METHODS OF DIAGNOSIS IN CERVICAL NEOPLASIA

MARIANA BRATU [1]*, EDUARD CRAUCIUC [1], OVIDIU TOMA [2], DRAGOS CRAUCIUC [1], DOINA IANCU [1], FLORENTINA PRICOP [1]

Keywords: cervical cancer, cytology, colposcopy, biopsy

Abstract. The early screening of a precancerous lesion that can develop spontaneously into a cancerous lesion that is first non-invasive and then invasive. **Materials and methods**. The study group was made of 1485 patients who were hospitalized between 2001 and 2009 in the Section of Obstetrics and Gynecology of „Sf. Apostol Andrei" Emergency Hospital in Galaţi. The patients filled in a questionnaire on a sheet of paper in a freely consented way and they were diagnosed with cervical cancer by a cytologic and colposcopic examination, biopsy and other complementary examinations. **Results and discussions**. It is obvious that, even if cervical carcinoma benefits now from a remarkable methodology of detecting the early forms and even the precursor lesions, in our country this lesion has an important frequency and even represents a public health issue with important social-economic implications; in most cases it affects people in full physical and procreative activity; it implies a laborious therapy, long time hospitalization and high costs. The risk of getting infected with HPV(human papilloma virus) is at least 50% for the sexually active people for the rest of their lives. Although most infections eliminate with the help of our own immunity, the people who are infected are not aware of HPV presence and they can spread the virus. When our own immune system cannot eliminate the infection, the persistence of the viral oncogenic strains from the cervical mucosa can lead to the appearance of precancerous lesions. The cytological examination is a simple and fast method that is also cheap and reliable being considered the most effective technique for preventing and detecting the precancerous conditions of the cervix, which, treated correctly, can offer a primary prevention of cervical cancer. The diagnostic certainty was accomplished exclusively by histopathology of the material obtained during biopsy. **Conclusions.** We consider that the patients with cervical cancer, no matter what their condition stage is when they come to see the doctor must never be abandoned because in many cases they have a satisfactory evolution after following a complex and well led treatment.

INTRODUCTION

The early detection of cancer consists of the discovery of an asymptomatic cancerous lesion in a person who is considered to be in good health. The asymptomatic cervical cancer is generally small in dimensions and the right treatment can cure it in high percentages - 80-90% of the cases (the patients survive without signs of the illness and get to be over 72.5 years old) (10).

It is also very important to discover precancerous lesions that represent the secondary prevention of cancer if diagnosed and treated.

Screening is a medical examination that is practiced on asymptomatic people with the purpose of establishing the suspicion if the disease exists there or not (14).

MATERIAL AND METHODS

The study group was made of 1485 patients who were hospitalized between 2001 and 2009 in the Department of Obstetrics and Gynecology of „Sf. Apostol Andrei" Emergency Hospital in Galaţi.

We used the following examinations for establishing the diagnosis of cervical cancer: cytologic smear (5, 7, 13, 20); colposcopic examination (15, 21); biopsy (9); complementary examination (11, 12).

RESULTS AND DISCUSSIONS

When talking about cervical cancer we know there are no symptoms that are characteristic to a certain form or stage, so there can be some forms with no symptoms or forms that are dominated by a certain symptom or having an association of signs and symptoms that are more or less important (10, 14). In about 29.0% of the patients the cervical cancer is detected following a routine medical check up.

The haemorrhage at sexual intercourse appeared in 305 patients (20.5%) or during the local cleaning (289 cases – 19.5%); this is the most important symptom that suggests a cervical neoplasia (especially in menopause) and it has a double role:

- it triggers alarm for the woman in question;
- it is supposed to draw the doctors' attention and to lead the case towards specialized examinations.

According to the cases we studied, we can positively predict that the patients who bleed during the sexual intercourse are over 40 years old in a percentage of 61.3% (p=0.0004). Statistically speaking, bleeding during the sexual intercourse for the women over 40 means that the risk of cervical neoplasia is 1.35 times higher for them than in the case of women under 40 (RR=1.35; IC95%: 1.14÷1.59).

The positive predictive value that the patients bleeding during sexual intercourse come from the urban area is of 72.8%, which is a significant difference, statistically speaking (p=0.027). These patients who come from the urban area have a relative risk of developing cervical neoplasia 1.23 times higher if they bleed during sexual intercourse (RR=1.23; IC95%: 1.02÷1.28).

After examining the women in our study group we could find no significant differences between the married patients and the single ones in terms of bleeding during sexual intercourse (p=0.113).

Table 1. The structure of the group depending on bleeding on age groups, environment and marital status

Epidemiologic characteristic	haemorrhage				Statistic significance
	during sexual intercourse		during local cleaning		
	n	%	n	%	
Age group					
≤ 40 years old	118	7.9	155	10.4	χ^2=12.75; GL=1; **p=0.0004**
> 40 years old	187	12.6	134	9.0	
Environment					
Urban	222	14.9	185	12.5	χ^2=4.90; GL=1; **p=0.027**
Rural	83	5.6	104	7.0	
Marital status					
Married	178	12.0	149	10.0	χ^2=2.21; GL=1; p=0.113
Single	127	8.6	140	9.4	

The early symptom appeared was the bleeding, especially during sexual intercourse and more rarely between menses.

For the present cases haemorrhage (with different characters and having a variable intensity) was dominant as unique symptom or associated with other signs and symptoms: *leucorrhoea; diffuse pain in the abdomen, loss of appetite; loss of weight; pallor etc.*

In the case history the patients had the following conditions:
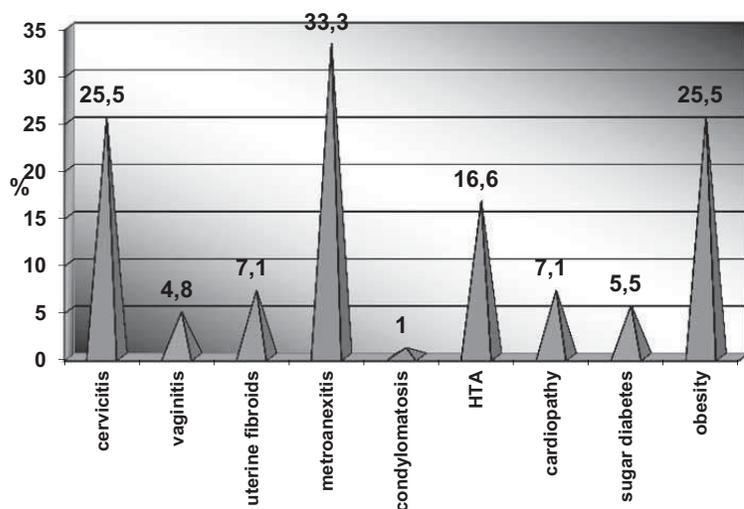
Fig. 1. The share of the cases depending on the pathological antecedents

We can notice an increased frequency of *genital inflammatory diseases.* The most frequent etiological agents involved are *Trichomonas*, *E.coli*, staphylococcus, *Chlamidia*.

All this data suggests that in the county of Galaţi the frequency of genital inflammatory diseases is very high and it exposes the population in this area to an increased risk of cervical cancer.

Obesity, of all associated diseases, has the highest share (25.5%).

HBP *(high blood pressure)* has a pretty high share, too (16.6%), and we have met it both in women with cervical neoplasia who were about to be treated, but also in women who had gone through surgical procedure and radiotherapy.

All the other diseases met have their role, as they lead to a decrease in the general resistance of the body and to a change in the hormone status.

Diagnosis by cytologic smear

Cervical exfoliative cytology is the first examination in the series of examinations for cervical cancer and it is the most accessible one from the point of view of the simplicity of the method and the economical advantage, having unlimited addressability for the feminine population. A cytological-diagnostic smear that is rhythmically made to all the feminine population at risk and not only, decreases considerably the incidence of cervical neoplasia and mortality by this disease, being in fact the principle at the base of cytological-screening. The statement is based on the studies made in countries where the introducing of screening determined a decrease of the incidence of cervical cancer to half (USA, Norway, Sweden).

In order to accomplish the active surveillance of the entire feminine population at risk you need to collaborate with public health organizers, general practitioners and especially with gynecologists, because automatic sampling of a cytological smear from every sick woman does not satisfy the principles of a rhythmic surveillance (10, 16, 17).

This is intended in the near future for our country, too.

Considering the cases we studied, the cytological examination was performed to all patients, except the ones sent by other medical centres for a direct biopsy examination, when they were sampled Pap smear.

Colposcopic diagnosis

The colposcopic examination was performed on 168 patients (11.3%) and confirmed the diagnosis in 99.4% of the studied cases. From the statistic point of view we did not find any significant differences in the distribution of the patients who had a colposcopic examination on age groups (p=0.888).

The positive predictive value that the patients with colposcopic examination would come from the urban area is 94%, which is a significant difference from the statistic point of view (p<0.001). The colposcopic examination reveals the fact that the patients coming from the urban area have a relative risk of having cervical neoplasia which is five times higher when compared to the ones coming from the rural area (RR=5.02; IC95%: 2.68÷9.40).

We could not find any significant differences for the group studies between the married patients and the single ones regarding their distribution depending on the performing of the colposcopic examination (p=0.358).

Table2. The structure of the group in accordance with the colposcopic examination on age groups, environment and marital status

Epidemiologic characteristic	Colposcopic Examination				Statistic significance
	performed		Not performed		
	n	%	n	%	
Age group					
≤ 40 years old	66	4.4	510	34.3	χ^2=0.02; GL=1; p=0.888
> 40 years old	102	6.9	807	54.3	
Environment					
Urban	158	10.6	969	65.3	χ^2=32.82; GL=1; **p<0.001**
Rural	10	0.7	348	23.4	
Marital status					
Married	120	8.1	890	59.9	χ^2=0.85; GL=1; p=0.358
Single	48	3.2	427	28.8	

Diagnosis by biopsy

The positive predictive value that the age of the patients with biopsy would be over 40 was of 88.2%, which is a significant difference, statistically speaking, when compared to the one for the patients under 40 (p<0.001). Biopsy shows that the patients over 40 years old have a relative risk of having cervical neoplasm 4.75 times higher than the ones under 40 (RR=4.75; IC95%: 3.82÷5.92).

The positive predictive value that the patients with biopsy would come from the urban area is 65.8%, which is a significant difference from the statistic point of view (p<0.001). The biopsy shows that the patients who come from the urban area have a relative risk 1.63 times higher of getting cervical neoplasia when compared to the ones coming from the rural area (RR=1.63; IC95%: 1.46÷1.83).

When we observed the study group we noticed significant differences for the distribution of married and single women depending on their performing of the biopsy or not (p<0.001), with

a positive predictive value of 90.6%, so the relative risk of getting cervical neoplasia is 4.54 times higher in married patients when compared to the single ones (RR=4.54; IC95%: 3.56÷5.80).

Table 3. The structure of the group depending on biopsy on age groups, environment and marital status

Epidemiologic characteristic	Biopsy				Statistic significance
	performed		Not performed		
	n	%	n	%	
Age group					
≤ 40 years old	74	5.0	502	33.8	χ^2=333.64; GL=1; **p<0.001**
> 40years old	555	37.4	354	23.8	
Environment					
Urban	414	27.9	713	48.0	χ^2=59.57; GL=1; **p<0.001**
Rural	215	14.5	143	9.6	
Marital status					
Married	570	38.4	440	29.6	χ^2=254.54; GL=1; **p<0.001**
Single	59	4.0	416	28.0	

Histopathology examination

The histological examination was performed on 614 patients (41.3%).

The histological examination of the excision part showed the following anatomic-pathological forms:

Table 4. The distribution of cases depending on the microscopic shape of the tumour

Histological type	No cases	Percentage
Unkeratinized epidermoid carcinoma with big cells	412	27.7
Unkeratinized carcinoma with small cells	2	0.1
Undifferentiated carcinoma	3	0.2
Adenocarcinoma with clear cells	55	3.7
Fibroma	6	0.4
Dysplasia	43	2.9
Hyperplasia	73	4.9
Mixed Tumours	10	0.8
Previously stated	871	58.7

The 417 carcinomas were divided like this:
- 241 cases of epidermoid carcinoma (16.2%)
- 6 patients with endometrium carcinoma (0.4%)

- 89 patients with pavimentous carcinoma (6.0%)
- 57 patients with squamous carcinoma (3.8%)
- 12 patients with spinocellular carcinoma (0.8%)
- 1 case of papilloma carcinoma (0.07%).

Staging cervical neoplasia

Staging appeared because of the need to systematize the data of the objective examination of a given case, which is situated in a certain stage of the disease evolution, with the purpose of getting an optimum therapeutic instruction and also for comparing the results of the different types of treatment or the results of the different centres of oncologic therapy.

The staging of cervical cancer reflects the degree of extension of the tumour. There have been a few trials in the last years, which were statistically founded, that intended to represent elements of prognostic appreciation, depending on the dimensions of the lesion – when it is strictly limited to the cervix- or by the direction and degree of neighbouring extension in the cases where the tumour goes beyond the limits of the cervix.

Staging cervical cancer serves to attain the following objectives:
1. Establishing the plan of treatment.
2. Indications on the prognosis.
3. Assessment of the treatment result
4. Scientific and research purpose.
5. Exchange of information between the treatment centres.

When staging you must consider two major elements: staging must be done before starting the treatment; in case of hesitation between two stages you will always choose the less advanced stage in order not to increase the number of healings in advanced stages without reason.

When dealing with the distribution of neoplasic lesions depending on the anatomo-clinical classification, we noticed a worrying thing: we could not find any case in stage 0 and we found only three cases in stage Ia.

This is due on the one hand to the lack of an appropriate health education (the woman does not come to the doctor for the annual check up, but only when there are some symptoms and when they are annoying), but also to the lack of an efficient sanitation in Romania, where the women at risk in special can have periodic and systemized check ups in order to identify the disease in its early stages.

Based on the cases we studied, we remark the following aspects (fig. 2):
- 21.4% of the cases were identified in stage Ia; - 19.3% of the patients in stage Ib, with obvious clinical lesions of the cervix or a pre-clinic lesion;
- 38.6% of the patients were in stage II and in 26.9% of them there was an obvious invasion of the parameters;
- 6.9% were in stage III of the disease and in 4.1% of them the lesion was extended to the pelvic wall, hydro-nephrosis or non functional kidney;
- 17.2% of the cases were in stage IV and the carcinoma was extended beyond the pelvic wall or clinically invaded the bladder mucosa and/or that of the rectum, all of the cases having a tumour invasion towards the adjacent organs.

Staging has a relative character, as there is a percentage of errors in the clinical assessment of the extension of the cancer process (14, 18).

Sometimes it is very difficult to stage a case correctly. We are referring to the case of infiltration of parameters which can't be always appreciated exactly (18).
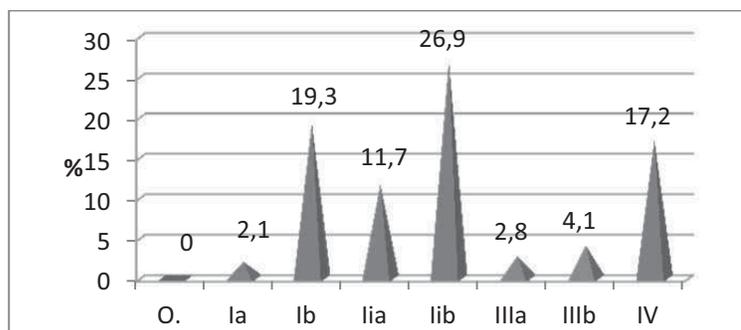
Fig. 2.The distribution of cases on lesional stages

The fact that a parameter is infiltrated does not necessarily mean a certain neoplasic invasion; it is difficult to establish precisely just how much of it is neoplasic infiltration and how much inflammatory, whether pre-existent or happening at the same time with an exofitic cervical neoplasic lesion, usually very infected.

In these cases palpation is sometimes extremely painful, so it is recommended to perform it under narcosis in order to avoid the reflex contraction of the abdominal muscles.

There is no doubt that present staging is far from being perfect. In fact, the study of the disease evolution at a certain point is reflected by the degree in which the neoplasia extended, the way it is determined by using the means of investigation that are presently used for a diagnostic purpose, but also by a series of other factors that are not integrated in the above-mentioned stages, for example the histological type of the tumour, the relationship between the tumour and its host, the interval of time between the first sign perceived by the patient and the moment of the diagnosis etc.

The present stage of knowledge creates objective premises for selecting the cases of cervical lesions with an irreversible potential of evolving towards malignancy, from the ones with a benign evolution.

The infections with the oncogenic HPV types would need a more aggressive treatment, in order to block the progression towards cervical neoplasias with high malignancy (1, 2, 3, 4).

CONCLUSIONS

Cervical cancer is an important public health issue, as it is the second in Romania after breast cancer, in terms of incidence and mortality by malignant tumours in women. Its incidence is continuously increasing and the therapeutic results are not satisfactory, in spite of the progress made in the last few years in getting to know the natural evolution of the disease, in improving the diagnose methods and also in improving the treatment quality. It is a chronic disease with a severe evolution, especially when it is identified in its advanced stages.

The increasing incidence of the disease in the last years, especially in young people requires an increase in the level of health education of the population and in starting some efficient screening programmes that will be able to cover all the feminine population at risk.

The efficiency of the screening by cervical-vaginal cytology was proved in the countries where it was repetitive and extended, by reducing the mortality rate with up to 80%.

We consider that the patients suffering from cervical cancer, no matter what their stage is when they come to the doctor, should not be abandoned because they sometimes have a satisfactory evolution after a complex and well conducted treatment.

REFERENCES

1. Bachtiary B, Boutros PC, Pintilie M, et al. 2006. *Gene expression profiling in cervical cancer: an exploration of intratumor heterogeneity*. Clin Cancer Res. Department of Radiation Oncology, Clinical Study Coordination and Biostatistics, Division of Cancer Genomics and Proteomics, Princess Margaret Hospital, Toronto, Ontario, Canada, 12(19): 5632-5640.
2. Balbi C, Di Grazia F, Piscitelli V, Martini S, Cardone A, Balbi GC. 1996. *Retrospective study of cervical papillomavirus lesions: early herpes simplex virus proteins as markers of risk for progression*. Minerva Ginecologica, 48(5): 175-179.
3. Bjorge T, Engeland A, Luostarinen T, et al. 2002. *A prospective study implicates human papillomavirus infection as a risk factor for anal and perianal cancer.* Br J Cancer, 187: 61-64.
4. Bolger Bs, Dabbas M, Lopes A et al. 1997. *Prognostic value of preoperative squamous cell carcinoma antigen level in patients surgycally treated for cervical carcinoma;* Gynecol. Oncol, 65: 309
5. Crauciuc E., Doina Iancu, Pricop Florentina. 2000. *Cervical cancer and the importance of the cytologic investigation.* I National Oncology Congress, Chişinău, Collection of articles and theses, 58-61.
6. Crauciuc E, Pricop FL, Masheh O. 1998. *HPV implications in cervical cancer aetiology.* The -V-th Symposium of the military gynecologists.
7. Crauciuc E, Pricop Fl, Masheh O. 1999. *The value of the cytologic examinations in diagnosing cervical cancer.* The British Journal of Family Planning (ed. lb. rom.), 4(1): 3-5.
8. Cronje HS, Divall P, Bam RH, Cooreman BF, Niemand I. 1997. *Effects of dilute acetic acid on the cervical smear.* Acta Cytologica, 41(4):1091-1094.
9. Durst M, Gissmann L, Ikenberg H, Zur Hausen H. 1983. *A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions.* Proc Natl Acad Sci USA, 80: 3812-3815.
10. Gurbuz A, Karateke C, Kabaca G. 2005. *Atypical glandular cells: improvement in cytohistologic correlation by the 2001 Bethesda system,* Int J Gynecol Cancer, 15: 5-903.
11. Hendrickson Mr, Kempson RL. 1980. *Smooth muscle neoplasms. In: Surgical Pathology of the Uterus.* Philadelphia:Saunders, 472.
12. Horn LC, Richter CE, Hentschel B, Schutz A, Pilch H, Leo C, Hockel M. 2006. *Juxtatumoral desmoplastic stromal reaction is associated with high tumor cell dissociation in squamous cell carcinomas of the uterine cervix,* Ann Diagn Pathol. 10(5): 253-256.
13. Iancu Doina, Eduard Crauciuc, Ovidiu Toma, Dragos Crauciuc. 2010. *The cytological diagnosis of cervical cancer.* Scientific Annals of Alexandru Ioan Cuza University, The Department of Genetics and Molecular Biology, XI(1): 49-55.
14. Iancu Doina. 2009. *General aspects of cervical cancer,* Junimea Publishing House Iaşi; ISBN 978-973-37-1374-6.
15. Jones MH, D Jenkins, A Singer. 1996. *Regular audit of colposcopic biopsies from women with a mildly dyskaryotic or borderline cervical smear results in fewer cases of CINIII*, Cytopathology, 7: 1-17.
16. Katz IT, Wright AA. 2006. *Preventing cervical cancer in the developing* world, N Engl J Med, 354: 1110.
17. Moss Sue, Alastair Gray, Rosa Legood, Martin Vessey, Julietta Patnick, Henry Kitchener - *Liquid Based Cytology/Human Papillomavirus Cervical Pilot Studies Group - Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study,* BMJ, Jan 2006.
18. Munoz N, Bosch X, De Sanjose S, et al. 2003. *Epidemiological classification of human papillomavirus types associated with cervical cancer*. N Engl J Med; 348: 518-27
19. Naoki Takeda, Noriaki Sakuragi, Mahito Takeda, et al. 2002. *Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy,* Acta Obstetricia et Gynecologica Scandinavica, 81(12): 1144.
20. Norstrom A, Jansson I, Andersson H. 1997. *Carcinoma of the uterine cervix in pregnancy. A study of the incidence and treatment in the western region of Sweden 1973 to 1992*. Acta Obst Gyn Scandinavica. 1997, 76(6):583-589.
21. Prislin MD, Dinh T, Giglio M. *On-site colposcopy services in a family practice residency clinic: impact on physician test-ordering behavior, patient compliance, and practice revenue generation.* Journal of the American Board of Family Practice. 10(4): 259-264.

[1] **"Gr.T.Popa" University of Medicine and Pharmacy, Iasi, Romania**
[2] **"Alexandru Ioan Cuza" University, Iasi, Romania**
∗ **Bratu Mariana , adibr06@yahoo.com**