LNE +RAD/CT (2 LN+) 6 RH + LNE	23 NED (18-120) 5 DOD at 22.4 months of average follow – up period
Kim et al(11)	2014	20	47 (32-72)	3 Ia1 17 Ib1	4 CONS 1 LAVH + LNE (Ia1) 3 RH + LNE 4 RH + LNE + BSO + RAD (1 LN+) 2 RH + LNE + USO 2 LRH + LNE + USO + RAD 2 RH + LNE + BSO 1 VH + RAD	4 NED (18–55) 1 ROD 25 months after CON recurrence (cervix), underwent RH, 15 NED (9–150)
Takeuchi et al(59)	2014	01	38	Inos	RH	NED (Publication date)
Dilley et al(60)	2015	02	35 (33-37)	Ib1	CONS	NED (18-41)
Zhao et al(16)	2016	11	36 (31-42)	Ib1	2 RVH + LNE + BSO + AT 2 RVH + LNE + USO + AT 7 RVH + LNE + BSO	NED (7–57)
Zhou et al(61)	2016	04	55 (47-70)	Ib1	2 RH + LNE + BSO 1 RH + LNE 1 SH + RAD	NED (49–83)
Niu et al(62)	2017	04	55 (47-70)	Ib1	1 SH + RAD 3 1 amputation of cervix + LNE 1 RH + LNE 1 1 RH + LNE + BSO	NED (8–34) NED (publication date)
Guo et al(13)	2018	35	42 (27-66)	3 Ia1 1 Ia2 28 Ib1	2 CONS 1 vaginal. trachelectomy + LNE 12 RH + LNE + BSO 31 8 LRH + LNE + BSO 4 NSLRH + LNE + BSO 1 LRH + BSO 3 LRH + LNE + BS 1 RVT + LNE 1 NSARH + LNE + BS 1 LRH + BS 1 CS + RH + LNE + BS Including 9 patients with neo-/ adjuvant treatment (CT and/ or RAD)	NED (6–104) 1 ROD (8), (pelvic, adenocarcinoma) AWD (37)
Ju et al(63)	2018	14	49 (28-64)	11 Ib1 2 Ia1 1 Ia2	1 CON 1 VH + BSO 1 TLH 3 MRH + LNE + BSO 2 LRH + LNE + BSO 2 LMRH + BSO 1 RH + LNE + BSO + RAD/CT (1 LN +) 1 RH + LNE + BSO 1 LRH + LNE 1 LMRH	8 NED (44-65) 1 ROD (22) (vaginal stump) 1 ROD (42) (liver) 1 ROD (34) (adnexa) 1 ROD (12) (adnexa), DOD (42)
Awolola et al(17)	2018	02	25-30	1b!	1 CS+ Excisional biopsy	NED (12-16)

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					followed by MRH 1 RAD	
Wei et al(64)	2018	10	42 (28-50)	Ib1	2 CONS 1 TLH + BSO 1 TLH + BSO + LNE 1 RH 2 RH + LNE RH + BSO + LNE 2 LRH + LNE 2 LRH + BSO + LNE 3 LRH + BSO + LNE + CT/RAD	NED (5–113)
Zhang et al(15)	2020	03	46 (37-58)	IB1	2 RH + LNE + BSO 1 RH + LNE + BSO + CT	NED (56–120)
Chen et al(19)	2021	60	43 (32-68)	35 Ib1 4 Ia2	1 SH + BS 1 SH + BSO 1 TLH + BS 1 trachelectomy + LNE 19 RH + LNE + BSO (1 LN +) 10 LRH + LNE + BSO (1 LN +) 3 RH + LNE + BS 1 LRH + LNE + BS 1 SH + LNE + BS + RAD/CT 1 SH + BS + CT Including further 11 patients with adjuvant treatment (CT and/or RAD)	NED (5–152)
This case	2022	01	32	Ib1	RH + LNE	NED (24)
Total cases	332					

AT=adjuvant treatment, AWD=alive with disease, Brachy=brachytherapy, BS=bilateral salpingectomy, BSO= Bilateral salpingo-oophorectomy, CRH=Caesarean Radical Hysterectomy, RH=radical hysterectomy, CONS=Conservative management, CS=caesarean section, CT=chemotherapy, DOD=dead of disease LMRH=laparoscopic modified radical hysterectomy, LN=lymph node, LRH=laparoscopic radical hysterectomy, LNE= Lymph node exenteration; NED=no evidence of disease, NOS=not otherwise specified, NSLRH=nerve sparing laparoscopic radical hysterectomy, m= month, PP=post-partum, RAD=radiation, ROD=recurrence of disease, RVH=radical vaginal hysterectomy, RVT=radical vaginal trachelectomy, SH=simple hysterectomy, TLH= total Laparoscopic Hysterectomy; USO=unilateral salpingo-oophorectomy, VH=vaginal hysterectomy, Y=year
a =Including all patients of both groups

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