

Epidemiology Cervical Cancer in Dolj County during 1987-2007

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ABSTRACT In the situation of cervical cancer on second place like cause of death in the world, the authors propose a descriptive epidemiology study in a range considered significant for 21 years between 1987 and 2007, on a number of aspects of the incidence this disease in Dolj County, whose population distribution by sex and age group suitable conclusions with direct implications in screening, treatment and survival in patients with cervical cancer. As in the incidence is observed followed a net increase since 2002 with the introduction of Order 219/1980 declaring a nominal cancer patients. Such active involvement of the family doctor on one hand, and declared by updating the files ONC1 specialist on the other hand, it requires urgent. Also important in screening programs for cervical cancer in order to found early stages, it is high in percentage of patients diagnosed in stages with clear therapeutic potential, with direct implications on survival patients. A brawl involving a oncology medical practitioner is required urgently, increasing diagnostic accuracy, and taking biopic material by experienced specialists, with the possibility discovery histopathological factors with implications in the correctly therapy and prognosis of patients.

KEY WORDS *cervical cancer, incidence, stage, age, histopathological type, screening, prospects*

Introduction

Cervical cancer occupies the second place worldwide in malignancies in women (after breast cancer) annually register the 500,000 new cases and 270,000 deaths per year worldwide.

Cervical cancer sum 44% of all female genital malignancies, and represents the second cause of death by cancer in women worldwide.

To data provided by the Center for Health Statistics and Computing in Romania cervical cancer is the third cause of death by cancer in women, after lung cancer and breast cancer and the first cause of mortality in young women between 25-44 years, being 3 times more frequent than ovarian cancer.

In the situation of cervical cancer on third place like cause of death in Romania, we found useful a study on descriptive epidemiology of a range of 21 years (1987-2007) on the incidence and mortality of this disease in Dolj Country, which suitable to conclusions with direct implications in the detection, treatment and survival of patients default.

The incidence of cervical cancer in recent years in Romania has been growing slowly but continue: 19,04‰ in 1980, 21,29 ‰ in 1990, 24,74 ‰ in 1996, 29,55‰ in 1999, in 2005 were detected 3202 new cases of cervical

cancer, of the total 37,335 malignancies registered at the end of which lies in second place Romania in Europe. In terms of mortality by this disease, Romania occupies the first place in Europe, the annual register of deaths between 1500-1600. Gross mortality rate has increased over time, from 12.3‰ in 1980 to 15.55‰ in 2000.

Increased mortality rate demonstrates the large number of cases detected in advanced stages, which justify efforts for population education and implementation of screening programs extremely useful in detecting disease in early stages, potentially curable. Such active involvement of the family doctor on one hand, and declared by updating the files ONC1 specialist on the other hand, it requires urgent.

Etiology of cervical cancer is multifactor being involved sexual risk factors, viral, hormones, food and smoking. Based on epidemiological evidence, clinical and laboratory revealed the existence of a causal link between human papillomavirus (HPV) and cervical cancer. There are 15 types of HPV which can cause cervical cancer, the most common worldwide are types 16, 18, 31, 45. Types 16 and 18 are responsible for approximately 71.5% of cervical cancers in Europe. The persistent HPV virus in the cells causing cellular

damage that untreated have developed slowly (10-20 years, but possibly even more quickly) to carcinoma in situ and then invasive carcinoma.

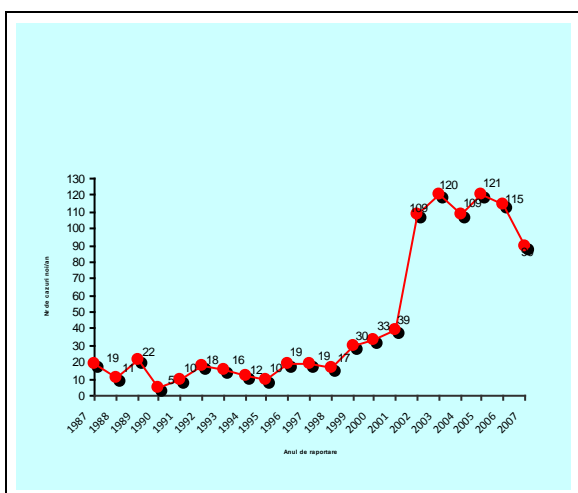
Materials and methods

We conducted a retrospective study over a period of 21 years between 1987 and 2007, to highlight the particularities of this disease within the county of Dolj, in terms of incidence, age of patients, disease stage at presentation, histological type and death by disease. Files were followed by evidence ONC2 cancer patients take the evidence at the oncology office Dolj county, and according to their files ONC1, their completion as well as accuracy of the information contained in them medical, clinical observation sheets, protocols operators register pathological anatomy service to confirm malignant evaluation and determination of histological type.

Results

During the period analyzed by the Dolj county have registered 944 new cases. We noted a growing trend in the incidence until 2005, with a sharp increase since 2002, but fortunately finding the trend in the incidence in 2006 and 2007.

We analyzed the contribution of each year in the total number of new cases registered during the studied period. Between 1987-2001 the number of reported new cases is below 5% of all cases registered between 1987 and 2007. Instead the new cases registered during 2002-2005, was at least 2 times higher compared to previous- over 10% of all new cases registered during the study (chart 1).



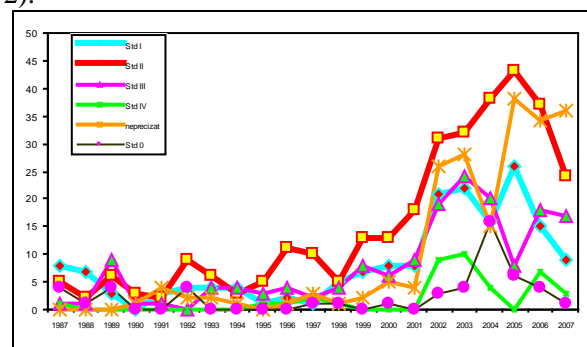
Graph 1 The incidence of cervical cancer during 1987-2007

This reflects to what extent the failure of Order 219/1980 declaring a nominal cancer patients has

found the correct influence on the results and analysis of cervical cancer in Dolj County.

I had in mind in the analysis that we made it, the main prognostic factors in cervical cancer, which give a picture of the evolution of the disease and provide necessary information for deciding treatment: stage of disease (tumor volume), age, histological type.

Stage of disease was analyzed retrospectively on the clinical data (gynecological examination) and was available to most patients analyzed. For the 21.29% of all patients included in the study stage disease could not be inferred, either through lack of medical documents, lack anatomopathological the staging postoperative, or death of patients before it can be analyzed (graph 2).



Graph 2 Distribution by stage of disease/year during 1987-2007

Most patients were diagnosed with stage I or II disease.

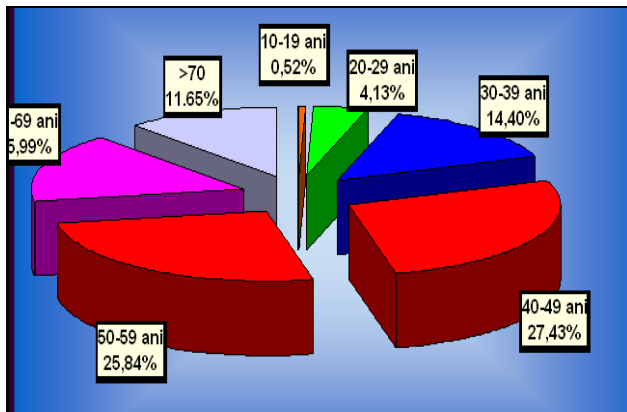
Stage II disease has predominated for most of the period studied: 1990, 1992-1993, 1995-2007, and the stage I was more frequently met in 1987, 1988, 1991, 1994.

Just for one year of the period studied (1989) predominated patients with advanced cancer of the cervix (stage III). Stage IV with unfavorable prognosis had a small weight for the entire period studied. We consider these results as positive, given that the stages of localized cervical cancer were favorable prognostic likely curability.

But large percentage of therapeutic failure is explained by the large number of patients who have received an inaccurate staging at diagnosis, which involved incorrect treatment and consequently a reduced survival of patients. This negligence of diagnosis, noted especially in the last period study (2002-2007), when a notice of 2-3 times more patients diagnosed in stage II. The explanation would be to create overcrowding in the field offices, with superficial examination " in a hurry " to patients and consequently an incorrect clinical staging and the lack of correlation clinicoimaging (determining actual disease

tomography extension). But an explanation in a more favorable premise, would be present in patients in a timely manner to health, the actions required by the screening, which allowed the diagnosis of early stages of how long the disease.

In our study, most cases reported each year were ranked in the age groups 40-49 years and 50-59 years (the only exception in 1988 when almost half of the registered patients were aged between 60 and 69 years)



Graph 3 Distribution by age during 1987-2007

Analysis of a whole period 1987-2007, we found that 5 patients (0.52% of cases) were aged between 10-20 years, 39 patients (4.13%) aged between 20-29 years, 136 patients (14.40%) aged between 30-39 years, 259 patients (27.43%) aged between 40-49 years, 244 patients (25.84%) aged between 50-59 years, 151 patients (15.99%) aged between 60-69 years and 110 patients (11.65%) were aged over 70-ani

As a result most patients with cervical cancer registered in the territory of our county for a long period of study have been shown to have diagnostic aged over 40-59 years.

This can be explained by the important role of virus papilloma in disease occurrence. It was demonstrated that the ADN oncogeny types of HPV is present in 99.7% of tissue samples taken from malignant tumors of the cervix in worldwide. In fact, the infection with HPV oncogeny is "necessary cause" of cervical cancer. Persistent HPV virus in the cells causing cellular damage that untreated have developed slowly (10-20 years, but possibly even more quickly) to carcinoma in situ and then invasive carcinoma, invasive forms explaining the diagnosis to advanced age.

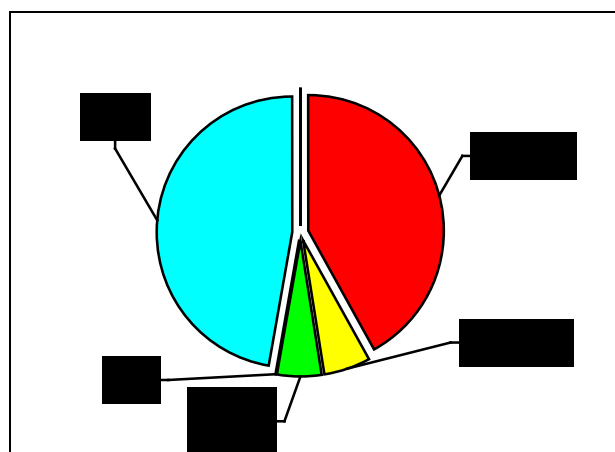
Cervical cancer takes birth at the junction squamo-cylindrical. The first cell lesions are those of dysplasia or carcinoma in situ intraepithelial: slight dysphasia (CIN1) or moderate (CIN2), which may evolve or regress (60% cases) to

severe dysphasia (CIN3) or carcinoma in situ (CIN 4/5). The carcinogenic process may evolve later to microinvazive or invasive carcinoma.

According to the International Society of Gynecology Oncology, microinvazion is defined as an invasion stoma from point of origin up to a depth of less than 3 mm and up to 7 mm surface extension; invasive carcinoma lesions include more extensive than 7 mm in area and with a depth greater than 3 mm. For invasive cervical carcinoma, histologic type knowledge has prognostic value. Studies suggest an unfavorable prognosis for adenosquamous carcinoma and non-small cell carcinoma, which is the histopathological more aggressive type for evolution and responsivity treatment. The study noted the predominant squamous carcinoma-397 patients (42.05%), followed by a much lower frequency of adenocarcinoma - 51 patients (5.40%) and carcinoma in situ-50 patients (5.29 %).

Overall squamous carcinoma of the cervix was the most frequently reported in the period 1987-2003; in contrast between 2004-2007 predominated as frequent cases with unknow histology does, but keeping the report squamous carcinoma and adenocarcinoma, net in favor of squamous carcinoma . In the period 1987-2007 was registered one case of sarcoma and haven't met cases of malignant melanoma.

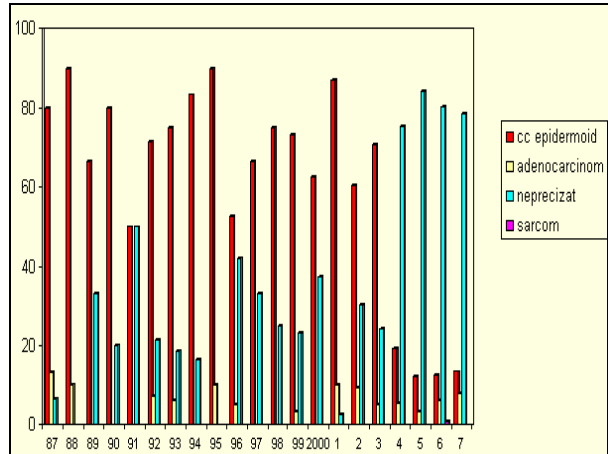
These results should be analyzed in the context in which approximately half of the total number of patients registered (predominant periodoada1987-2003), histology could not be inferred from the data that we held (445 patients-representing 47.13% of total patients) [graph 4.5].



Graph 4 Distribution by histopathologic type during 1987-2007

These results reflect the need to make certain how long guided biopsies and complete (4 cadran the cervix, as well as from the vagina) by specialists with experience in taking bioptic

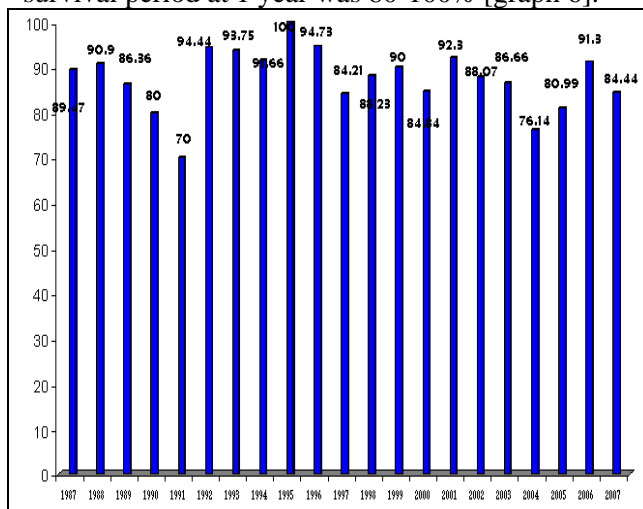
matherial sufficient for histopathological examination.



Graph 5 Distribution by histopathological type/year during 1987-2007

In this study we watched two objectives: epidemiological analysis of cervical cancer in a range considered significant for a number of aspects of the incidence, histological type analysis, distribution by sex, age group, and survival analysis of patients with cervical cancer.

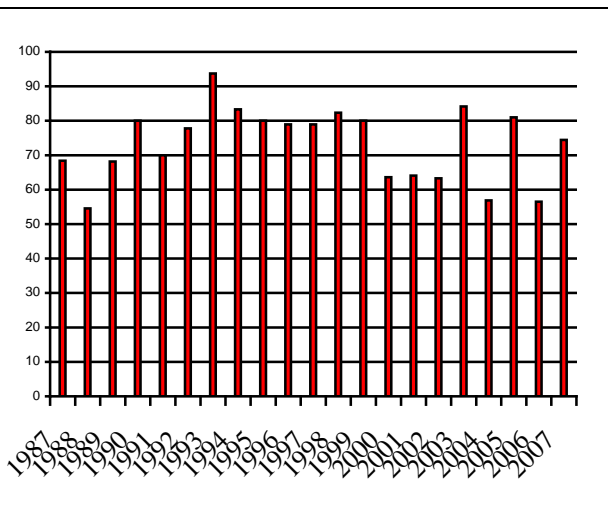
We analyzed for each year reported, the number of patients who died of the total number of patients registered as new cases in the data we have been useful in calculating survival at 1 year. Recorded data were encouraging, consistent with those cited in the literature, throughout the study survival period at 1 year was 80-100% [graph 6].



Graph 6 Survival at 1 year

We also tried to report for each year to track the number of patients who died after a period of 5 years of the total number of patients registered per year to obtain data on survival at 5 years with cervical cancer. This was possible for the period 1987-2002, for which we had a tracking period of at least 5 years in the time of analysis. For the period 2003-2007, for

which the pursuit was less than 5 years, we can only provide data on the number of deaths reported when the analysis: patients in 2003 -19, 2004 - 47 patients in the 2005-23 patients, 2006-50 patients and in 2007 - 23 patients [graph 7].



Graph 7 Survival at 5 years /each year reported

Date encouraging and consistent with the literature were recorded in the period after 1990, with survival at 5 years by 70-90% due to the means of perfecting therapeutic and more specifically as a standard therapeutic radiochemotherapy concomitant with radiosensibilizatory agents (derivatives of platinum).

Discution

Dolj county population, that number of inhabitants, divided evenly between urban and rural as well as the age groups are susceptible to a descriptive epidemiological study, and the number of new cases of cancer reported annually, can imagine for an analytical study.

Approximately constant values and reduced to the years 1987-2001 (under 5% of all cases registered between 1987 and 2007) and sharp increase since 2002-2007 (from 10% of all new cases registered during the study) reflects a non-faithful new cases of cervical cancer, regulated with the introduction of Order 219/1980 declaring a nominal confirm histopathological cancer patients.

This sharp increase since 2002, reflect the actual values on the urgent measures necessary to control patients with need to make a regular gynecological examination, clinical and cytological exfoliate. Maximum incidence of malignancies in this two age groups 40-49 years and 50-59 years, involves too a close attention to this age group.

The methods of screening cancer are to demonstrate if early detection of cancer cells (cancer diagnosis before the appearance of symptoms) reduced the chances of death of a person.

Papanicolau test is most commonly used screening for cervical cancer. Papanicolau test consists to scratch or brush cells from the cervix and vagina. A piece of cotton, a brush or a small wooden switch is used to easily scrape cells from the cervix or vagina. The cells are then observed under a microscope to see if they are modified.

A new method of sampling and observation of cells was discovered recently, the cells were placed in a liquid before being stretched on the blade. Is not yet known if the method works better than the standard method. Studies show that deaths by cervical cancer can be reduced by Papanicolau screening test performed at least once in 2 or 3 years, starting from 3 years after onset of sexual life. Women who have a total hysterectomy do not need the cytology Babes Papanicolau. Women over age 60 years and negative test result Papanicolau rarely have abnormal tests in the future.

Examination is recommended for cytology Papanicolau asymptomatic women over 20 years and under 20 years sexually active are 2 consecutive annual tests, and at least one test every 3 years until the age of 65 years.

Classical terminology Papanicolau were added in the time of dysplasia and CIN, the last approach is represented by the Bethesda classification (TBS), which grouped precursor lesions noninvasive in the categories of low malignancy grade (LSIL) and high malignancy grade (HSIL), each with its own algorithm for treatment and follow [table 9].

If cytology is abnormal, but no visible lesions on the gynecological examination is performed colposcopia method to analyze very carefully exocol surface and the initial portion cervical canal.

If tests are positive, can do a ADN test to find out if the disease etiology is infection with human papilloma virus.

Ten per cent of teenage suffer from a sexually transmitted disease that can generate cancer. More and more young women under the age of 16 years are infected with human papilloma virus (HPV), which develop cervical cancer. Agency for Health Protection has warned that Britain risks that young to be infected with HPV increases substantially after age 14 years. Up to age 18, about 20% of girls contact this virus, while the percentage increases to 40% for girls up to 24 years. Results

and have led many representatives of organizations that advocate for attention to health, the need to implement a vaccination program for girls and boys before they become sexually active, and also the programs on prevention education for young people.

Thus announced the granting of marketing authorization for Cervarix, the vaccine against cervical cancer, in all 27 EU Member States.

Cervarix [Silgard, tetravalent recombinant vaccine produced by Merck Sharp & Dohme (MSD)] approved by the European Commission, to be administered to children between 9-15 months and young women between 16-25 years before contact with HPV infection (before the beginning of life sexual or after onset of sexual life, but condom-protected). Formulated with the innovative adjuvant system AS04 is indicated to prevent cervical lesions precancerous high grade (cervical cancer intraepithelial CIN 2 and 3 and cervical cancer caused by Human Papillomavirus, risk types with 16 and 18 (70% of cancers). There is a family of over 100 viruses with low-risk HPV 6, 11 which causes veracity on hands and feet, and vegetation veneering region genital infection by both men and women and are called genital HPV [figure 1, 2].

HPV is a virus circular ADN, low and high risk types with 16, 18 were involved in oncogenesis head and neck cancers.

Continuous expression viral oncogenes E6 and E7 is responsible for maintaining the proliferate status of HPV in the cells of squamous carcinoma of the cervix.

Regression E6 and E7 genes cause reactivation of Rb and p53 suppression and apoptosis of cells.

The virus can be transmitted from one person to another during sexual act, and get inside cervix cells. If successful to "hide" the immune system of the body, then the place to be removed will remain in the cervix cells. This is called persistent infection. Gradually, the cells are damaged and eventually (usually after 10-20 years) can turn into cancer.

However, sometimes the disease can progress more quickly.

It is widely recognized that infection with high risk HPV is not sufficient for the pathogenesis of cervical cancer, some conditions are needed complementary. Reasons for certain infections that are persistent can be dependent on: inter-individual variation in ability to give an adequate immune answer of clonally persistence and viral heterogeneity of oncogenes interfering with viral protein supressor tumors, epigenetic events.

Up to 80% of sexually active women will become infected with human papillomavirus sometime during life, the risk of persistent infection increases with age. HPV infection occurs frequently in young women, sexually active, the incidence of cervical cancer is higher in women but more than 35 years, suggesting slow progression of viral infection to cancer.

GlaxoSmithKline continue the information campaign for women to prevent cervical cancer, released early 2008 year. The campaign began in January 2008 (January 20-26) by marking the first time in Romania to the European Week for Prevention of cervical cancer and was supported by two women known and appreciated by the Romanian public, Mihaela Radulescu and Sanda Nicola, who and provided further support for the continuation of educational actions. The campaign aims to give women more information about cervical cancer and the link with the strains oncogenes of human papillomavirus (HPV), and the methods of prevention.

During the European Week for the Prevention of cervical cancer (ECCA) has launched an online petition seeking uniform implementation of programs to prevent cervical cancer in Europe. The objective is to obtain one million signatures of people who cause the authorities to develop more strategic programs to prevent cervical cancer and to give greater importance to prevention of this disease.

Regarding prognosis patients included in the present study, evaluating survival at 1 year but at 5 years, revealed high rates of survival (survival 1 year 80-100% at 5 years and 70-90%, and the result is in line with the results cited in the literature, which is clearly a direct correlation between disease stage and risk failure pelvin and distance, so the survival of patients default [table 9].

In support of a diagnosis but more correctly, and also a fair treatment, there are modern methods of imaging, which require high performance equipment such as TC, MRI, PET (tomography with positron emission) or CAT (computerized axial tomography).

These advanced techniques are useful especially in assessing the actual extension of the disease, invasion paracervical, rectal, bladders and the wall pelvin view of metastasis lymph nodes very small (PET) and, MRI is considered the most reliable method staging and treatment implementation plan; in comparative clinical staging accuracy with MRI was 83%, compared with TC 63% and 70% clinical staging.

MRI can accurately identify the invasion of stroma (st. IB), the parameters extension (IIB), invasion vagina or pelvin wall (st. II and III), the invasion of bladder or rectal (st IV). MRI also allows differential diagnosis between recurrent tumor and fibrosis radical, if the diagnosis is made more than 12 months of treatment.

Type of histology has also predictive value both in terms of survival and evolution of patients.

Even if some authors have observed that there is significant differences in this respect between adenocarcinoma and squamous carcinoma, other investigators have reached other conclusions, showing that patients with adenocarcinoma were treated surgically rates very high relapse rate and survival very low.

In a study of 1767 patients with FIGO IB stage, Eifel and Coleb reported a strong correlation between the histology and survival. Even if local control pelvin is similar for the two histological types, the risk of death is higher for patients with adenocarcinoma, the ability to develop metastases. Regarding the correlation between histological grade and clinical evolution, it is evident for adenocarcinoma and still disputed for squamous carcinoma.

But there are a number of other factors involved in assessing histoprostic survival, but not the subject of our study, the lack of complete histopathological bulletins, on the one hand, and on the other hand due to the imbalance created between operable patients (most of those with stage II), and the non operable.

Thus there is a direct correlation between disease stage and risk of ganglion invasion (at stage IB, the pelvin nodes invasion incidence is approximately 15%, stage IIB 30%, stage IIIB 50%).

This ganglion invasion is a factor of unfavorable prognosis for survival. Studies have demonstrated a survival at 5 years by about 90% for patients operated with this ganglion invasion compared with 50-60% for patients without invasion in ganglions pelvini or 20-45% for patients with metastases in pelvin ganglions and lomboartical ganglions.

Morito and Ivona show that there is a correlation between survival and size of nodes invaded, and other authors between survival and number of nodes invaded. Decrease rates of survival at 5 years was associated with increasing the number pelvin positive nodes: 62% for a loop, 36% for two ganglions, 20% for three or four ganglions and without survival for more than five ganglions.

Limfovascular space invasion (LVSI) for operable patients (total hysterectomy with bilateral anexectomy) is associated with unfavorable prognosis, as deep stoma invasion (greater than or equal to 10 mm or greater than 70%) and extension parameters.

All these histoprognostic factors were evaluated in several studies. T. Roman and colleagues reported a correlation between the amount of invasion LVSI (percentage histopathologic sections containing LVSI) and the incidence of ganglion invasion.

C. Kamiz show in an article that a strong inflammatory stoma response may have strong predictive value for good survival.

Invasion at the uterine body is associated with increased rates metastasizes distance for patients treated surgically or radiotherapy.

In 1986 R. Bush, and several other studies have shown the existence of a direct causal relationship between hemoglobin levels and prognosis of patients with advanced disease. Anemia should play a causal role in recurrent pelvina by a small randomized study conducted by Princess Margaret Hospital (comparative analysis of treatment outcomes in patients with a hemoglobin value of at least 10g% and at least 12g%, a value maintained by transfusion).

Other studies have not confirmed these results and some investigators have linked low levels of intratumoral oxygen with a high rate of metastasis ganglion are and consequently a reduced survival.

Concentration of serum antigen specific squamous carcinoma seems to be correlated with stage, tumor size and presence lymphatic metastasis, but most investigators not accept the predictive value of this test.

Age seems to influence the prognosis of the disease. Some investigators showed a decrease in survival for younger patients 35-40 years of which have a high frequency of weak or non-differentiated tumors. Results of studies on the prognostic value of age patients were contradictory (some studies in patients aged 35-40 years under the non- differentiated tumors forms had lower survival, while other studies have had higher survival compared with older patients). A only done Rutledge analysis showed that there is a correlation between age and patients survival.

Correlation disease prognosis tumors with polyploidy or aneuploid distribution has been the subject of numerous studies. Some authors have discovery a significant correlation between rate for recurrence and di or aneuploidia, while other studies find a less favorable prognosis for tumors with diploid or tetraploid DNA content in

comparison with those nondiploid or nontetraploid tumors, when these was correlated with age (under 51 years) and degree of differentiation of tumors (non-differentiated tumors), but these differences are not statistically significant. Strang and colleagues observed an increased frequency relapse for tumors in which the proportion of cells in S phase is greater than 20%.

Oncogen HER2/neu supraexpression in squamoas cancers of the lower genital tract is rare, but when there is associated with aggressive biological behavior.

Other biological factors that were investigated are peritoneal cytology, number of platelets, and tumor vascularisation subtype of HPV.

In two studies on patients without histological ganglion invasion determinates have reported increased rates of recurrence, when the polymerization reaction of the ADN chain in ganglions were mostly positive for ADN of HPV.

The expression STK15-tyrosine kinas (that interacts with centrozom during mitosis), has been associated with an increased risk of cancer of the gland mamare. La patients with cervical cancer were identified two genotypes STK15: F31I (T / A) and V57I (G / A). Homozigota AA F31I variant of SNP was associated with an increased risk of cervical cancer (OR 2.63, CI95% 1.20-5.76). For V57ISNP, no variant homozygote AA, no variant heterozigot GA, was not associated with increased risk of cervical cancer (OR 0.76, 95% CI 0.18-3.25 and OR 0.88, 95% CI 0.52-1.49).

In the analysis performed in the study being, correlated with the results cited in the literature, we can conclude that the prognosis of patients registered within the county of Dolj was favorable, with short-term survival and increased long.

The explanation consists in detecting the majority of patients in localized stages of disease, predominant squamous histopathological type with marked radio and chimiosensibility, favorable prognostic factors, and especially applicability and compliance with standard treatment protocols, is the simultaneous radiochemiotherapy.

Remain a problem, correct the record on histopathological confirmation, and performing clinical examinations with high accuracy, achievable goals, both in the involvement of the family doctor as well as a specialist gynecologist, oncologist and / or radiotherapist.

Future prospect, but growth remains accurate diagnosis and treatment forms pre-invasive, possible only through the continuation of a fierce

policy of allocating the funds necessary actions exhibition population screening (cytology examination Babes Papanicolau).

Conclusions

1. It requires urgent 219/1980 compliance order, declaring a nominal patients with neoplasm of the cervix.

2. Transfer responsibility to detect precursor lesions malignancy especially for patients at high risk to the generalist doctor and proper fitting equipment cabinets.

3. Control actions for detect cancer by doctors detect cancer in the county.

4. Detected, tracking and treatment of patients with lesions malignității precursors (cervical cancer intraepiteliala) decelate ago exfoliate cytology examination. Opinion only medical insurance can cause citizens to present periodic preventive controls with certain repercussions on found early.

5. Continued campaign to inform women on measures for protection against specific HPV infection.

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