ANTICANCER RESEARCH *40*: 3049-3053 (2020)
doi:10.21873/anticanres.14285

Review

Tumor Handling of Early-stage Cervical Cancer: A Literature Analysis of Villoglandular Adenocarcinoma of the Cervix

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Abstract. *Background/Aim: Recent studies have demonstrated the inferior overall survival outcomes of patients with early-stage cervical cancer who undergo minimally invasive surgery (MIS). One possible explanation for these unexpected results is intraoperative tumor manipulation. Materials and Methods: Considering this hypothesis, we have reviewed the literature on the oncological outcomes of patients with villoglandular adenocarcinoma (VGA) of the cervix, an uncommon variant of cervical cancer that has an excellent prognosis. Results: VGA generally presents as an exophytic mass arising from the endocervix. In a systematic review, we identified 221 patients treated surgically for VGA (FIGO stage Ia-Ib$_1$). Of these, 11 developed recurrence, and four died. The recurrence sites in 8 cases were the pelvis (n=3), vaginal cuff (n=3), episiotomy scar (n=1), and cervix (n=1). Furthermore, 23 VGA-patients were treated by MIS, four experienced recurrence, and one died. Three intraabdominal metastases after MIS were reported. Conclusion: Excessive tumor-handling during MIS or manipulations, e.g. cervix-dilation (during delivery), can worsen the otherwise excellent prognosis.*

Recent findings suggest that minimally invasive surgery (MIS) in patients with early-stage cervical cancer is associated with a higher risk of local recurrence and death than open surgery (1-3). Several mechanisms have been proposed that might explain these results. Insertion of a uterine manipulator or intraperitoneal colpotomy during MIS can cause tumor spillage and tumor contamination of the pelvic peritoneum. These frequently discussed mechanisms are thought to be surgeon-related and preventable (4-6).

An uncommon variant of cervical cancer is villoglandular adenocarcinoma (VGA). VGA of the cervix generally presents as a friable, polypoid, or exophytic mass arising from the endocervical canal. Microscopically, VGA is well differentiated, with a surface papillary component and long and slender papillae, and typically shows only superficial invasion. VGA of the uterine cervix occurs in young women and has an excellent prognosis (7). Because of the superficial endocervical growth pattern and low malignancy of VGA, this tumor appears to be a "model" for iatrogenic tumor spread by manipulation. The question is this: can manipulation of this exophytic friable tumor worsen the prognosis of VGA?

Materials and Methods

Data were collected through PubMed searches and from references in relevant articles published up to 2018. We used the search term "villoglandular adenocarcinoma of the uterine cervix". All papers that reported VGA and contained adequate information (patient age, stage, primary surgical treatment, survival status) were included. Only patients with FIGO stages Ia-Ib$_1$ were recorded, and those with stages Ib$_2$-III were excluded.

Results and Discussion

The PubMed search generated 53 reports (1989-2018) and comprised a total of 308 patients. Of these, 221 patients met the inclusion criteria (FIGO stage Ia$_1$-Ib$_1$). The most common surgical procedures were open radical hysterectomy, conization alone, hysterectomy alone, and MIS. Eleven patients developed recurrence, and four died of the disease (Table I). The recurrence sites of 8 cases were the pelvis (n=3), vaginal cuff (n=3), episiotomy scar (n=1), and cervix (n=1). Twenty-three patients with VGA were treated by MIS,

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Key Words: Early-stage cervical cancer, villoglandular adenocarcinoma of the uterine cervix, minimal invasive surgery, minimal handling, review.

Table I. *Recurrences of VGA in the literature.*

Reference	Age (yr)	FIGO stage	Preoperative diagnosis	Treatment	Outcomes (follow up, months)
13[a]	35	I_{nos} (30%)[b]	NR	TAH, BSO, LNE	ROD (17) (Pelvis), NED (27)
	53	I_{nos} (40%)[b]	NR	TAH, BSO, LNE	ROD (61) (Vaginal cuff), DOD (79)
8	28	Ib_1	Single biopsy	Termination of pregnancy 8 gw, RH	ROD (42) (pelvis), DOD ("on the fifth year of first diagnosis")
9	32	Ib_1	"Polypoid mass detected during delivery"	RH, LNE	ROD (44) (Episiotomy scar), NED (96)
14	34	Ib_1	Single biopsy[c]	RH, BSO, LNE	ROD (22) (Vaginal cuff), DOD ("few months later")
12	44	Ib_1	-	Conization	ROD (25) (Cervix), NED (62)
11	41	Ib_1	"Complete excision of the primary tumor"	MIS, BSO, LNE	ROD (8)[d] (Pelvis), ROD (20), AWD (37)
10	55	Ib_1	Punch biopsy	RH, BSO, LNE	ROD (22) (Vaginal cuff), NED (67)
	54	Ib_1	Punch biopsy	MIS, BSO	ROD (42) (Liver), NED (71)
	46	Ib_1	Punch biopsy	MIS, LNE	ROD (34) (Adnexa), NED (67)
	31	Ib_1	Punch biopsy	MIS	ROD (12) (Adnexa), DOD (42)

Nos: Not otherwise specified; NR: not reported; TAH: total abdominal hysterectomy; LNE: lymphadenectomy; BSO: bilateral salpingooophorectomy; ROD: recurrence of disease; NED: no evidence of disease; DOD: dead of disease; gw: gestational week; RH: radical hysterectomy; AWD: alive and well with disease; MIS: minimally invasive surgery. [a]In one patient out of 12 cases the VGA was detected during delivery; [b]Depth of invasion (percentage of cervical wall); [c]Initial diagnosis was "cervical adenocarcinoma, endometriod type"; [d]Histology revealed a usual type of "endocervical adenocarcinoma".

four had recurrences, and one died. Three intraabdominal metastases were reported after MIS.

Of the 11 cases of recurrence, 5 had tumor manipulation during treatment. One patient (8) received a cervical punch biopsy at the 8th week of gestation revealing a VGA. After termination of the pregnancy in the presence of the tumor, an abdominal radical hysterectomy was performed. The tumor recurred in the pelvis 42 months after primary surgery, and the patient died because of tumoral complications in the fifth year of first diagnosis of the disease. In another patient (9), the tumor was detected during vaginal delivery, and an abdominal radical hysterectomy was performed immediately after. Forty-four months later, VGA recurred in the episiotomy scar.

Ju *et al.* (10) have reported on three patients with intraabdominal metastases: two in the ovary and one in the liver. The three patients were treated by MIS. The histological diagnosis in all cases was carried out by punch biopsy. Conization was conducted only for uncertain tumors. One patient had progressive disease and died 42 months after primary treatment.

One patient (11) had a recurrence in the pelvis 8 months after MIS. The histology of the pelvic mass revealed a usual type of endocervical adenocarcinoma. Twenty months after the initial surgery, the tumor recurred at the vaginal cuff.

Another patient (12) developed a recurrence in the cervix 25 months after conization, underwent a radical hysterectomy and was alive for 26 months during follow-up. The margins of the cone were uninvolved but close to the tumor.

Jones *et al.* (13) have reported on 12 patients without details on clinical stage but with information on the depth of invasion (percentage of cervical wall). In one woman, a "polypoid lesion" on the cervix was detected during delivery. Two patients developed local recurrence: one at 17 months in the perirectal region and another at 61 months in the vaginal cuff. The first patient was treated with radiation and was alive with no evidence of disease at 27 months. The second patient had a recurrent tumor and died at 79 months. There was no evidence of metastatic disease outside the pelvis in any of the patients.

Korach *et al.* (14) have reported on a 34-year-old patient with a pretreatment misdiagnosis by punch biopsy (cervical adenocarcinoma). The final histology was consistent with VGA limited to the cervix. The patient was readmitted two years following radical hysterectomy because of tumor recurrence in the pelvic sidewall and presacral lesions. She was treated with chemotherapy and radiation but died just a few months later.

Although the interpretation of the results of this literature review on VGA is limited by the small number of cases, one can conclude that direct manipulation of the tumor in the uterine cervix may be associated with iatrogenic tumor spread. It is evident that when VGA was present, VGA recurred due to dilation of the cervix during termination of pregnancy or delivery (8, 9). Conversely, among pregnant patients (Table II) whose VGA tumors were either removed before delivery by conization (16, 17) or "untouched" during cesarean section or radical surgery (15, 18, 19) no recurrences were reported.

Table II. *VGA excised (e.g. conization) before or not manipulated during delivery.*

Reference	Age (yr)	FIGO stage	Preoperative diagnosis	Delivery	Outcome (follow up, months)
15	22	Ib	Biopsy, 20 gw	CRH 32 gw	NED (14)
16	31	Ib_1	CON, 14 gw	CRH 37 gw	NED (18)
17	28	Ib_1	CON, 16 gw	Vaginal delivery, 38 gw	NED (44)
18	31	Ib_1	Biopsy, 28 gw	CRH 36 gw	NED (84)
19	32	Ib_1	Biopsy "during pregnancy"	CON, CRT	NED (6)

NED: No evidence of disease; CRH: cesarean radical hysterectomy; CRT: cesarean radical trachelectomy; gw: gestational week; CON: conization.

Hemorrhage and tumor dissemination at delivery are the main concerns for vaginal delivery through a cervix with cancer (20). Vaginal delivery remains a significant adverse prognostic factor for recurrent disease and the poor survival of women who are diagnosed with cervical cancer postpartum (20, 21).

In this literature analysis, 23 patients were treated only by MIS (Table III) (10-12, 22). Four patients had recurrences, and the histology of one case showed a usual type of adenocarcinoma (11). Within a VGA, an adenocarcinoma can focally exist, and in some cases, a second histological opinion regarding the primary specimen is advisable (23). The recent case series (n=15) of Ju *et al*. (10) included three patients with intraabdominal metastases. These three patients had no risk factors for metastasis (no lymphovascular space invasion, or no lymph node involvement and had superficial invasion only). Every primary tumor (stage Ib1) had a macroscopic "exophytic mass", "polypoid mass", and "ulcerative surface", and VGA was diagnosed after a punch biopsy. This intraabdominal metastasis of VGA is very remarkable because VGA has an unusually favorable prognosis.

The Laparoscopic Approach to Cervical Cancer (LACC) trial showed that MIS was associated with a 4-fold higher rate of recurrence and a 6.6-fold higher rate of all-cause mortality than open surgery in patients with cervical cancer (1, 24). Additionally, the analysis of recurrence patterns showed that the women in the MIS group frequently suffered from nonvaginal peritoneal recurrences.

Among the potential reasons for the inferior oncological outcomes of women with cervical cancer who underwent MIS, the risk of tumor spillage with routine use of a uterine manipulator has been suggested (5, 6, 25-27). The unavoidable damage to the tumor and its vasculature during surgery leads to the shedding of cancer cells into the uterine blood stream. Because the manipulator is used for many hours, the influx of tumor cells into veins is more or less constant. The ovaries (one or both) are the first organs through which the venous blood of the uterus passes. In cases of ovary preservation among young VGA patients, this manipulation can lead to tumor dissemination into the ovaries.

Table III. *Treatment of VGA by MIS (n=23).*

Reference	n	Age, yr, mean (range)	FIGO stage	Surgery
12	2	43 (42-44)	Ia_1	LAVH
			Ib_1	LRH
22	1	33	Ib_1	RoH
11	13	38 (32-60)	3 Ia_1	LRH
			10 Ib_1	
10	7	46 (31-54)	1 Ia_1	TLH
			6 Ib1	LRH

LAVH: Laparoscopic assisted vaginal hysterectomy; LRH: laparoscopic radical hysterectomy; RoH: robot-assisted laparoscopic hysterectomy; TLH: total laparoscopic hysterectomy.

Peritoneal dissemination of cancer cells by intracorporeal colpotomy may also be an important factor for peritoneal recurrences in patients treated by MIS (4, 28, 29).

Peritoneal contamination of cervical secretion during intracorporeal colpotomy for routine hysterectomy has been detected (30). Some authors have indicated that transabdominal intracorporeal colpotomy should be avoided and that the use of uterine manipulators should be forbidden in patients without parametrial spread of cervical cancer who undergo laparoscopic radical hysterectomy (6, 31).

The present literature review indicates that the manipulation ("excessive handling") of a cervical VGA can worsen the prognosis of an otherwise rather harmless tumor. An important prerequisite for minimizing the risk of tumor cell spillage is "minimal handling" of the cervical tumor during surgery (4) or the complete preoperative removal of the tumor by conization.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

AD conceived the idea for the study. All Authors are responsible for the writing, critical review, and final approval of the manuscript.

Acknowledgements

The Authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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Received April 19, 2020
Revised May 8, 2020
Accepted May 11, 2020