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Cervical adenocarcinoma: a retrospective clinicopathologic study of 16 cases

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Abstract

Endocervical adenocarcinomas account for about 10–30% of cancers of the uterine cervix and display a variety of disparate morphologies. As an objective of the present work, we analyzed the clinicopathologic characteristics and prognostic factor of cervical adenocarcinoma. Clinicomorphological data of 16 cases of endocervical adenocarcinoma were reviewed during 2006–2011. Histopathologically, seven cases were of mucinous endocervical type, one intestinal type, two mucinous villoglandular type, four endometrioid type and two of serous type. The immunohistochemical investigation showed a tipically endocervical carcinoma profile ER-/PR-/Vim-/CEA+ in 10 cases (62.5%), which morphologically corresponded to: five mucinous endocervical type, one villoglandular type, three endometrioid type and one serous type. Regarding the prognosis we established that endometrioid endocervical adenocarcinoma is the histological variant with the worst prognosis, most cases been diagnosed in advanced stages (IIIA and IIIB) while at the opposite pole were papillary villoglandular and serous endocervical adenocarcinomas, diagnosed in less advanced stages of disease (IB and IIB). We concluded that the clinicomorphological diagnosis of endocervical adenocarcinoma is a challenging task, given to its multitude of histological variants and to the fact that immunohistochemistry investigations proved to be useful in only 63% of cases. In addition, we confirmed that the clinical stage is the most important prognostic factor and to some extent, the histomorphologic features can condition the biological behavior of these tumors.

***Keywords*:** cervical adenocarcinoma, retrospective study, 16 cases.

Introduction

Despite to a dramatically decline over the time of cervical cancer, the incidence of cervical adenocarcinoma has recently been increasing, especially among younger women [1]. In the United States, during the past 20 years was noticed an absolute as well as a relative increase in the incidence of adenocarcinoma of the cervix [2–4], and this disease subtype currently accounts for approximately 24% of all cervical cancers diagnosed in each year [5].

It has been hypothesized that increasing duration of oral contraceptive use, human papillomavirus type 16 and 18, increasing parity, younger age at first full term pregnancy are linked with a particularly high rate of cervical adenocarcinomas [6, 7]. Unlike squamous cell carcinoma, earlier neoplastic precursors (low-grade or high-grade lesions) to cervical adenocarcinoma *in situ* (AIS) and adenocarcinoma are not well characterized. The duration of progression has been estimated to be 5–13 years, cervical AIS originating in the squamocolumnar junction of the transformation zone by oncogenic virus infection of the reserve cells that are re committed to glandular differentiation, which eventually leads to the proliferation of atypical glandular cells (AGC) and AIS [8].

Worldwide, cervical cancer is the most common cause of cancer death and years of life lost owing to cancer [9]. Poor prognostic factors for early stage cervical cancer include pelvic lymph node metastasis, parametrial involvement, positive surgical margins, large tumor diameter, deep stromal invasion, and the presence of tumor in the capillary lymphatic spaces [10]. It remains controversial whether or not histologic subtypes influence prognosis of patients with cervical carcinoma [11–14]. It is also not clear whether cervical adenocarcinoma metastasizes earlier or is detected later, or whether a poorer response to radiotherapy or the inclusion of special subtypes such as clear cell carcinoma could account for an apparent poorer prognosis [15].

The objective of this study was to report our experience in diagnosis of endocervical adenocarcinoma and to evaluate the major clinicopathological factors that might be involved in the prognosis of these patients.

Materials and Methods

We reviewed medical records from the Pathology Laboratory of the Emergency County Hospital, Slatina, and identified those patients who had been operated for cervical carcinomas from 2005 through 2010. As clinical data we noted each patient's age and as pathological parameters we looked for the histopathological variant, tumor size (≤4 cm; >4 cm), histological differentiation degree (well moderate; poor),

depth of stromal invasion (≤1/2; >1/2 of layer), depth of muscular invasion (≤1/2; >1/2 of layer), parametrial involvement, vagina involvement lymph node metastasis, and pTNM (Table 1).

Table 1 – ***The major clinicopathological features of the investigated cervical adenocarcinoma***

Cervical adenocarcinoma type (No.)	Age [years]	Tumor size [cm]		Differentiation		Depth of stromal invasion		Depth of muscular invasion		Parametrial involvement		Lymph node metastasis		Vaginal margins		TNM
		≤4	>4	W–M*	P*	≤1/2L**	>1/2L	≤1/2L	>1/2L	+	-	+	-	+	-	
Mucinous endocervical (1)	45	+		+			+	+		-			-		-	IB1
Mucinous endocervical (2)	56		+	+			+	+		-			-		-	IB2
Mucinous endocervical (3)	58		+	+			+	+		-			-		-	IB2
Mucinous endocervical (4)	69		+	+			+		+	+			-		-	IIB
Mucinous endocervical (5)	64		+		+		+		+	+			-		-	IIB
Mucinous endocervical (6)	55		+	+			+		+	+			+	+		IIIB
Mucinous endocervical (7)	61		+		+		+		+	+			+	+		IIIB
Mucinous intestinal	57		+	+			+		+	+			-		-	IIB
Mucinos villoglandular (1)	37	+		+			+	+		-			-		-	IB1
Mucinos villoglandular (2)	40		+	+			+	+		-			-		-	IB2
Endometrioid (1)	59		+	+			+		+	+			-		-	IIB
Endometrioid (2)	62		+	+			+		+	+			-	+		IIIA
Endometrioid (3)	58		+	+			+		+	+			+	+		IIIB
Endometrioid (4)	63		+		+		+		+	+			+	+		IIIB
Serous (1)	47		+	+			+		+	-			-		-	IB2
Serous (2)	67		+	+			+		+	+			-		-	IIB

* – Tumor degree of differentiation: W–M – well to moderate, P – poor; ** L – Layer.

Paraffin blocks from these patients were process by classical histological techniques (HE stain) and for more detailed histopathological investigation were stained with Masson's trichrome kit (BioOptica, Albedo, Romania, code 21-010802IC) and Alcian Blue (AB) pH 2.5–PAS stain (BioOptica, Albedo, Romania, code W01030799).

To exclude endometrial adenocarcinomas we made for each investigated cases a panel of three immunohistochemical markers: ER (1D5, mouse anti-human, monoclonal, Dako, Redox, Romania, code M7047), PR (PgR 636, mouse anti-human, monoclonal, Dako, Redox, Romania, code M3569), Vim (V9, mouse anti-human, monoclonal, Dako, Redox, Romania, code M 0725) and CEA (II-7, mouse anti-human, monoclonal, Santa Cruz, Redox, Romania, code sc-46657). The slides were unmasked by 20 minutes heat induced epitope retrieval in DakoCytomation Target Retrieval solution, code S1700, and than the endogenous peroxidase activity was blocked with 3% hydrogen peroxide in PBS for 15 minutes and then the unspecific binding sites were blocked with 5% BSA/PBS for one hour. The primary antibodies were used at a dilution of 1:35 for ER and 1:50 for PR, Vim and CEA, incubating the slides overnight at 4^0C. The reactions were amplified with LSAB2 (Dako, Redox, Romania, code K0675) and visualized with 3,3'-diaminobenzidine (DAB) (Dako, Redox, Romania, code K3468). For counterstaining, we used Mayer's Hematoxylin. Negative-control stainings were done by omitting the primary antibodies, and as external positive control were used normal endometrial specimens.

Immunostaining assessment was done by the same algorithm used by several authors in previous studies [16–20]. The intensity of marker expression was quantified using the following scores: 0 – negative, 1 – weakly positive, 2 – moderately positive, 3 – strongly positive. The extent of marker expression was quantified by evaluating the percentage of the positive staining areas in relation to the whole cancer areas in the core. A score of 0 point was given for 0% reactivity, 1 point was assigned for 1–10% reactivity, 2 points were assigned for 11–50% reactivity, 3 points were assigned for 51–80% reactivity, and 4 points were assigned for 81–100% reactivity. The final immunoreactive score was determined by multiplying the positive intensity and the positive area extent scores, yielding a range from 0 to 12. The threshold for differentiating between final positive and negative immunostaining was set at 4 for interpretation, dividing cases in positive one if the final score has values >3 and negative for scores ≤3.

The histopathological criteria for cervical adenocarcinomas diagnosis were those established by *WHO* (2003) [21] and the images were acquired by utilizing a Nikon Eclipse 55i microscope (Nikon, Apidrag, Bucharest) equipped with a 5-megapixel cooled CCD camera and the Image ProPlus AMS7 software (Media Cybernetics Inc., Buckinghamshire, UK).

Results

According to the data presented in Table 1, the majority of cervical adenocarcinoma developed in the

fifth and six decade of life (both with an equal number of cases – six cases), with an average of 56.125 years. The median onset age was 58.285 (range: 45–64) in mucinous endocervical subtype group, while for endometrioid subtype was about 60.5 (range: 58–63) and mucinous villoglandular was 38.5 (range: 37–40) and in serous variant group was 57 (range: 47–67).

According to the *WHO* classification criteria (2003) the most encountered histopathological variant of endocervical adenocarcinoma was the mucinous type with eight cases (62.5%), from which the largest forms were reported for the mucinous endocervical subtype (seven cases, 43.75%). As the second most frequent form there were the endometrioid subtype tumors counting four cases (25%). Other cases diagnosed included: intestinal mucinous variant (one case), mucinous villoglandular type (two cases) and serous variant (two cases).

In the mucinous endocervical type, the tumoral pattern was that of a glandular type but with a complex architecture (a mixture of simple or branching, tubular or papillary glands) (Figure 1, A and B).

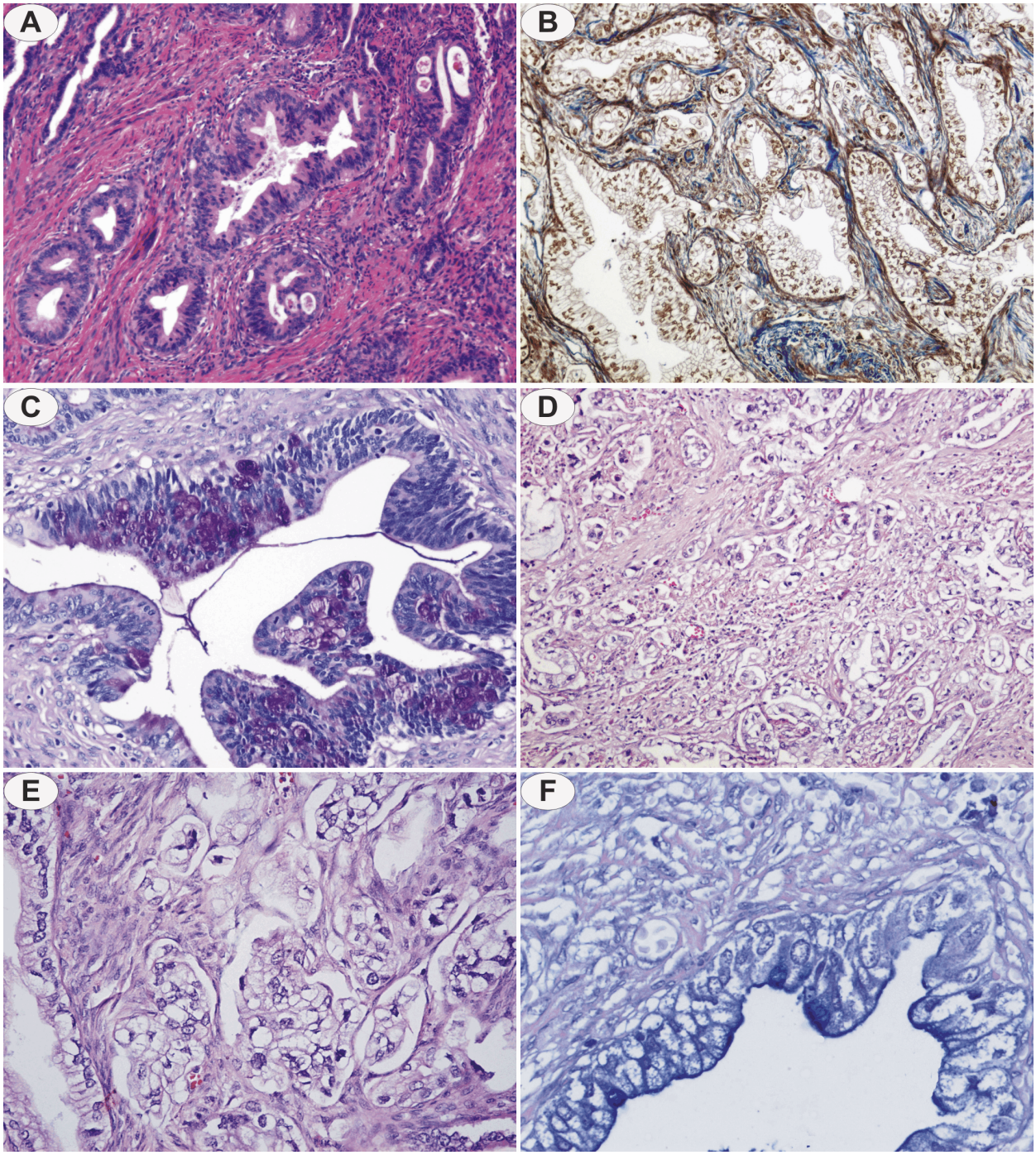

Figure 1 – ***Cervical adenocarcinoma – mucinous endocervical type: (A and B) Well-differentiated tumor with prominent tubular gland pattern (HE stain / Masson's trichrome stain, ×100); (C) Neoplastic cells with variable intracellular quantities of neutral mucins (AB–PAS stain, ×200); (D) Poor differentiated with few recognized neoplastic tubular glands (HE stain, ×100). Cervical adenocarcinoma – mucinous intestinal type: (E) Neoplastic glands with intestinal mucinous differentiation (HE stain, ×200); (F) Malignant cells with goblet cell morphology that apically present a pool of acidic mucins (AB–PAS stain, ×400).***

The neoplastic cells resembled those that lined the endocervical glands, stratified with basal nuclei and abundant pale granular cytoplasm that stained positively for mucin (Figure 1C). Almost 71.5% of the cases were well to moderately differentiate forms. In only two cases, tumors were poorly differentiated with neoplastic cells that contained less cytoplasm but usually still forming recognizable glandular structures (Figure 1D).

In almost all cases (seven cases), the tumor size was of more than 4 cm, and in all cases there was a wide stromal invasion. In four cases (57.15%), we noticed wide muscular invasion and parametrial involvement. In other cases invasion did not exceed half of muscle layer thickness.

Only in two cases (28.57%), the tumors invaded the vagina and presented regional lymph node metastasis. In addition, we observed an even distribution of cases with TNM staging, with two cases in IB2, IIB and IIIB stages and one case in IB1 stage.

The intestinal mucinous cervical adenocarcinoma type was diagnosed only in one case. Histopathology showed an endocervical mucinous adenocarcinoma that focally showed an intestinal mucinous differentiation (Figure 1E). In these areas there were present neoplastic glands lined by malignant-appearing cells, some of which had their cytoplasm distended by a single large vacuole of mucin, forming a goblet cell (Figure 1F). It was a well to moderate differentiated form, had more than 4 cm in the maximum diameters, fully invaded the muscle layer and exhibited parametrial involvement, but without involving the vagina and with no regional lymph node metastasis. According to these clinico-pathological aspects, this tumor was classified as IIB TNM stage.

Two cases were diagnosed as mucinous villo-glandular cervical adenocarcinomas. These tumors were characterized by surface papillae that varied from long, delicate, finger-like projections to short, broad, complex, and branching structures with variable amounts of stroma (Figure 2, A and B). These neoplastic structures were lined by one or several layers of columnar cells, some of which contain mucin. In one cases this cytoarchitectonic was barely recognizable and only in a small portion of the tumor; for these reasons it was classified as a poor differentiated tumor. Clinically, this case was more aggressive; the tumor had more than 4 cm in diameters invading the surrounding tissues, and was thus classified as IB2 TNM stage.

The histopathological diagnosis of cervical endo-metrioid adenocarcinoma was established in four cases. In three cases we noticed well to moderate differentiated tumors with glandular or villoglandular structures lined by simple to pseudostratified columnar cells that have their long axes arranged perpendicular to the basement membranes with elongated nuclei that are also polarized in the same direction (Figure 2, C and D).

In one case, the glandular differentiation was partially replaced by solid nests and sheets of neoplastic cells. Little or no intracellular mucin was present. In one case, the tumor had more than 4 cm in diameters, invaded the full thickness of muscular layer and also involved the parametrium, being classified as a IIB TNM stage. In other case, the tumor invaded the vagina and was classified as an IIIA TNM stage.

The two remaining cases were classified as IIIB TNM stage as they disseminated into the regional lymph nodes.

The serous cervical adenocarcinoma diagnosis was established by us in two cases. They are composed of papillae or branching, gaping glands lined by cells with pleomorphic nuclei and often centrally protruding apical cell cytoplasm, resulting in a scalloped configuration (Figure 2, E and F).

In one case, the tumor with more than 4 cm in diameters, invaded the full thickness of muscular layer but without parametrial involvement being classified as IB2 TNM stage.

In the other case, the tumor invaded in addition the parametrium but without lymph node metastasis and so it was classified in the IIB TNM stage. Little or no intracellular mucin was present.

To certify the endocervical origin of the investigated cases, we performed for each case an immunohisto-chemical assessment on a panel of four antibodies (ER/PR/Vim/CEA), commonly used in differentiation of the endometrial carcinomas (ER+/PR+/Vim+/CEA-) from those of endocervical origin (ER-/PR-/Vim-/CEA+) (Figure 3, A–D).

In Table 2 there are summarized the results of the immunohistochemical investigation regarding the reactivity of each of those 16 investigated cases for each of the four used markers.

Table 2 – *Immunohistochemical staining results*

		Mucinous endocervical type	Mucinous intestinal type	Mucinous villoglandular type	Endometrioid type	Serous type
ER	Score 0–3	6/7 (85.7)	1/1	2/2	4/4	1/2
	Score 4–12	1/7 (14.3)	0/1	0/2	0/4	1/2
PR	Score 0–3	5/7 (71.4)	0/1	1/2	3/4	1/2
	Score 4–12	2/7 (29.6)	0/1	1/2	1/4	1/2
VIM	Score 0–3	6/7 (85.7)	0/1	2/2	3/4	2/2
	Score 4–12	1/7 (14.3)	0/1	0/2	1/4	0/2
CEA	Score 0–3	2/7 (29.6)	1/1	1/2	1/4	1/2
	Score 4–12	5/7 (71.4)	0/1	1/2	3/4	1/2

Immunohistochemical scoring of the reactions showed significant difference of the four markers reactivity in different subtypes of cervical adenocarcinoma. The ER-marker staining was positive in 1 out of 7 (14.3%) mucinous endocervical type (Figure 4, A and B) and in one out of 2 of the serous type. The PR-marker staining was positive in 2 out of 7 (29.6%) of the mucinous endocervical type, in one out of 2 of the mucinous villoglandular type, in 1 out of 4 of the endometroid type and in one out of 2 of the serous type. The Vim-marker staining was positive in 1 out of 7 (14.3%) of the mucinous endocervical type and in 1 out of 4 of the endometroid type (Figure 4C). The CEA-marker staining was positive in 5 out of 7 (71.4%) of the mucinous endocervical type (Figure 4D), in one out of 2 of the villoglandular type, in 3 out of 4 of the endometroid type and in one out of 2 of the serous type (Figure 4 E–F).

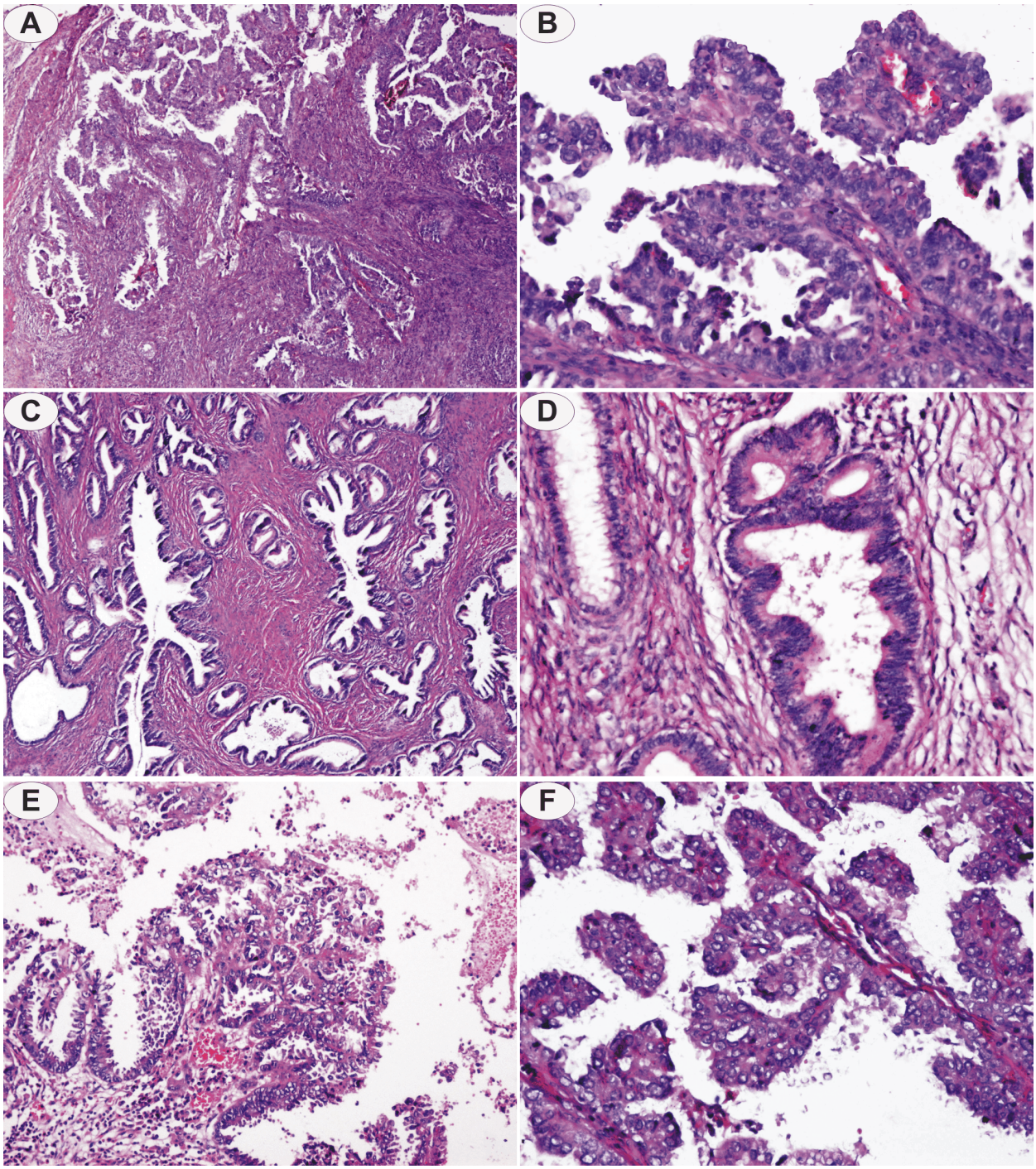

Figure 2 – ***Cervical adenocarcinoma – mucinous villoglandular type: (A and B) Neoplastic proliferations with papillary growth pattern consisting in long, delicate, finger-like projections outlined by one to several layers of columnar cells (HE stain, ×40/×200). Cervical adenocarcinoma – endometrioid type: (C and D) Neoplastic glands lined by pseudostratified columnar cells that have their long axes arranged perpendicular to the basement membrane with elongated nuclei that are also polarized in the same direction (HE stain, ×40/×200). Cervical adenocarcinoma – serous type: (E and F) Papillae lined by cells with pleomorphic nuclei and often centrally protruding apical cell cytoplasm, resulting in a scalloped configuration (HE stain, ×40/×200).***

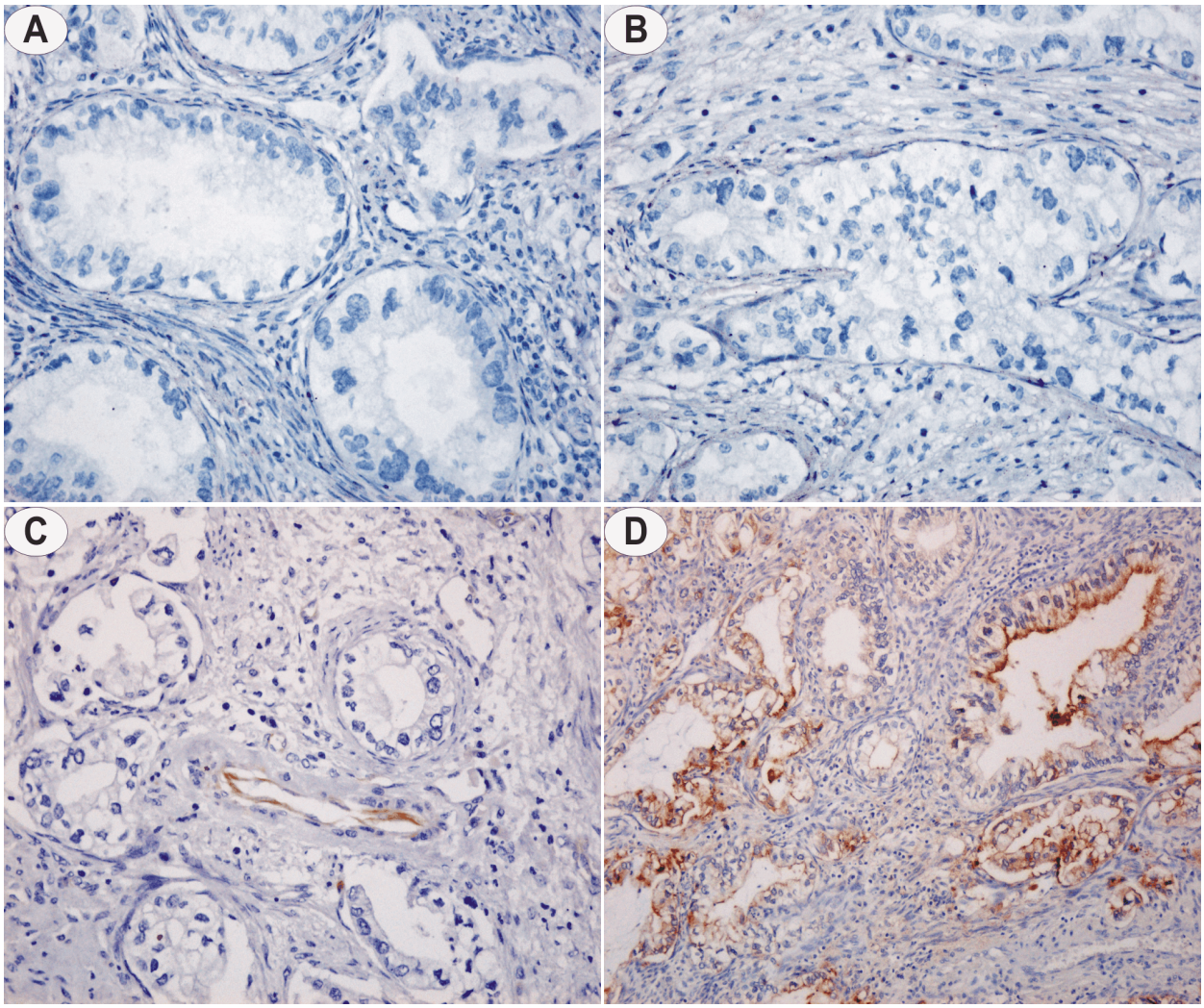

Figure 3 – ***Cervical adenocarcinoma – mucinous endocervical type, immunohistochemical stains for ER, PR, VIM and CEA: (A and B) ER and PR negative reactions in the nuclei of neoplastic cells, ×200; (C) VIM negative reaction in the cytoplasm of neoplastic cells but positive in blood vessels endothelial cells (internal positive control), ×200; (D) CEA positive reaction PR in the cytoplasm of neoplastic cells, ×100.***

In addition, in Table 3 there are presented the ER/PR/Vim/CEA- assessment panel results for the diagnosis of different types of endocervical adenocarcinoma.

Table 3 – ***Assessment panel for the diagnosis of different types of endocervical adenocarcinoma***

ER>3	PR>3	VIM>3	CEA>3	No. of cases of different types					Total No.
				Endocervical	*Intestinal*	*Villoglandular*	*Endometrioid*	*Serous*	
-	-	-	-	0	1	0	0	0	1
-	-	-	+	5	0	1	3	1	10
-	+	-	-	1	0	1	0	0	2
-	+	+	-	0	0	0	1	0	1
+	+	-	-	1	0	0	0	1	2
+	+	+	-	0	0	0	0	0	0

The typical immunoprofile of endocervical carcinoma, respective ER-/PR-/Vim-/CEA+ was encountered in 10 cases out of 16 (62.5%), from which morphologically five corresponded to the mucinous endocervical type, one to the villoglandular type, three to the endometrioid type and one to the serous type.

In the rest of the cases (37.5%), we recorded other non-typical expression pattern for this four-marker immunoprofile.

Noteworthy is the fact that none of the cases investigated did not expressed a four-marker immunoprofile characteristic to endometrial adenocarcinoma (ER+/PR+/Vim+/CEA-), so the cervical origin of these tumors cannot be challenged.

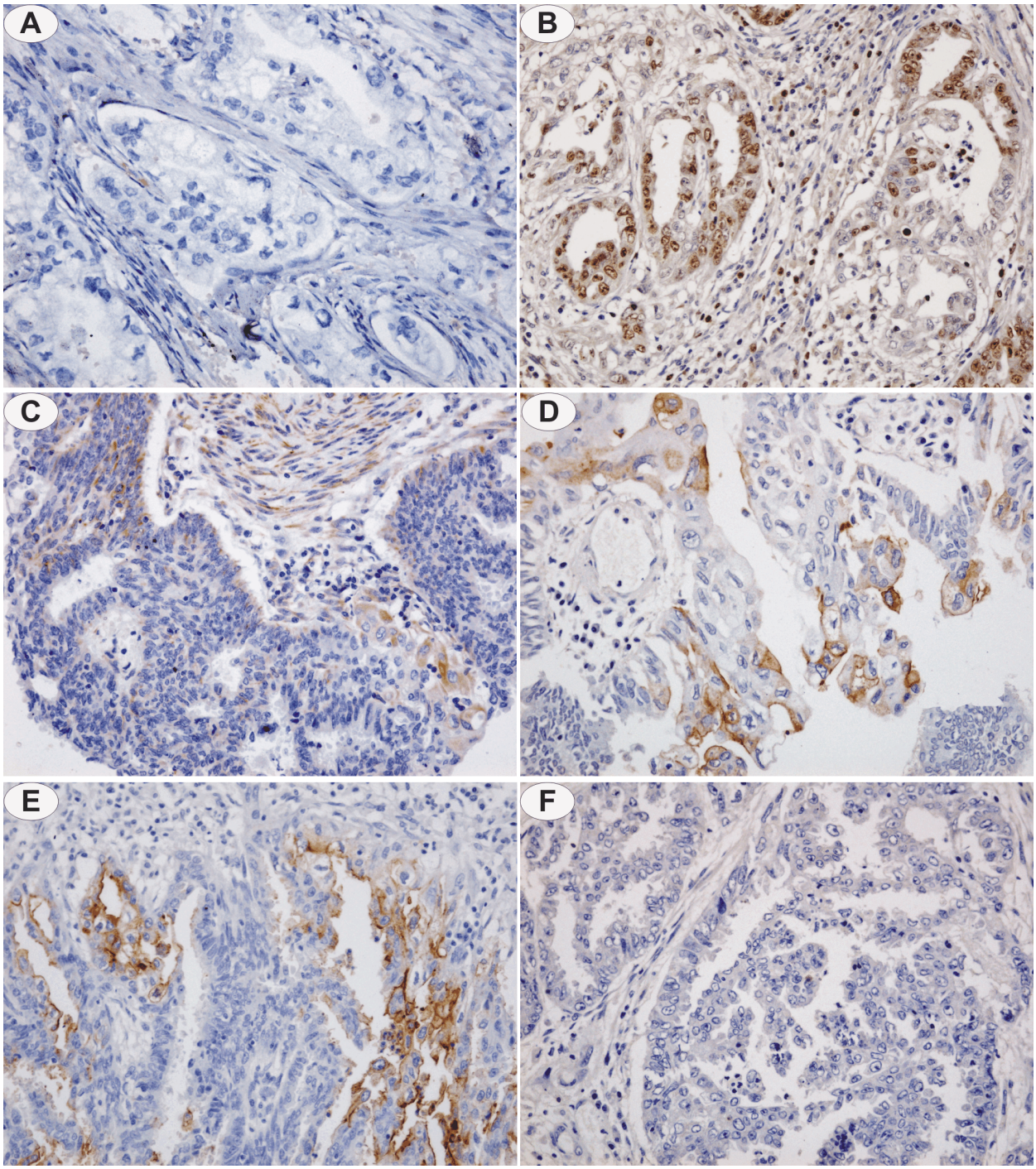

Figure 4 – ***Cervical adenocarcinoma – different types, immunohistochemical stains for ER, PR, VIM and CEA: (A) ER negative reaction in cytoplasm of neoplastic cells from mucinous endocervical type carcinoma, ×200; (B) ER positive reaction in cytoplasm of neoplastic cells from endometrioid type carcinoma, ×400; (C) VIM positive reaction in cytoplasm of neoplastic cells from endometrioid type carcinoma, ×200; (D) CEA positive reaction in cytoplasm of neoplastic cells from mucinous endocervical type carcinoma with squamous cell metaplasia, ×200; (E) CEA positive reaction in cytoplasm of neoplastic cells from endometrioid type carcinoma, ×200; (F) CEA negative reaction in cytoplasm of neoplastic cells from endometrioid type carcinoma, ×200.***

Discussion

Cervical carcinoma is the second most common cancer in women worldwide, and it remains a leading cause of cancer-related death for women in developing countries. The incidence of invasive cervical cancer has declined in many developed countries, mainly due to cytological screening programmes with Papanicolaou tests [22].

In the ninety years, cervical cancer was responsible for about 10% of women cancers with a total of 470 000 cases worldwide [23]. Also, it was estimated that about 230 000 women die annually from cervical cancer, and over 190 000 of those are from developing countries. In respect to this, Levi F *et al.* found a somewhat relatively high-incidence for cervical cancer in Eastern and Central Europe [24]. Unlike those countries, in United States the *American Cancer Society* estimated in 2010

that 1.3% of all cancer deaths and 6.5% of deaths from gynecologic cancers are related to cervical cancers [25].

According to the last *WHO* (2003), histological classification of tumors of the uterine cervix, epithelial tumors were grouped into five broad categories: (1) squamous tumors and precursors; (2) glandular tumors and precursors; (3) other epithelial tumors; (4) neuroendocrine tumors and (5) undifferentiated carcinoma [21]. The best represented are squamous tumors which comprise about 80% of cancers of the uterine cervix, and the majority of the remainder are adenocarcinomas [26]. During the past 20 years, in United States was observed a relative increase in the incidence of cervical carcinoma [2–4].

Despite its low incidence (10–30%), diagnosis of cervical adenocarcinomas is clinically very important because of its poorer prognosis and lower sensitivity to radiotherapy and chemotherapy in comparison with squamous cell carcinoma [12, 27]. Carcinomas that arise in the endocervix can display a variety of disparate morphologies, some of which are associated with a distinctive biologic behavior. Histopathologically, the two most common subtypes of cervical adenocarcinoma are the mucinous endocervical type and the endometrioid type [28].

In our study, during the last five years there were diagnosed 16 cases of endocervical carcinoma. The majority of these tumors were of the mucinous type (62.5%) with the endocervical subtype as most encountered (43.75% form all cases and 70% from the all mucinous endocervical tumors). The second most encountered endocervical adenocarcinoma was the endometrioid tumors, which accounted for 25% of all cervical carcinomas. Other types of endocervical carcinomas diagnosed by us were: serous adenocarcinomas (12.5%), mucinous villoglandular adenocarcinomas (12.5%) and mucinous intestinal adenocarcinomas (6.25%).

Data from the literatures indicates that mucinous endocervical carcinoma accounts for 70% of cervical adenocarcinomas [21]. Regarding the incidence of the endometrioid cervical carcinomas the data are contradictory. Therefore, while Young RH and Clement PB [29] reported that this endocervical carcinoma type is uncommon, others noticed that this tumor accounts for up to 30% of all primary endocervical adenocarcinomas [21]. Moreover, Alfsen GC *et al.* reported an increase in the proportion of non-squamous carcinomas of the cervix over the past few decades in Norway, endometrioid adenocarcinoma accounting for 21% [30]. Cervical serous adenocarcinoma is a rare tumor and its frequency is not known [31]. The largest series published in the literature included 17 cases and was described by Zhou C *et al.* [32]. Villoglandular papillary adenocarcinoma of the uterine cervix was first described by Young RH and Scully RE in 1989 [33], and is a rare well differentiated type of cervical adenocarcinomas that accounts for about 4% of these tumors [21]. Cervical mucinous adenocarcinoma of the intestinal type is a rare tumor and its frequency as a percentage from all cervical adenocarcinomas or cervical tumors was not yet established [21].

In many situations, especially when a tumor involves both the lower uterine segment and upper endocervix, the distinction between a primary endometrial and endocervical adenocarcinoma may be difficult. This distinction is important because the treatment plans and adjuvant therapies are totally different for endometrial and primary cervical cancers [34, 35]. This problem is partial solved by using appropriate immunohistochemical markers in pathological examinations. Several studies have reported that typical endocervical adenocarcinoma-type immunoprofile tends to be ER-/PR-/Vim-/CEA+, whereas typical endometrial carcinoma-type immunoprofile tends to be ER+/PR+/Vim+/CEA- [36–39].

Our immunohistochemical investigation proved that typical four-marker immunoprofile of endocervical adenocarcinoma was recorded in 62.5% of the investigated cases. In other cases, we recorded atypical four-marker immunoprofile but none similar to that characteristic to endometrial adenocarcinoma (ER+/PR+/Vim+/CEA-). So, the tumor immunoprofile depended on the histopathological subtype. The typical four-marker immunoprofile (ER-/PR-/Vim-/CEA+) was most frequently recorded in the mucinous endocervical type followed by the endometrial type. The intestinal type and to a certain extent the mucinous villoglandular and serous types had an atypical four-marker immunoprofile questioning their endocervical origin. These results are comparable to those from the literature [32, 40, 41]. Many studies proved that the accuracy rate of this four-marker panel in definitive diagnosis of primary endocervical carcinomas varied from 57.1% [20] to 80% [42]. So, they concluded that further exploration of other markers needs to be conducted to make the definitive distinction between primary endocervical and endometrial adenocarcinomas.

Many studies had suggested that the prognosis for typical adenocarcinoma was worse than that for squamous cervical cancer [43–49]. However, this has not been confirmed in other studies using carefully matched controls [4, 50–53]. Moreover, other authors showed that this difference in survival is limited to stage I and II tumors treated with radiotherapy [45, 54–56]. It seems that the 5-year survival rate for cervical adenocarcinoma depends primarily on the clinical stage of the disease and also on the histological type and the degree of differentiation of the tumor [57]. However, some studies reported that the histological subtype of adenocarcinoma has no prognostic significance [53, 58–60]. On the contrary, Saigo PE *et al.* found that endometrioid cervical type would have a more favorable prognosis to the other histological variants [61]. Several studies have shown that villoglandular (papillary) type of adenocarcinoma has an excellent prognosis [62, 63]. More recently, Dede M *et al.* drew attention to the fact that this tumor is not innocent, and it can be complicated by recurrence and metastasis requiring more radical surgical and medical attempts [64]. Another variant of endocervical adenocarcinoma suspected to have an unfavorably prognosis is papillary serous carcinoma [65]. However, Zhou *et al.* investigating 17 such cases, concluded that papillary serous endocervical adenocarcinoma has an

aggressively behavior when is diagnosed at an advanced stage, but the outcome for patients with stage I tumors is similar to that of patients with cervical adenocarcinoma of the usual type [32]. Our retrospective clinicopathological study investigating a small number of cervical carcinoma sub-variants did not allow us to establish significant prognostic correlations. However, we can conclude that endometrioid endocervical adenocarcinoma is the histological variant with the worst prognosis, most cases been diagnosed in advanced stages (IIIA and IIIB). At the opposite pole were papillary villoglandular and serous endocervical adenocarcinomas, diagnosed in less advanced stages of the disease (IB and IIB).

Conclusions

Our retrospective study revealed that morphological diagnosis of endocervical adenocarcinoma is extremely difficult given the multitude of histopathological variants, each with different possible biological behavior. In at least 63% of the investigated cases, we showed that endocervical origin of these tumors could be supported by conducting a typical four-marker immunoprofiling (ER-/PR-/Vim-/CEA+). For a more accurate diagnosis, further exploration of other markers still needs to be conducted. In addition, we confirmed that the clinical stage is the most important prognostic factor, and that to some extent, their histomorphologic features can condition the biological behavior of these tumors.

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