Cervical Adenocarcinoma. Past, Present and Future

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Abstract

Due to preventive measures taken in the Western world, cancer of the cervix is placed in the category of rare cancers. Cervix adenocarcinoma represents 15% to 20% from cervical cancers, so it is more a rare cancer. Staging and current treatments of cervical cancer are not differentiated according to the histology of adenocarcinoma. However the risk of metastasis and death is higher for adenocarcinoma although the response is similar to patients with squamous cell cancer. The CA125 marker has proven to be an important predictor factor and HER2/new when present is associated with an aggressive biological behavior. AJCC staging manual suggests the following 5-year survival rates: 80-93% for early stages-0, IA, IB, 58-63% for IIA, IIB, 32-35% for stages IIIA, IIIB, and low survival rates for stage IV, only 15%.

Key words: cervical cancer, adenocarcinoma (ADC), rare cancer.

Background

Special attention has been given lately to the concept of rare cancers. What are rare cancers or orphan diseases? Orphan Diseases or illnesses without parents, which have not been adopted, by the researchers, or by the pharmaceutical companies. According to ESMO, rare cancers are a group of rare diseases which meets diseases with a prevalence of less than 5 cases out of a population of 10,000 (1). In the EU, around 4 million people are affected by rare cancers. Despite the rarity of the 186 rare cancers, they are in total about 22% of all cancers and are included here all cancers even those in children (1). Lately, incidence is considered the best indicator to define rare cancers. As far as incidence is concerned (newly diagnosed cases per year), rare cancers are defined as those that appear with an incidence of less than 6/100,000 persons/year (1). The 5year free survival in rare cancers is worse than common cancers 47% vs. 65%, due to ESMO research (1).

Cervical cancer, globally, is the second commonest cancer in females, but his incidence is highly variable in different countries.

In Europe, the incidence of cervical cancer was highly reduced after the introduction of the screening methods. There are 23 types of cervical cancer, as per ESMO, most frequent, squamous cell carcinoma with variants of the cervix, counting 80%. Adenocarcinoma is the second most common subtype of cervical cancer, making up 15-20% of all cervical cancers. Cervical adenocarcinoma arises within glands located in the endocervix. According to the ESMO classification of rare cancers, there are 12 variants of adenocarcinoma: adenocarcinoma with no other specifications (NOS), adenocarcinoma with squamous metaplasia, mucinous, clear cell, endometrioid, serous chistadenocarcinoma, signet ring cell carcinoma, mesonephroma malignant, villous adenocarcinoma, mucinous adenocarcinoma-endocervical type, adenocarcinoma intestinal type, mixed cell adenocarcinoma (Table I) (2).

The etiology of adenocarcinoma is not completely known, but human papilloma virus is highly incriminated to produce the disease. However, only a very small percentage of women having the infection will ever develop cancer.
Cervical adenocarcinoma treatments include surgery, radiation therapy and chemotherapy, or a combination of these methods, depending on stage at diagnosis.

The 5 year survival rates in cervical adenocarcinoma depends mostly on stage at diagnosis (80-93% for early stages-0, IA, IB, 58-63% for IIA, IIB, 32-35 % for stages IIIA, IIIB, and low survival rates for stage IV, only 15%), published in 2010 in the 7th edition of the AJCC staging manual (3).

**Epidemiology**

Among the distribution on the family of rare tumors, female genital tract owns a second important place with 18% from all rare cancers, after hematological cancers (22%). Cervical adenocarcinomas fall into the category of rare cancers, with a rate 1.01/100000 persons with a total of 8123 patients each year, respectively 0.67 for the pure adenocarcinoma and <0.01/100.000 persons adenocarcinoma with scuamous metaplasia (Fig. 1), (1).

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 (4). The most frequent are squamous carcinomas totaling about 80% of cancers of the uterine cervix and the majority of the remaining are adenocarcinomas (7).

**Fig. 1.** Families of rare cancers (1).

| Table I. Surveillance of rare cancers in Europe (1)* Layer 1=Families of tumors; Layer 2= clinically meaningful tumours; Layer 3 = tumour entities (2). |
|---|---|---|---|---|
| C = common | Layer | Tumour | Rate | Patients | Morphology code |
| R = rare | | | | | |
| 1 | 1 | EPITHELIAL TUMOURS OF CERVIX UTERI | 6.08 | 46,888 | 8000, 8001, 8010, 8011, 8015, 8020-8022, 8032, 8050-8054, 8120, 8123, 8140-8144, 8143, 8144, 8147, 8190, 8200-8201, 8210-8211, 8221, 8230, 8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8360-8364, 8430, 8440-8441, 8460-8462, 8490, 8504, 8510, 8512, 8514, 8526, 8542, 8550-8551, 8560, 8562-8575, 9110 |
| R | 2 | Squamous cell carcinoma with variants of cervix | 4.28 | 34,441 | 8015, 8120, 8123, 8050-8054 |
| 3 | Squamous carcinoma | 2.62 | 23,473 | 8070 |
| 3 | Squamous cell carcinoma nonkeratinizing, NOS | 0.40 | 3,258 | 8072 |
| 3 | Squamous cell carcinoma keratinizing, NOS | 0.42 | 3,401 | 8072 |
| 3 | Papillary squamous cell carcinoma | 0.01 | 77 | 8062 |
| 3 | Papillary carcinoma, NOS | <0.01 | 26 | 8050 |
| 3 | Verrucose/Warty carcinoma | <0.01 | 24 | 8051 |
| 3 | Basaloid carcinoma | <0.01 | 22 | 8123 |
| 3 | Squamous cell carcinoma spindle cell | <0.01 | 20 | 8074 |
| 3 | Lymphoepithelial carcinomas | <0.01 | 12 | 8060 |
| 3 | Transitional cell carcinoma, NOS | <0.01 | 13 | 8120 |
| 3 | Glassy cell carcinoma | <0.01 | 8015 |
| R | 2 | Adenocarcinoma with variants of cervix uteri | 1.01 | 8,123 | 8140-8141, 8143, 8144, 8147, 8190, 8200-8201, 8210-8211, 8221, 8230, 8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8360-8364, 8430, 8440-8441, 8460, 8460-8462, 8490, 8504, 8510, 8512, 8514, 8526, 8542, 8550-8551, 8562-8575, 9110 |
| 3 | Adenocarcinoma, NOS | 0.67 | 5,352 | 8140 |
| 3 | Adenocarcinoma with squamous metaplasia | <0.01 | 35 | 8070 |
| 3 | Mucinous adenocarcinoma | 0.03 | 213 | 8480 |
| 3 | Clear cell adenocarcinoma, NOS | 0.03 | 247 | 8310 |
| 3 | Endometroid adenocarcinoma, NOS | 0.02 | 186 | 8380 |
| 3 | Serous cystadenocarcinoma, NOS | <0.01 | 6 | 8441 |
| 3 | Signet ring cell carcinoma | <0.01 | 13 | 8480 |
| 3 | Mucinous carcinoma malignant | <0.01 | 17 | 8110 |
| 3 | Villous adenocarcinoma | <0.01 | 9 | 8262 |
| 3 | Mucinous adenocarcinoma, endocervical type | <0.01 | 4 | 8482 |
| 3 | Adenocarcinoma intestinal type | <0.01 | 2 | 8144 |
| 3 | Mixed cell adenocarcinoma | <0.01 | 4 | 8323 |
| R | 2 | Undifferentiated carcinoma of cervix uteri | 0.03 | 202 | 8020-8022 |
In terms of clinical practice, diagnosis of cervical adenocarcinomas is extremely important because of its poorer prognosis and lower sensitivity to radiotherapy and chemotherapy than squamous cell carcinoma, even if incidence is lower (10-30%) (8). In recent years, the incidence of cervical adenocarcinoma has been increasing among younger women, even if, over the past years cervical cancer was decreased in population (9). Following a population-based study conducted in United States, cervical adenocarcinoma represents currently 24% of all cervical cancers diagnosed each year (10) and also this subtype of cervical cancer experienced a noticed growth during the past two decades in United States (11).

It is well known that screening based on exfoliative cytology introduced in the 1950s by Papanicolau, followed by colposcopy in appropriate patients, is an effective method for identifying squamous intraepithelial lesions (12, 13). Unfortunately, the Pap-smear screening is less efficient, or even of no benefit in cervical adenocarcinomas (14, 15). That is why there is a contrast between marked decrease of the incidence of cervical squamous cell carcinoma in the last decades thanks to the efficiency of screening methods and the increasing rate of cervical adenocarcinomas.

**Risk factors**

There are discussions in literature regarding etiology-risk factors for cervical adenocarcinoma. We summarize above the most studied (16):
- human papillomavirus type 16 and 18;
- prolonged use of oral contraceptives;
- increasing parity;
- younger age at first full term pregnancy.

Epidemiologic studies about the relation between human papillomavirus (HPV) and cervical adenocarcinoma have shown strong associations, suggesting that the relation is causal, as is the case between HPV and squamous cell carcinomas of the cervix (17).

In a multicenter study of International Agency for Research on Cancer, Multicenter Cervical Cancer Study Group, Xavier C et al. demonstrates the existence of a consistent, strong, and robust increased association between high-risk HPV types infection and risk of adenocarcinoma. HPV types 16 and 18, estimated odds ratios for adenocarcinoma linked to six other HPV types, demonstrating very strong associations (OR > 100) for HPV 59 and 33, and strong associations (OR > 18) for HPV 35, 45, 51, and 58 (18).

Some cofactors have been associated with the risk of squamous cell carcinomas: smoking, endogenous and exogenous hormonal factors such as parity, oral contraceptive use, obesity, co-infection with other sexually transmitted agents such as herpes simplex virus 2 (HSV-2) and Chlamydia trachomatis. Nowadays, the impact of these cofactors on the risk of adenocarcinomas is still unclear, future studies remain to demonstrate their implications in development of cervical adenocarcinoma.

Several evidences indicate that cofactors that contribute to the progression of HPV infected cervical cells to adenocarcinoma are distinct from those that contribute to the progression to squamous cell carcinoma. For example, smoking and high parity have been associated with increased risks of squamous cell carcinoma, but they have no or an inverse association with adenocarcinoma (18, 19), obesity seems to be a risk factor for adenocarcinoma but not for squamous cell carcinoma (20).

Xavier C et al. (18), in their multicenter study demonstrated that hormonal factors, both endogenous (parity) and exogenous (use of hormonal contraceptives) are cofactors in the pathogenesis of cervical adenocarcinoma. More than that, relative risk for cervical adenocarcinoma correlated with the use of hormonal contraception is substantially higher than that previously reported in the literature systematic review. The evidence involving parity as a cofactor for cervical adenocarcinoma was weaker and less consistent than is observed for squamous cell carcinoma.

The results of a meta-analysis show consistent qualitative differences between the risks for squamous cell and adenocarcinomas of the cervix in relation to cigarette smoking. Smoking appears to be a risk factor for squamous cell carcinoma, with an increased risk of around 1.5 for current smokers, but not for adenocarcinoma. The other risk factors investigated did not differ qualitatively between squamous cell and adenocarcinomas; both types of cervical cancer were strongly related to the number of sexual partners and to duration of oral contraceptive use, and both were related to early age at first intercourse and to parity (21).

**Histology**

According to the WHO (2003), histological classification of tumors of the uterine cervix, epithelial tumors were grouped into five broad categories (22):
- squamous tumors and precursors;
- glandular tumors and precursors;
- other epithelial tumors;
- neuroendocrine tumors;
- undifferentiated carcinoma.

Pathologically, the two most common subtypes of cervical adenocarcinoma are the mucinous endocervical type and the endometrioid type (23).

**Diagnosis**

Although cervical adenocarcinomas and adenosquamous carcinomas account for only 10–20% of all cervical cancers, they are responsible for up to 80% of all cervical cancer malpractice suits because of the low sensitivity of cytology and colposcopy for this type of disease (26).
DNA testing for human papillomavirus (HPV) has been shown to detect more preinvasive cervical lesions than standard cytology screening. HPV screening can detect progressive lesions earlier, but also brings a risk of increased detection of non-progressive lesions (24).

Typically,  α -7 genotypes, which include HPV-18 and -45, are more commonly associated with cervical adenocarcinoma than squamous cell carcinoma. The difficulty in detecting ADC through screening, as well as changing sexual habits and increased HPV transmission may account for its increase (25).

Detection of cervical adenocarcinoma has some special features compared with squamous cell carcinoma. Glandular precancerous lesions are less known and only adenocarcinoma in situ is diagnosed by consensus among pathologists; adenocarcinoma in situ develops in the squamo-columnar junction by reserve cells but it is hard to be located by colposcopy in the endocervical canal or in the deep glandular recess. Sampling of endocervical cells requires brushes rather than an Ayre spatula.

Cytological diagnosis of glandular cells abnormalities is based on the Bethesda System 2001 terminology, which redefined endocervical cells abnormalities and also introduced the entity of adenocarcinoma in situ. This entity is characterized by specific morphological features, such as the radial arrangement of nuclei in the periphery, like “at the end of the feathers of a bird’s wing” (feathering of cells), images of nuclei palissading or rosette without tumoral diathesis. Glandular cells abnormalities are rare and represent less than 0.1% of all smears and less than 5% of abnormal smears (27).

By improving the collection and the interpretation of abnormal cells, cytological screening should allow the diagnosis of in situ adenocarcinoma and detection of invasive adenocarcinoma at a very early stage. This will lead to a decrease in mortality from adenocarcinoma (27).

According to Katki HA et al., women aged 30 years and older in routine clinical practice who are negative both HPV and cytology, 3-year screening intervals were safe because a single negative test for HPV is sufficient to reassure against cervical cancer over 5 years. including HPV testing with cytology also resulted in earlier identification of women at high risk of cervical cancer, especially adenocarcinoma. Thus, testing for HPV without adjunctive cytology might be sufficiently sensitive for primary screening for cervical cancer (28).

In the future, insight into the biological behavior and distinct molecular carcinogenetic processes of the cervical adenocarcinoma and cervical squamous adenocarcinoma subtypes may contribute to the development of more tumor-specific treatment strategies.

**Clinical Staging**

The main staging classifications approved in cervical cancer are:

- FIGO staging - developed by the International Federation of Gynecology and Obstetrics, which refers to the tumor size and extension, excluding extension to lymph nodes (27);
- MD Anderson staging system assessing tumor volume, as well as FIGO(27);
- UIICC TNM staging (International Union against Cancer) – offers a complete overview of extension considering for staging tumor, lymph nodes invasion and distant metastasis (29);
- Staging system proposed by the „American Joint Committee on Cancer” - is a pathological classification system (29);

Obvious, the main goal of this staging was to improve the future management of cervical cancer patients.

FIGO staging is universally accepted for carcinoma of the cervix, introduced in 1929, was amended several times since then.

FIGO staging must be done before any treatment and once established, this does not change. When there is any doubt about the status, it must be classified in the lowest stage.

FIGO staging is based on clinical examination (examination under anesthesia (EUA) is desirable, but not required), colposcopy, endocervical curettage, biopsy, hysteroscopy, cystoscopy, proctoscopy, intravenous urography and radiological examination of the lungs and skeleton. Rectum and bladder invasion must be confirmed by biopsy. Bullous edema or malignant cells in cytology bladder washing fluid are not sufficient to diagnose bladder invasion. Laboratory examinations as lymphangiography, laparoscopy, CT and MRI are important for treatment planning, but because they are not always possible to be performed and their results are variable, they are not accepted for FIGO staging.

Numerous studies have compared the accuracy of imagistic methods MRI / CT versus Clinical Staging. MRI is considered the most accurate method of staging. The accuracy rate of these modalities for parametrial status was 90% for MRI, 55% for CT and 82.5% for EUA (Examination under Anesthesia). MRI is superior to CT and EUA in assessment of the parametrium (30). MRI can accurately identify stromal invasion (std. IB), parametrial invasion (IIB), vagina or pelvic wall invasion (std. II and III), invasion of bladder or rectum (std. IV). Whenever available, MRI should be routinely used in conjunction with clinical staging to determine appropriate therapy in patients with cervical carcinoma.

As well, MRI allows differential diagnosis between tumor recurrence and fibrosis if the diagnosis is made in less than 12 months after treatment (31).

**Prognostic factors**

Although survival rates are correlated with clinical stage, disease prognosis is still influenced by a number of several prognostic factors not included in staging.
Tumor diameter is closely correlated with prognosis. The disease-specific survival and pelvic disease control were strongly correlated with tumor diameter, FIGO stage, histological subtype, and lymph node invasion (31).

Liu WX et al (32), analyzed 144 patients between 1995 and 2004, showing poor prognosis in non exophytic tumor, tumor diameter>4cm, advanced clinical stage, mucinous adenocarcinoma and clear cell carcinoma, or poorly differentiated tumor. Five year survival rates were 80.1%, 59.7%, 6.3% and 0.0%, respectively in patients with stage I, II, III and IV cervical adenocarcinoma, and 5 year overall survival was 59.0%.

They also found that the prognosis was related to lymph node metastasis and deep myometrial invasion and besides clinical stage, myometrial invasion and lymph node metastasis; tumor shape was also an independent prognostic related factor.

Survival rates vary with the number of positive lymph nodes, so metastases in lymph nodes is another important predictor factor. Kasuya G. et al, based on multivariate analysis of 141 patients with stage IB-IIIA cervical cancer treated with postoperative radiotherapy from 1985 to 2004 revealed that positive lymph node status (p=0.001) and histological type (p=0.015) were independent prognostic factors for overall survival. The group with three or more involved lymph nodes was significantly associated with extra-pelvic recurrence when compared with the groups with no positive lymph node (p=0.006) and up to two lymph nodes (p=0.024) (33).

In their study, Leveque et al, investigated retrospectively 45 cases of adenocarcinoma, with a follow up of 96 months. They concluded that clinical stage (FIGO) and pelvic node invasion were the most important parameters influencing the overall survival. Histological grade and pelvic node status were significant predictive factors for metastasis (40%, average period of 29 months) (34).

Histology also seems to be predictive in terms of survival and progression (33).

In a study of 1767 patients with FIGO IB, undergoing initial radiotherapy, published by Eifel et al report a strong correlation between the histology and survival. The risk of death is higher for patients with adenocarcinoma, as well as the the risk of distant metastasis. The same study also demonstrated that even if the local response to initial radiotherapy is similar for both histological types, probability of distant metastasis is higher for those with adenocarcinoma.

In the study of the Obstetrics and Gynecology Department, Central Hospital of Helsinki, conducted on 520 patients with cervical carcinoma, demonstrated no significant difference in survival rates in patients with adenocarcinoma and squamous cell carcinoma (35).

There are also other factors cited to have a prognostic role in the disease, such as hemoglobin (Hb) level. Barkati et al., from Montreal University, Canada, conducted a study on 263 patients assuming that low hemoglobin level, either before or during radiotherapy (RT), is a surrogate for a more infiltrative and therefore aggressive disease, with uterine corpus invasion and nodal metastases. They considered patients with pretreatment hemoglobin level of less than 120 g/L were more likely to have positive nodal disease (47%) compared with patients with a high pretreatment Hb level (32%; P = 0.034). The 3-year disease-free survival and overall survival (OS) were significantly lower in the positive nodal disease group compared with the remaining patients (40.1% vs. 76.1%, P<0.001, and 59.7% vs. 83.1%, P<0.001, respectively). Patients with low Hb nadir were more likely to have a positive nodal disease (P<0.001), and low Hb nadir during RT was a significant indicator of a higher recurrence rate (P=0.002) and lower OS (P<0.001). The combination of corpus invasion and nodal metastases is associated with lower Hb level and poor prognosis (36).

Elevated CA125 value can be considered as a significant predictor for survival. In their study, Bender et al, aim to determine the prognostic significance of a pretreatment serum CA 125 value in patients who were diagnosed with adenocarcinoma of the cervix. Pretreatment clinical variable that included CA125 value, age, stage, grade, and tumor diameter were evaluated in a Cox proportional hazards model and an elevated CA125 value was the most significant predictor of survival. (p=0.001) (37).

Some oncogenes are also cited in some articles, HER2/neu oncogene over-expression in cervical adenocarcinoma is rare, but when it appears, is associated with aggressive biological behavior. There was a pilot study of 24 cervical cancer patients, who explored the possible significance of HER-2/neu oncogene amplification in cervical cancer. The HER-2/neu FISH test was used to measure gene amplification, with a chromosome 17 centromeric, as an internal control. Out of 24 cases studied, 23 were informative. Of the 23 informative cases, 2 (8.7%) were found to be amplified. The rest (21 out of 23 or 91.3%) were non-amplified. Both amplified cases were invasive adenocarcinoma. This study demonstrated that detection of oncogene amplification in cervical cancer is very sensitive to predict invasive adenocarcinoma. (38).

Other biological factors that have been investigated are peritoneal cytology, platelet count, tumor vasculature and HPV subtypes but results were not statistically significant.

**Treatment**

Treatment protocols used for squamous cell carcinoma (SCC) and adenocarcinoma (AC) are similar and therapy is based on clinical staging according to FIGO (39).

In terms of treatment, it must be separated into 3 major categories. First category is the precancerous lesions, diagnosis of glandular lesions, observation of glandular atypia, endocervical dysplasia, most often used as adenocarcinoma in situ. The idea of loop excision has been widely disputed, MA Quinn in his review (40), quotes it as...
an inferior method compared to the cold knife conization. As well, this patients need to be followed up even if the cone margins were negative.

Radical hysterectomy with pelvic lymphadenectomy is recommended for micro invasive adenocarcinoma (stage IA). For selected cases, young women who want to conserve their fertility, cone biopsy can be performed, with tight follow up.

Treatment of invasive adenocarcinoma, is extensively discussed due to the low sensitivity to radiotherapy and chemotherapy, radical surgery is considered more effective in early stage adenocarcinoma (IB, IIA). Radiotherapy would be the second choice treatment for patients who cannot undergo surgery.

Radiotherapy or concurrent chemoradiotherapy represent the elective treatment for stage IIIB, III and IVA disease. In a review of 229 patients treated between 1991 and 2006, Rittiluechai K et al, concluded that adjuvant hysterectomy after radiotherapy in adenocarcinoma of the cervix, stage IIIB and IIB did not improve long term survival (41). Overall 2, 5 and 10 year survival for patients with adenocarcinoma of the cervix was 78.9%, 70.1% and 67.0 %. 5 year survival rates were 94.6% in std. I, 76.1% in std. II, 49.2% in std. III and 0% for std. IV. Patients with locally advanced adenocarcinoma of the cervix treated with radiation alone had a five year survival comparable with patients treated with chemoradiotherapy (62.4% vs. 64%) (41).

Baalbergen, in his review about primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix, concluded that results were favorable for surgery in patients with adenocarcinoma compared with radiotherapy (42). Although, primary chemoradiation remains a second best alternative for patients who are not suitable for surgery. Chemoradiation is first choice in patients with (MRI or PET-CT-suspected) positive lymph nodes and locally advanced disease.

This topic is still open and insufficiently explored, further studies are required to complete it in terms of early diagnosis and treatment. Unfortunately cervical adenocarcinoma face the same problems of all rare cancers and more precisely late diagnosis, limited treatment, few studies due to insufficient number of patients and the low interest shown by pharmaceutical companies.

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