Microinvasive carcinoma of the uterine cervix in University Hospital of Split

Babić, Anamaria

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Anamaria Babić

MICROINVASIVE CARCINOMA OF THE UTERINE CERVIX IN UNIVERSITY HOSPITAL OF SPLIT

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Prof. Deni Karelović, MD, PhD

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TABLE OF CONTENTS:

1. INTRODUCTION

1.1. Epidemiology and aetiology

1.1.1. Epidemiology of carcinoma of the uterine cervix in the world

Cervical cancer (CC) is the fourth most common cancer in females, and seventh overall. There was an estimated 528,000 new cases in 2012. Large majority (around 85%) of CC occurs in the less developed regions. Around 266,000 females died of CC in 2012, accounting for 7.5% of all female cancer deaths. About 85% of CC deaths occured in the less developed regions (1).

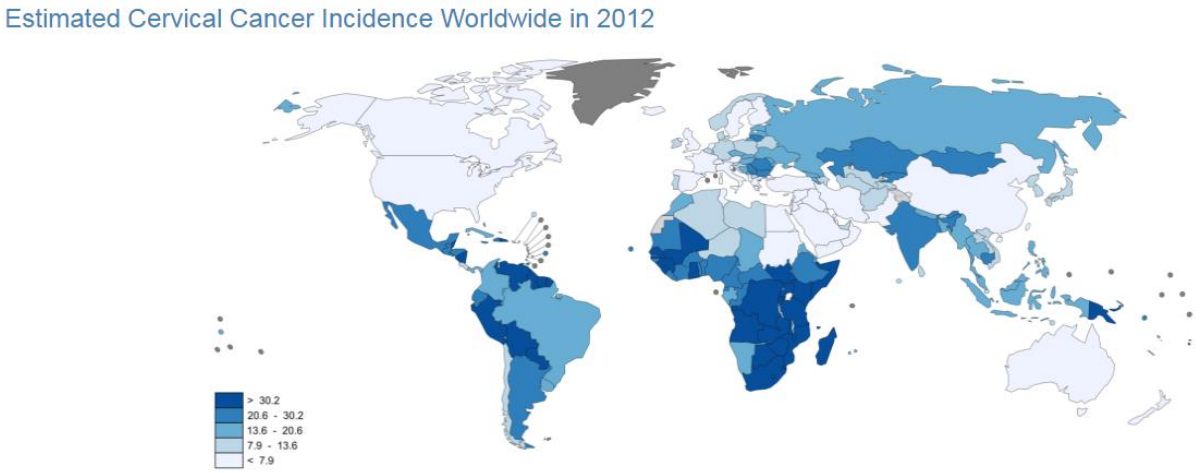

Figure 1. Estimated Cervical Cancer Incidence Worldwide in 2012 (1).

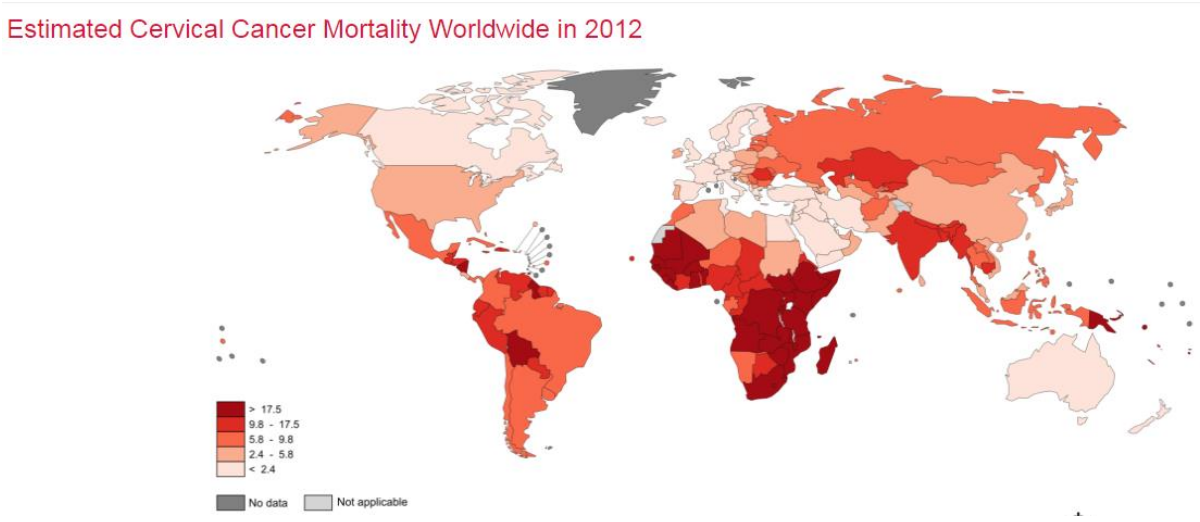

Figure 2. Estimated Cervical Cancer Mortality Worldwide in 2012 (1).

Carcinoma of the uterine cervix, unlike the majority of the other carcinomas, mostly affects young females (62% of diagnosed women are age 50 or less). Peak incidence is between 25 and 29 years of age (2).

1.1.2. Epidemiology of carcinoma of the uterine cervix in Croatia

According to the Croatian National Institute of Public Health data from 2016, the incidence of the CC in Croatia is 13.8/100,000. It is the tenth most common type of carcinoma in females in Croatia. Mortality of the CC in Croatia is 5.9/100,000. Highest incidence of in situ CC is between the age 30 and 34. Ratio of in situ – invasive CC in Croatia is 1:1 (3).

1.1.3. Risk factors

The foremost important risk factor regarding the CC is an infection with human papillomaviruses (HPV), especially HPV-16 and HPV-18 (4). HPV can be divided into high-risk, probable high-risk and low-risk types, regarding the development of the carcinoma. High-risk HPV types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82. Probable high-risk types are: 26, 53 and 66. Low-risk HPV types are: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81. The most comon HPV types in patients (figure 3.), in descending order of frequency, are types 16, 18, 45, 31, 33, 52, 58 and 35 (5).

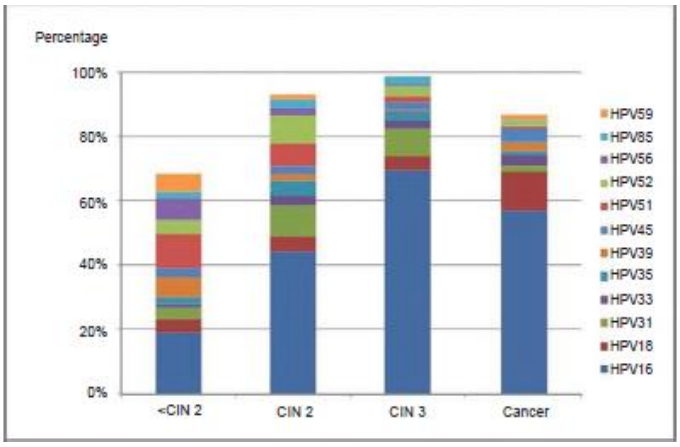

Figure 3. Attribution of carcinogenic HPV types to cervical disease categories (7).

Peak prevalence of infection with HPV is 20-40% in women aged 20 to 30 years, but in the majority of these women (80%), the infection is transient and resolves within 12 to 18 months. Women with persistent oncogenic HPV infection are at risk of developing high-grade precancer and ultimately CC (6). HPV type is the strongest factor affecting the risk of viral persistence. Women exposed to HPV-16 are consistenly documented to be at increased risk. According to Kaiser Permanente cohort follow-up run in the USA, 16-year risk of developing CIN 3+ in women of 30 years and younger was 14.6% for women with HPV-16 at the baseline, 7.0% for women with other oncogenic types, and 1.8% for women with no HPV infection. For women older than 30 years, the risks were 8.5% for HPV-16, 3.1% for other oncogenic types, and 0.7% for HPV negative women (7).

However, according to many authors, HPV alone is not sufficient to induce CC, and multifactorial etiology is likely. Even though the incidence of HPV infection in patients with CC is approaching 100%, HPV can not stil be found in each and every patient. Other important risk factors contributing to the development of the CC are: early onset of sexual activity, increased number of sex partners, smoking, oral contraceptive use, genetic background (the position of the original squamocolumnar junction – junction in fetal life between stratified squamous epithelium of the vagina and ectocervix and columnar epithelium of the endocervical canal – determines the extent of cervical squamous metaplasia and is an important early influencer of risk for further neoplastic behavior), immunosuppresion –

exogenous and endogenous, multiparity and age of first pregnancy, sexually transmitted diseases (8).

1.2. Anatomy of female genital tract

1.2.1. Internal female genital organs

The uterus is a pear-shaped, hollow organ situated in the pelvis, between the bladder anteriorly and the rectum posteriorly. It is covered posteriorly by serosa or peritoneum, which also covers the upper anterior side,while the lower anterior side is connected to the bladder via loose connective tissue. The uterus is suspended from the pelvic wall by various ligaments. The broad ligaments extend in a wing-like manner from both lateral portions of the uterus. At the upper portion, the broad ligaments give rise to the mesosalpinx to which the fallopian tubes are connected, and to the suspensory ligaments of the ovary where ovarian vessels pass through. At the lower portion broad ligaments give rise to the cardinal ligaments which fuse with connective tissue adjacent to the cervix. The round ligaments extend from the lateral portions of the uterus, through the broad ligament, to the upper portions of the labia majora. The uterosacral ligaments suspend the uterus in the height of the supravaginal portion of the cervix. The uterus can be divided in the two main portions: the broad triangular body, which makes up the upper two thirds of the uterus, and the narrow cylindrical cervix which makes up the lower one third. The wall of the uterus has three distinctive layers: endometrium containing abundance of blood vessels and glands, hormonally sensitive bulky myometrium composed of smooth muscle, and outermost layer perimetrium. Uterus plays the central role in female reproductive tract. It is the place of implantation of the blastocyst and further development of embryo and fetus (9,10).

Ovaries are paired almond shaped organs situated in the upper part of the pelvic cavity, on either side of the uterus. They are connected to the uterus via the ovarian ligaments, and to the posterior abdominal wall by suspensory ligaments of the ovary. The ovary is the place of maturation and release of sex cells as well as of formation and release of female sex hormones (9,10).

Fallopian tubes are cylindrical organs where fertilization takes place. They can be divided in four anatomical regions: the interstitial portion embedded in the uterine wall, the isthmus which opens into the ampulla, and infudibulum ending in fimbria. The tubes are lined with ciliated cells participating in peristalsis (9,10).

The vagina is a hollow organ connecting the cervix with the vulva. It is placed between the urethra and rectum. It hosts significant portion of the cervix anterosuperiorly. Inferior portion of the vagina is a part of perineum (9,10).

1.2.2. External female genital organs

The external genitalia is comprised of the labia majora, labia minora, mons pubis, clitoris, vulvar vestibule and urethral meatus, and glandular structures opening to the vaginal vestibule. Beneath these structures lay the fascial and muscular layers of the perineum. The muscles of the external genitalia consist of the deep and superficial transverse perineal muscles, the ischiocavernosus muscles that cover the crura of the clitoris, and the bulbocavernosus muscles lying on either side of vagina covering the vestibular bulbus (9,10).

1.3. Diagnosis

1.3.1. Screening

The primary goal of screening is to prevent CC by identifying asymptomatic women who are at high risk of having or developing a disease and to further asses them, treat them, and organize follow-up. It is known nowadays that CC arises from persistent infection with HPV and progression of a preinvasive lesion to invasive carcinoma. That is the reason why early detection, treatment and follow-up of precancerous lesions is of foremost importance. The higher incidence and death rates of CC described in low-income countries are likely to result from the lack of organized cervical screening, together with inadequate access to early treatment. On the other hand, screening with cervical cytology in many developed countries has resulted in significant decrease in incidence, as well as mortality, of CC (7).

Methods of screening are: cytology – conventional (Pap smear) and liquid-based (LBC), visual screening using 4% acetic acid or Lugol's iodine solution and HPV testing (11).

The International Agency for Research on Cancer (IARC) recommends starting screening at 25 years of age and many countries are starting to apply this recommendation. Population-based data have shown limited effectiveness of cytology in women younger than 25 years of age in preventing invasive cervical cancer before age 30 (11). According to nowadays guidelines issued by the American Cancer Society, American Society for Colposcopy and Cervical Pathology and American Society for Clinical Pathology, women younger than 21 years do not have to be screened, women from 21 to 29 years of age should be screened by performing cytological testing alone every three years, women from 30 to 65 years of age should be screened by performing cytological and HPV co-testing every 5 years (preffered) or cytologic testing alone every 3 years (acceptable) (12). In women older than 65 years, screening can be discontinued if there has been an adequate number of negative screening results (3 consecutive negative cytologic tests or 2 consecutive negative co-tests in past 10 years, with the most recent test performed in the past 5 years) and if there is no history of high-grade squamous intraepithelial lesion, adenocarcinoma in situ, or cancer (12).

1.3.2. Physical examination

Physical examination is of limited value when it comes to the diagnosis of early stage CC because of its asymptomatic nature, but nevertheless should always be performed. Besides examining the genital tract and pelvis, it should always include palpation of the liver and lymph nodes to exclude metastatic disease (13).

The first sing of the disease is vaginal discharge not related to menstrual cycle. Classical symptoms are painless bleeding, spotting and painful intercourse. As the disease progresses, symptoms become more common and more severe, as well as consistent with the metastatic spread of the disease (14).

1.3.3. Colposcopy

Women with positive / pathologic screening results should be directed to colposcopy. It should be kept in mind that if a carcinoma is entirely within the endocervical canal, the ectocervix may be colposcopically normal (13).

1.3.4. Biopsy

Any obvious tumor growth or ulceration, as well as any cervix that is unusually firm or expanded, should undergo office punch biopsy or loop excision for histologic confirmation (13).

1.3.5. Other

In order to be able to plan the treatment it is important to asses the extent of the disease. There are different imaging modalities that help us in doing so, one of the most commonly used ones being X-ray, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) (13).

1.4. Staging

Many different staging systems for CC exist. The FIGO (International Federation of Gynecology and Obstetrics) system is the most commonly used one (4). Other staging systems are AJCC (American Joint Commitee on Cancer) TNM staging system, SGO (Society of Gynecologic Oncology) staging system, and staging system brought by Japanese comitee.

1.4.1. FIGO staging system

FIGO staging system (table 1.) is the most commonly used staging system for CC. It is a clinical staging systemand permits following diagnostic studies in determining the stage: physical examination of the pelvis and assessment of lymphadenopathy, colposcopy, endocervical curretage, conization, hysteroscopy, cystoscopy, proctoscopy, intravenous pyelogram and plain radiographic imaging of the lungs and skeleton. Results from PET (Positron Emission Tomography), MRI (Magnetic Resonance Imaging) or CT (Computed Tomography) cannot be utilized to assign a FIGO stage (4).

The FIGO definition for stage IA changed six times between 1961 and 1985 before the FIGO 1995 criteria were suggested. The definition of stage IA did not change from 1995 to the most current revision in 2009.FIGO stage I is defined as carcinoma strictly confined to the cervix. Stage I is further subdivided in stages IA and IB. Stage IA is amicroinvasive carcinoma that can be diagnosed only by microscopy, with deepest invasion 5mm or less and largest extension not more than 7mm. All macroscopically visible lesions are allocated to stage IB. Stage IA is subdivided into 2 subtypes as well: stage IA1 defined as invasive carcinoma with stromal invasion of 3.0mm or less in depth and extension of 7.0mm or less, and stage IA2 (15).

FIGO stage is not determined by lymphovascular invasion (LVI), but LVI status should be included in pathology reports (16).

1.4.2. AJCC TNM staging system

AJCC TNM staging system (table 2.) is based on tumor size, involvement of the lymph nodes and presence of metastases. FIGO stage IA1 corresponds to TNM T1a1* – measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread (18).

1.4.3. SGO staging system

SGO staging system defines microinvasive CC as carcinoma of invasive depth 3 mm or less from the basement membrane of the point of origin with no lymphovascular invasion present (17).

1.4.4. Japanese comitee staging system

Japanese comitee defines microinvasive CC as stage 1A: depth of the invasion is 3 mm or less, without lymphovascular invasion (19).

Table 1. Revised FIGO classification of carcinoma of the uterine cervix, 2009 (17).

STAGE I	**The carcinoma is strictly confined to the cervix**
IA	Invasive carcinoma that can be diagnosed only by microscopy, with deepest invasion 5 mm or less and largest extension not > 7 mm
IA1*	**Measured stromal invasion of 3.0 mm or less in depth and extension of 7.0 mm or less ***
IA2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
STAGE II	**Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of vagina**
IIA	Without parametrial invasion
IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
IIB	With parametrial invasion
STAGE III	**The tumor extends to the pelvic wall and/or involves lower third of vagian and/or causes hydronephrosis or non-functioning kidney**
IIIA	Tumor involves lower third of vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
STAGE IV	**The carcinoma has extended beyond the true pelvis, or has involved (biopsy-proven) the mucosa of the bladder or rectum.**
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

Table 2. TNM classification for carcinoma of the uterine cervix (18).

T (primary tumor)	
TX	**Primary tumor can not be assessed.**
T0	**No evidence of primary tumor.**
Tis	**Carcinoma in situ.**
T1	**Cervical carcinoma confined to uterus**
T1a	Invasive carcinoma diagnosed only by microscopy. All microscopically visible lesions – even with superficial invasion – are T1b. Stromal invasion with a maximal depth of 5 mm, measured from the base of the epithelium, and a horizontal spread of 7 mm or less.
T1a1*	**Measured stroml invasion 3 mm or less in depth and 7 mm or less in horizontal spread.***
T1a2	Measured stromal invasion > 3 mm and not > 5 mm, with a horizontal spread 7 mm or less**.**
T1b	Clinically visible lesion confined to the cervix, or microscopic lesion greater than T1a2.
T1b1	Clinically visible lesion 4 cm or less in greatest diameter.
T1b2	Clinically visible lesion > 4 cm in greatest dimension.
T2	**Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina.**
T2a	Tumor without parametrial invasion.
T2b	Tumor with parametrial invasion.
T3	**Tumor extends to the pelvic wall and/or involves the lower third of vagina, and/or causes hydronephrosis or non-functional kidney.**
T3a	Tumor involves lower third of vagina; no extension to pelvic wall.
T3b	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney.
T4	**Tumor invades mucosa of the bladder or rectum and/or extends beyond true pelvis.**
N (regional lymph nodes)	
NX	**Regional lymph nodes can not be assessed.**
N0	**No regional lymph node metastasis.**
N1	**Regional lymph node metastasis.**
M (distant metastasis)	
MX	**Distant metastasis can not be assessed.**
M0	**No distant metastasis.**
M1	**Distant metastasis.**

1.5. Pathohistology

The most common primary CC is squamous cell carcinoma. It comprised more than 90% of cervical cancers a few decades ago, but nowadays, owing to the effective cytologic detection, the incidence is steadily decreasing. The incidence of cervical adenocarcinoma, on the other hand, is increasing significantly. Other neoplasms affecting the cervix are neuroendocrine, mesenchymal and metastatic tumors (20).

1.5.1. Squamous cell carcinoma of the uterine cervix

Squamous cell carcinoma is the most common primary malignancy of the uterine cervix. Most cervical squamous cell carcinomas originate from the metaplastic squamous epithelium located between the original and new squamocolumnar junctions, the transformation zone (20).

1.5.1.1. Cervial intraepithelial lesions

Cervical intraepithelial lesions, that affect millions of women yearly, have traditionally been classified using a three tiered system (originally mild/moderate/severedysplasia, subsequently CIN 1/2/3), corresponding to a stepwise progression from intraepithelial lesion of grading severity to invasive carcinoma. In 2012, a new consensus about the terminology was brought in order to standardize the diagnosis – LAST (Lower Anogenital Squamous Terminology) project. The result was the change to two-tiered nomenclature – low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). Histologic LSIL corresponds to CIN1, including both mild dysplasia and HPV cytopathic effect without dysplasia. Histologic HSIL corresponds to CIN2 and CIN3, and includes spectrum from moderate dysplasia to carcinoma in situ (21).

1.5.1.2. Squamous cell carcinoma

There are many different variants of squamous cell carcinoma of the uterine cervix.

The one that is of the great interest in last years is superficially invasive squamous cell carcinoma (SISCC), also known as microinvasive carcinoma. This type of CC is of emerging importance because its presence offers the ability to manage the patients with more conservative treatment while stil having a low risk of lymph node metastases and recurrence (21).

Invasive squamous cell carcinoma is characterized by infiltrating nests of neoplastic epithelium in the stroma. Many different types of squamous cell carcinoma are known, some of which being keratinized SCC, non-keratinizing SCC, veruccous SCC, papillary SCC and basaloid SCC (21).

1.5.2. Adenocarcinoma of the uterine cervix

Adenocarcinomas currently account for 15-20% of all invasive CC in developed countries (22). They typically occur within the endocervical canal (21).

Microinvasive adenocarcinoma of the uterine cervix is defined by Teshima and associates as less than 5 mm stromal invasion as measured from the mucosal surface (23). FIGO staging system is applicable for adenocarcinomas as well. In contrast, the SGO microinvasive carcinomas classification is not applicable to adenocarcinomas (17).

Invasive adenocarcinoma of the uterine cervix is present when individual cells or incomplete glands of malignant cells are identified coursing thorugh the stroma. Alternatively, adenocarcinoma can also be identified when malignant glands are found coursing through a desmoplastic stroma, indicating a host response. Many invasive adenocarcinomas do not exhibit either of these two features, and in this case diagnosis is based on a third, more subjective criterion, that is the identification of different abnormal patterns of malignant glands that do not conform to the lobular configuration of normal endocervical glands. The

fourth possible criterion is the presence of malignant glands beneath the deep margin of normal endocervical glands (17).

1.6. Treatment

Treatment of the CC is a complex and multidisciplinary field. The most important factor in choosing the treatment is the stage of CC. Other factors can and should affect the decision-making process as well, including the exact location of the cancer within the cervix, the type of cancer, age of the patient, overall health of the patient, and whether the fertility is to be maintained or not (24). Treatment decision should also be made according to current algorithms of the institution in which the treatment is undertaken. The decision is, in most cases, brought by a team of specialists including gynecologist, anesthesiologist, radiologist, pathologist, cytologist, and other if necessary (25).

For early stages of the disease, it is enough to perform loop electrosurgical excision of transformation zone (LEETZ) or conization, or simple hysterectomy (surgical removal of the cervix and uterus only) for women older than 45 years of age in whom there is no need for fertility preservation. In the case of the advanced disease, neoadjuvant radiotherapy followed by radical hysterectomy (surgical removal of the cervix, uterus, vaginal cuff, pelvic lymph nodes, obturator lymph nodes, paracervical tissue and parametrial tissue) should be done. In the final stages of the disease, palliative treatment with radiotherapy or chemotherapy is the treatment of choice (6,26).

1.6.1. Treatment of carcinoma of the uterine cervix FIGO IA1

Treatment of carcinoma of the uterine cervix FIGO IA1 depends on whether or not fertility is to be maintained and whether or not the cancer has grown into blood or lymph vessels (lymphovascular invasion) (24).

For women who want to preserve fertility, conization or LEETZ is the preferred procedure. If the margins are negative, woman can be watched closely without further

treatment. If the margins are positive, the carcinoma should be treated either by repeated conization or LEETZ or by simple hysterectomy. Simple hysterectomy is preferred if there is lymphovascular invasion (27). Proven complication of conization or LEETZ is a negative effect on pregnancy. Compared with women who have not received treatment, women who have recieved cold-knife conisation or LEETZ have significantly higher rates of preterm delivery and infants with low birth weight. Analysis by depth of incised tissue found that risks of preterm delivery increased further if the depth was more than 10 mm (6).

For women who do not want to preserve fertility, the treatment of choice is simple hysterectomy. If there is lymphovascular invasion, the patient might need a radical hysterectomy and pelvic lymphadenectomy(27).

1.7. Follow-up

Theguidlines from 2017 recommend following steps regarding the follow-up of patients treated for CC: follow-up of patients with FIGO stage I disease depends on whether the patients received fertility sparing or non-fertility sparing treatment (28). If the patient underwent fertility-sparing treatment, pelvic MRI with contrast should be considered 6 months after surgery and then yearly for 2-3 years, if metastasis is suspected whole body PET/CT should be considered, other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease (factors that should rise clinical concern are abnormal physical exam findings or new pelvic, abdominal or pulmonary symptoms). In the case when the patient underwent non-fertility sparing surgery imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease (28). For patients with FIGO stage IB2 or patients who required postoperative adjuvant radiation or chemoradiation due to high risk factors (high risk factors include positive nodes, positive parametria, positive margins or local cervical factors), whole body PET/CT may be performed at 3-6 months after completion of treatment (28). Regarding the follow-up of patients with FIGO stage II-IV, whole body PET/CT is advised within 3-6 months of completion of therapy. Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease (factors that should rise clinical concern may be abnormal physical exam findings such as palpable mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms) (28).

1.8. Prognosis

The prognosis of the carcinoma of the uterine cervix depends on the stage of the disease. The 5-year survival rate for stage I carcinoma of the uterine cervix is 80-93%. For stage II survival rate is 58-63%. For stage III survival rate is 32-35%. Stage IV has a survival rate about 15%. There is a significant decrease in the 5-year survival rate between stage I and stage IV, which emphasizes once again the importance of screening and early diagnosis and treatment of the carcinoma of the uterine cervix (Table 3.) (29).

Table 3. 5-year survival of the carcinoma of the uterine cervix patients by FIGO stage (29).

FIGO stage	**5-year survival rate**
Stage I	
IA	93%
IB	80%
Stage II	
IIA	63%
IIB	58%
Stage III	
IIIA	35%
IIIB	32%
Stage IV	
IVA	16%
IVB	15%

1.9. Prevention

The natural history of the CC offers a variety of opportunities for prevention of the disease. It is known that persistent infection with high-risk HPV types leads to the

development of the carcinoma. The possibilities of primary prevention are the prevention of acquiring the HPV infection by education of adolescents, vaccination and development of effective vaginal microbicide.Cervical screening and early therapy are also a form of prevention and may lead to significant decrease in both incidence and mortality (30).

In Croatia, it is advised for women to be examined by their gynecologist and to do the Pap smear every 1-3 years from the onset of sexual activity or from the age 18 on. After 3 or more negative Pap smear results, the time between the two consecutive testings can be increased, but it should not exceed 3 years. Women with higher risk for developing the disease should be screened more often (31).

Vaccination against HPV is recommended for girls and boys ages 11 or 12, although some organizations recommend starting vaccination as aearly as age 9 or 10. Girls and boys should recieve the vaccine before they have sexual contact because once someone is infected with the virus, the vaccine might not be as effective or might not work at all. Nevertheless the vaccination is stil advised because even if people have already been infected with one or more HPV types they can stil get protection from other HPV types in the vaccine. Currently available HPV vaccines are bivalent, quadrivalent and nine-valent. All of them protect against HPV types 16 and 18, quadrivalent vaccine also protects against HPV types 6 and 11, and nine-valent targets five additional cancer-causing types (32).

2. OBJECTIVES

The aim of this paper is to examine the incidence of microinvasive carcinoma of the uterine cervix FIGO stage IA1 treated at the University Hospital of Split from 1.1.2000. to 1.1.2017., to examine the age of the patient at the diagnosis, to examine the incidence of patohistological types, to examine the incidence of lymphovascular invasion, and to examine the treatment choice.

3. METHODS

By retrospective analysis of medical histories and discharge letters of all patients with the carcinoma of the uterine cervix FIGO stage IA1 from 1.1.2000. to 1.1.2017., the following will be examined:

- the age of the patient at the diagnosis
- patohistological diagnosis
- lymphovascular invasion (LVI)
- treatment choice.

The main data source for this paper are medical histories and discharge letters and the protocol of surgeries of patients with carcinoma of the uterine cervix FIGO stage IA1, assessed from the archives of the Department of Gyneacology and Obstetrics and Department of Oncology in University Hospital of Split.

Statistical analysis was performed using NCSS statistical software, version 12.0.8. Descriptive methods were used to analayse the data from this study. Lilliefors test was used to assess the normality of data distribution.

4. RESULTS

In total 67 women with the CC FIGO stage IA1 have been diagnosed and treated at the Department of gynaecology and obstetrics and Department of Oncology in University Hospital of Split in the time span of 17 years. The highest number of diagnosed CC was in year 2011 (n=8), followed by year 2009 (n=7), and the lowest number was diagnosed in year 2002 (n=1) (Figure 4).

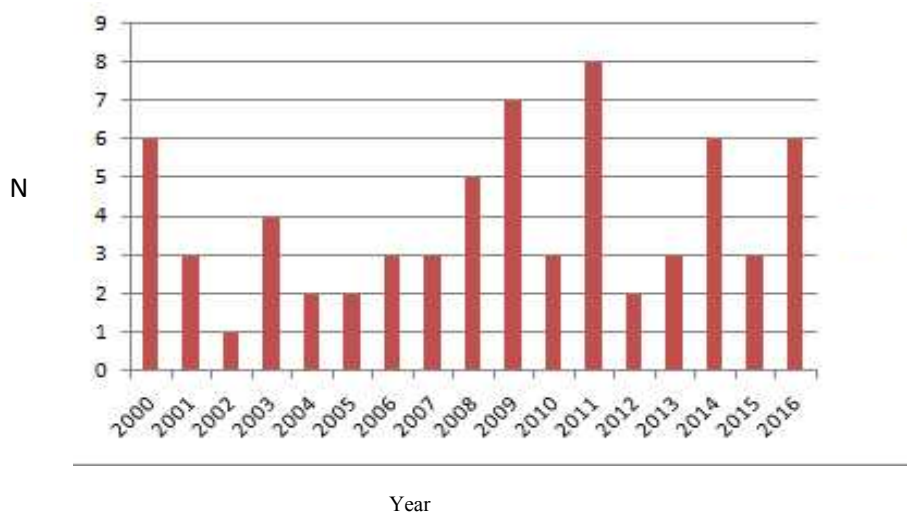

Figure 4. The number of patients with the carcinoma of the uterine cervix in years from 2000 to 2017

4.1. Age of patients

The youngest and the oldest age groups are 21-30 years of age and 71-80 years of age, respectively. The greatest incidence of CC was in age group 41-50 years of age (21 out of 67;31%), followed by age group 31-40 years of age (20 out of 67;30%), and the lowest incidence was in the age group 21-30 years of age (3 out of 67;5%) (Figure 5).

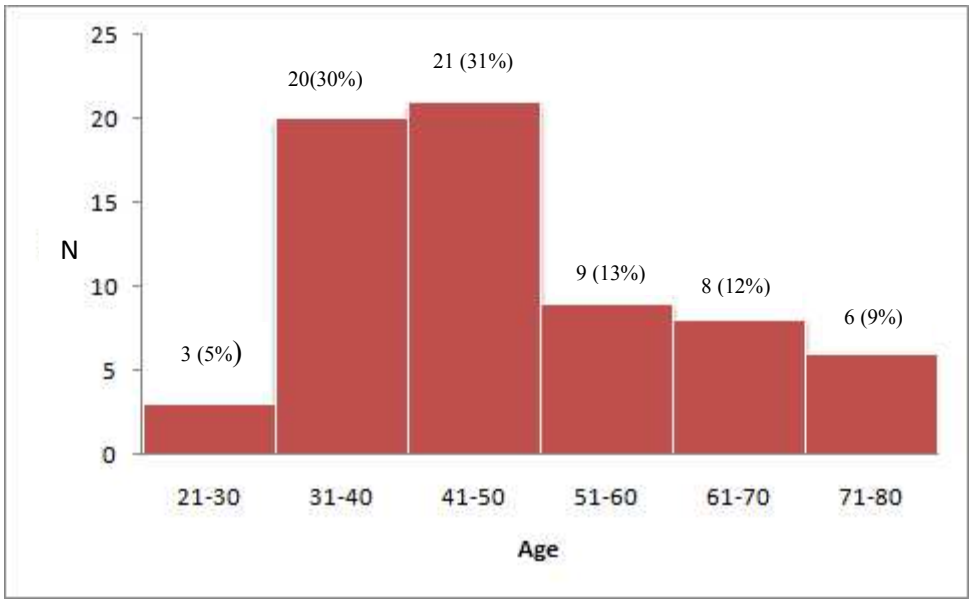

Figure 5. The incidence of the carcinoma of the uterine cervix in different age groups

The median age of the patients diagnosed with the carcinoma of the uterine cervix in the clinical hospital Split from 1.1.2000. to 1.1.2017. was 46 years (IQR 36-56).

4.2. Pathohistology

Squamous cell carcinoma was the most common type of the carcinoma of the uterine cervix in our patients (60 out of 67;90%). Adenocarcinoma was diagnosed in 6 patients (6 out of 67;9%). The third type of cancer diagnosed in our patients was adenosquamous carcinoma (1 in 67;1%). There were no other pathohistological types diagnosed in this period of time (Figure 7).

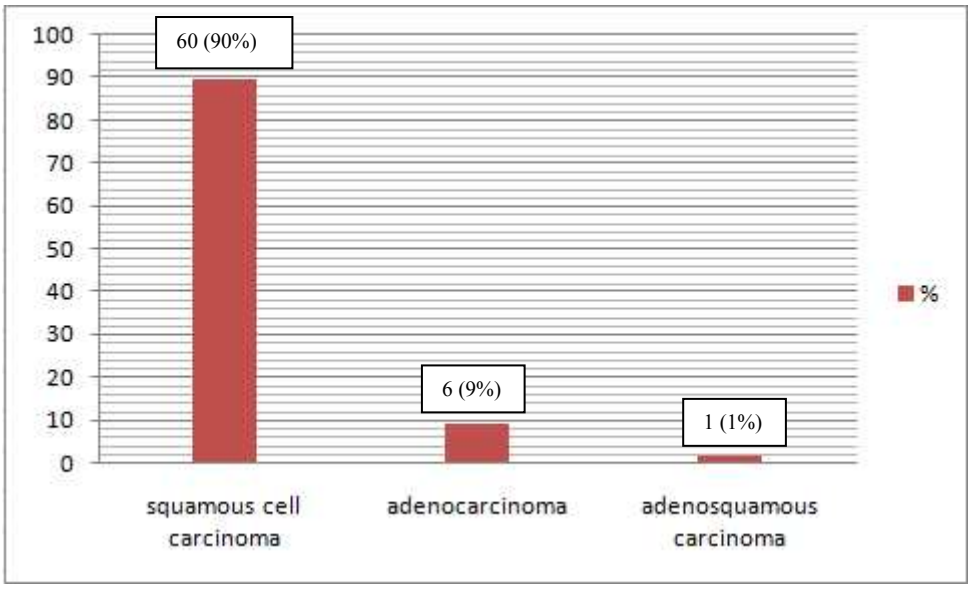

Figure 7. The incidence of pathohistological types of the carcinoma of the uterine cervix

4.3. Lymphovascular invasion

The majority of our patients were diagnosed with carcinoma which did not show signs of lymphovascular invasion (60 out of 67;90%). The minority of patients had cancer with evident lymphovascular invasion (7 out of 67;10%) (Figure 8.).

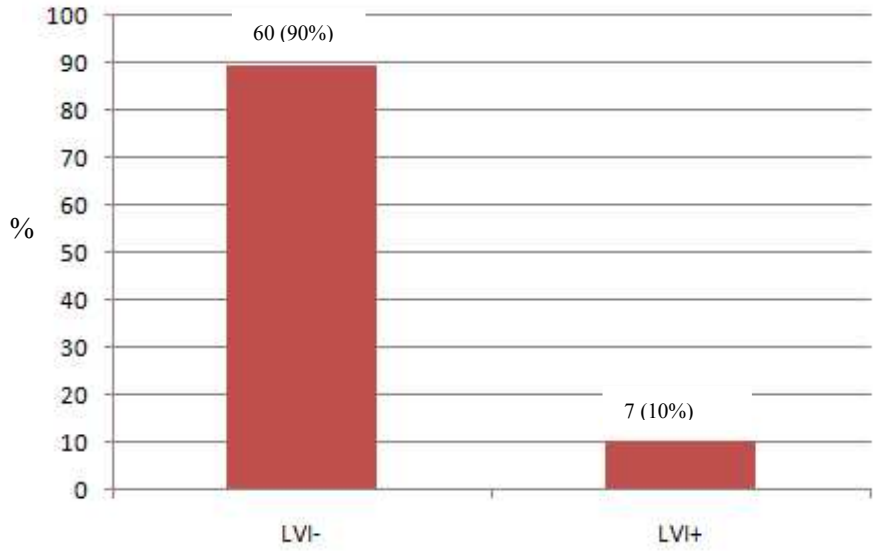

Figure 8. Lymphovascular invasion

Table 4 describes the relationship between the lymphovascular invasion and the histological type of the carcinoma. Fifty-four out of 60 squamous cell carcinoma did not show signs of lymphovascular invasion and only 6 of them were positive for lymphovascular invasion. Seven out of 7 adenocarcinomas did not show signs of lymphovascular invasion. The only one diagnosed adenosquamos carcinoma was positive for lymphovascular invasion.

Table 4. Lymphovascular invasion in relation to the pathohistological type of carcinoma

PhD	Squamous cell carcinoma	Adenocarcinoma	Adenosquamous carcinoma
LVI+	6	0	1
LVI-	54	6	0

The incidence of lymphovascular invasion of different pathohistological types is presented in figure 9. Ninety percent of squamous cell carcinoma were negative for lymphovascular invasion and 10% had positive lymphovascular invasion. One hundred percent of adenocarcinoma and adenosquamous carcinoma were negative for lymphovascular invasion or had positive lymphovascular invasion, respectively.

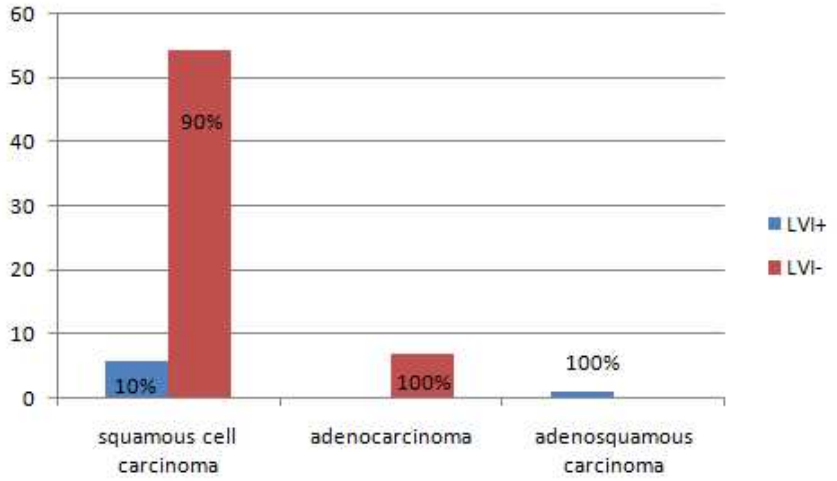

Figure 9. The incidence of LVI of different pathohistological types

4.4. Treatment

The most common surgical option overall was conization (39 out of 73;58%). Hysterectomy was performed in 25 out of 73 cases (37%), LEETZ in 5 out of 73 cases (8%), excochleation in 3 out of 73 cases (5%) and adjuvant radiotherapy was performed in only one case (1 out of 67;2%) (Table 5).

Table 5. Treatment options used for patients with the carcinoma of the uterine cervix FIGO IA1 from 1.1.2000. to 1.1.2017. in University Hospital of Split

Treatment options	n	%
Conization	39	58
Hysterectomy	25	37
LEETZ	5	8
Excochleation	3	5
Adjuvant radiotherapy	1	2

The choice of treatment and its relationship with the pathohistological type of carcinoma is presented in figure 10. The choice of treatment for squamous cell carcinoma was conization in most of the cases (32 out of 60;53%), followed by hysterectomy (23 out of 60;38%), LEETZ (5 out of 60;8%), excochleation (3 out of 60; 5%) and adjuvnt radiotherapy which was used only once (1 out of 60;2%). All adenocarcinomas were treated with conization (6 out of 6;100%) as well as all adenosquamous carcinomas (1 out of 1;100%).

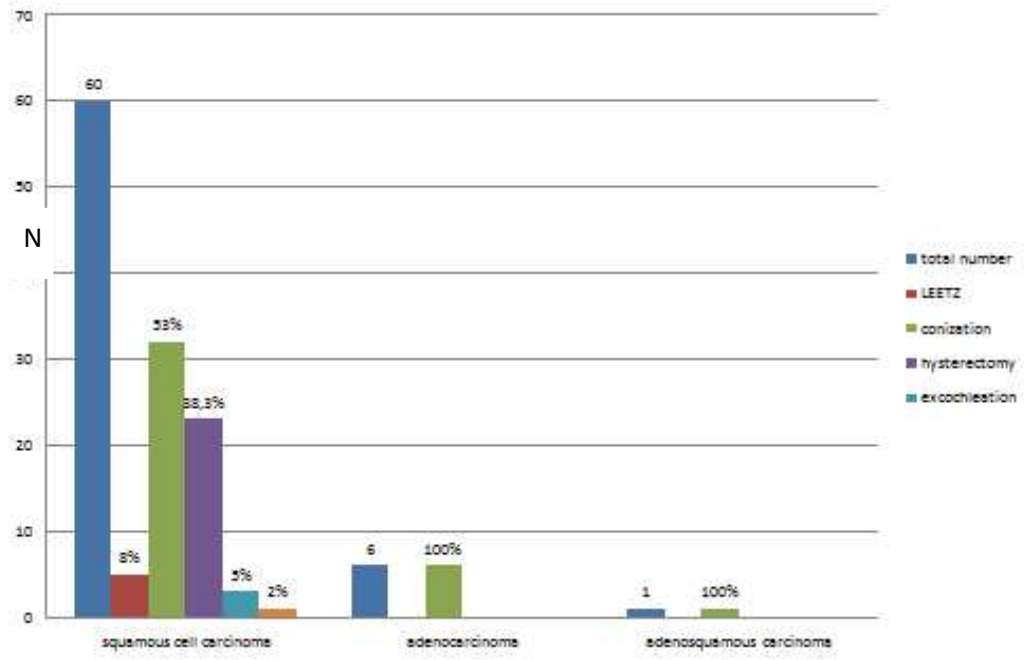

Figure 10. The incidence of different treatment options in relation to pathohistological type

Figure 11 shows the treatment option and its relationship with the lymphovascular invasion. Carcinomas with positive lymphovascular invasion (7 out of 67;10%) were in most cases treated by conization (5 in 7;71%), followed by hysterectomy (3 in 7;43%) and excochleation (1 in 7;14%). LEETZ and adjuvant radiotherapy were not used as a treatment for carcinomas with positive lymphovascular invasion. Carcinomas with negative lymphovascular invasion (60 out of 67;90%) were treated by conization in most cases (34 in 60;57%) as well, followed by hysterectomy (23 in 60;38%), LEETZ (5 in 60;8%), excochleation (2 in 60; 3%) and adjuvant radiotherapy was used in one occasion (1 in 60;2%).

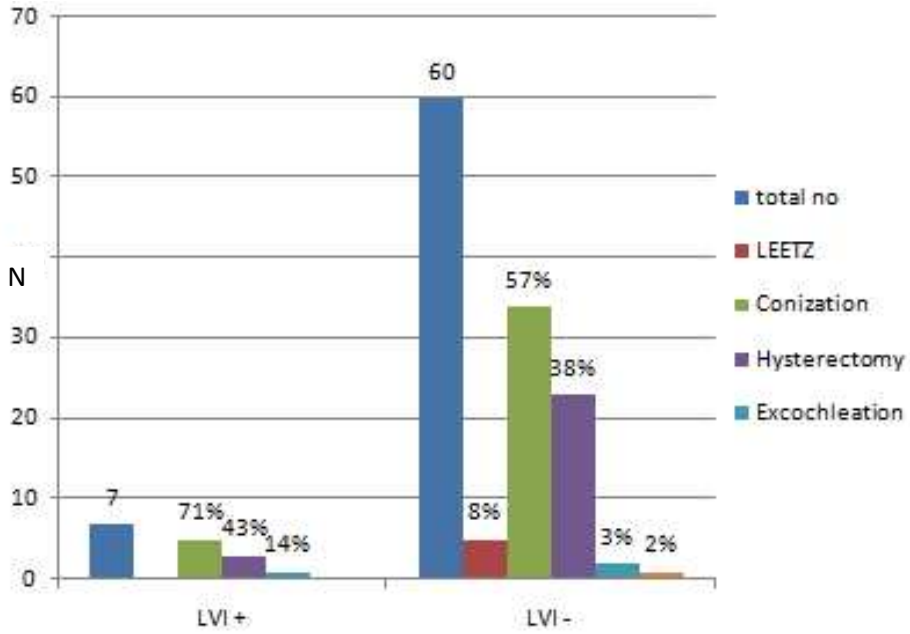

Figure 11. The incidence of different treatment options based on lymphovascular invasion

Figure 12 shows the treatment option and its relationship to the age of the patient. In age group 21-30 years of age conzation was used as an only treatment option (3 in 3;100%). In age group 31-40 years of age the most common treatment option used was conization (18 in 20;90%), followed by LEETZ (2 in 20;10%), hysterectomy (1 in 20;11%) and excochleation (1 in 20;11%). Adjuvant radiotherapy was not used in this age group. In age group 41-50 years of age the most common treatment option used was conization (10 in 21;48%), followed by hysterectomy (9 in 21;43%) and LEETZ (2 in 21;10%). Excochleation and adjuvant radiotherapy were not used as a treatment option in this age group. In age group 51-60 years of age most common treatment option used was hysterectomy (7 in 9;78%), followed by conization (3 in 9;33%), excochleation (1 in 9;11%) and adjuvant radiotherapy (1 in 9;11%). LEETZ was not used as a treatment option in this age group. In age group 61-70 years of age conization (4 in 8;50%) and hysterectomy (4 in 8;50%) were the only treatment options used. LEETZ, conization and adjuvant radiotherapy were not used as a treatment options in this age group. In age group 71-80 years of age the most common treatment option used was hysterectomy (4 in 6;67%), followed by LEETZ (1 in 6;17%) and conization (1 in 6;17%). Excochleation and adjuvant radiotherapy were not used as treatment options in this age group.

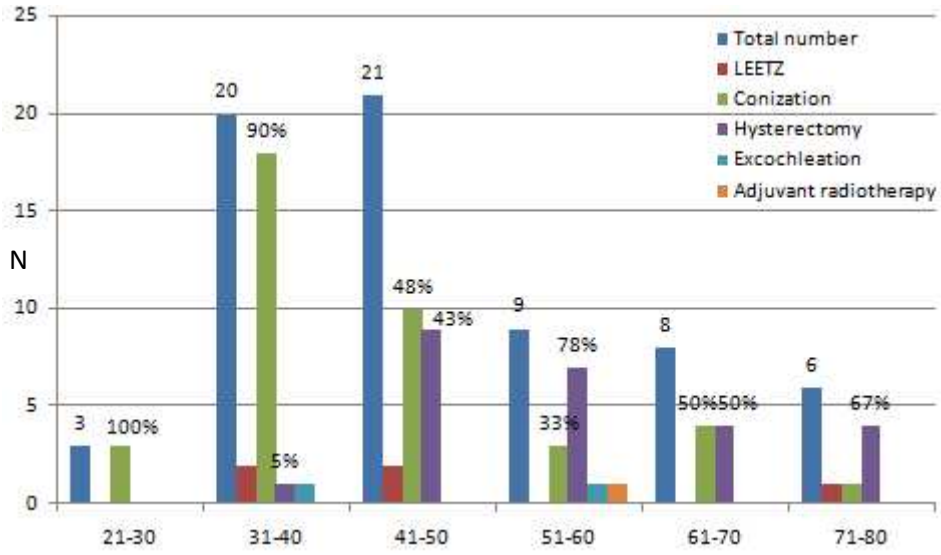

Figure 12. The incidence of different treatment options used in relation to the age of the patient

5. DISCUSSION

Carcinoma of the uterine cervix is one of the most commonly diagnosed carcinomas in females worldwide (3). In period of 17 years (1.1.2000.-1.1.2017.), 67 women in total were diagnosed with and treated for the CC in University Hospital of Split, Department of Gyneacology and Obstetrics.

The peak incidence of the CC in our hospital is between 41 and 50 years age, youngest age being 26 years and oldest age being 79 years, median age being 46 years. In the UK and the majority of the rest of the European Union member countries, based on the data from Office for National Statistics, the median age is 45 years (2). We conclude that, in Croatia, the results are similar to the results in the rest of the Europe.In Croatia, screening protocol is in concordance with screening protocols in the rest of the World, which could be the explanation for these findings (12).

In our hospital, the most common pathohistological type of the CC is squamous cell carcinoma, it occurs in 90% of cases (60 out of 67 women were diagnosed with squamous cell carcinoma), followed by adenocarcinoma occuring in 9% of cases (6 out of 67 women were diagnosed with adenocarcinoma) and there was only one case of adenosquamous carcinoma. Our results do not differ much from the results brought by other authors. Squamous cell carcinoma is the most common type of the CC worlwide (6,20). Articles published by International Agency for Research on Cancer (IARC) state that more than two-thirds of the CC are squamous cell carcinomas, and about 15% are adenocarcinomas (33,34).

Many differences exist between squamous cell carcinoma and adenocarcinoma of the uterine cervix, including anatomic origin, risk factors, prognosis, dissemination, sites of recurrence and rates of metastases. These differences are sufficient to warrant specific treatment recommendations. Nevertheless, despite differences, the lack of data evaluating adenocarcinoma is the reason why current treatment algorithms do not distinguish between squamous cell carcinoma and adenocarcinoma of the uterine cervix (35). The management of microinvasive adenocarcinoma of the uterine cervix remains controversial, and radical therapy is applied more frequently than is the case with squamous cell carcinoma, even though the data shows that the risk of the extracervical disease is low and the risk of recurrence is not affected by the radicality of resection and that microinvasive adenocarcinoma is amenable to treatment with nonradical surgery (36). In our hospital it is well recognized that microinvasive adenocarcinoma is amenable to nonradical treatment and

that radical resection is not the proper treatment option. Hundred percent of microinvasive adenocarcinomas diagnosed in University Hospital of Split was treated by conization.

Lymphovascular invasion, together wih the depth of stromal invasion and tumor diameter, is an independent risk factor because of its frequent association with increased incidence of lymph node metastases, recurrence and poor survival. The depth of stromal invasion is the most critical of these risk factors (37). Sixty out of 67 of our patients had negative lymphovascular invasion (90%) and only 7 out of 67 of them had positive lymphovascular invasion (10%). Most of the squamous cell carcinomas, 90% of them, were negative for lymphovascular invasion. All of the adenocarcinomas diagnosed in our patients were negative for lymphovascular invasion. The only one adenosquamous carcinoma diagnosed was positive for lymphovascular invasion. Lymphovascular invasion is one of the factors that should lead our decision when it comes to choosing the most appropriate treatment option for our patient. In the case of the positive lymphovascular invasion, simple hysterectomy is the preferred option (27), but its presence should not be considered as a contraindication for conization in patients with carcinoma of the uterine cervix FIGO stage IA1, rather it should impose the requirement for pelvic lymph node sampling, because positive lymph nodes per se are a contraindication for sparing procedures (38). In our hospital, majority of patients were treated with conization regardless of the status of lymphovascular invasion. Fifty-seven percent of our patients with negative lymphovascular invasion and 71% with positive lymphovascular invasion were treated with conization.. Second most common procedure performed was hysterectomy. Hysterectomy was performed in 38% of patients with negative lymphovascular invasion and in 43% of patients with positive lymphovascular invasion.

Treatment of the CC is a complex and multidisciplinary field. The decision about the treatment should be made by a team of specialists and according to the current algorithms of the institution where the treatment is to be performed (25). Factors that should affect the decision-making process when it comes to choosing the most appropriate treatment option for our patient are: the stage of the carcinoma (being the most important factor), exact location of the carcinoma within the cervix, the type of carcinoma, lymphovascular invasion status of the carcinoma, age of the patient, overall health of the patient and whether the fertility is to be maintained or not (24).

For the CC FIGO stage IA1 it is enough to perform LEETZ or conization or simple hysterectomy, according to the guidelines (6,26). The most common procedure performed in our hospital was conization. Conization was the preferred option in 58% of cases. Second most common treatment performed was hysterectomy, in 37% of cases.The results from this paper show that in our hospital the decision about the treatment follows the guidelines and does not differ much from the rest of the world. The only difference is that in our hospital, LEETZ is preferred option in only 8% of cases. There is no data to explain this finding.

For women who wish to preserve fertility, conization or LEETZ is the preferred treatment option. If the margins are negative, no further treatment is required. If margins are positive, repeated conization or LEETZ or simple hysterectomy should be performed. For women who do not wish to preserve fertility, the treatment of choice is simple hysterectomy (27). Fertility is defined as the capacity to concieve or to induce conception.Fertile women are considered to be in childbearing age. Childbearing age is the period in a woman's life between puberty and menopause. A woman of childbearing age is usually considered to be between ages 15 and 44, it should be noted that these numbers are used only as a generalized guidelines, and women can have offspring earlier as well as later than the years indicated. In Clinical hospital Split, the age of the patient is the factor participating in the guidance of the treatment decision-making process as well. Women in the age group 21-50 years of age, roughly representing the childbearing age group, were most commonly treated with conization, being one of the fertility sparing procedures. The younger the patient was, conization was more commonly used as a tretment option. In age group 21-30 years of age all patients were treated by conization. The most common treatment option for women older than 51 years of age, roughly representing the non-childbearing age group, was hysterectomy. We can conclude that in our hospital, the age of the patient is the important factor when it comes to deciding about the most proper treatment option and that it correlates with the guidelines in the rest of the world (27).

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6. CONCLUSION

1. In the period of 17 years, 67 women in total were diagnosed with and treated for the carcinoma of the uterine cervix FIGO stage IA1 in University Hospital of Split, Department for Gynaecology and Obstetrics.
2. The youngest patient diagnosed with the carcinoma of the uterine cervix FIGO stage IA1 was 26 years old, and the oldest was 79 year old. The median age of our patients was 46 years.
3. The most common type of the carcinoma was squamous cell carcinoma, diagnosed in 90% of cases. Adenocarcinoma was diagnosed in 9% of cases. Adenosquamous carcinoma was diagnosed in only one patient, 1% of cases.
4. Most of the diagnosed carcinomas were negative for lymphovascular invasion (90%), and only a minority was positive (10%).
5. The most common treatment option used in our hospital for the carcinoma of the uterine cervix FIGO stage IA1 was conization, followed by hysterectomy, LEETZ and excochleation. Thirty-nine conizations, 25 hystrectomies, 5 LEETZ procedures and 3 excochleation were performed. In addition, radiotherapy was used as an adjuvant treatment in te case of one of our patients.
6. Conization was the most common procedure used regardless of the pathohistological type and lyphovascular invasion of the carcinoma.
7. Women younger than 50 years of age were most commonly treated with conization, being the fertility sparing procedure. Women older than 51 year of age were most commonly treated with hysterectomy, being the non-fertility sparing procedure.
8. In our hospital the approach to prevention, diagnosis and treament of the carcinoma of the uterine cervix is in concordance with the protocols used in the rest of Europe and the World, and all the results from this paper are similar to the results of other studies.

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8. SUMMARY

Title: MICROINVASIVE CARCINOMA OF THE UTERINE CERVIX IN UNIVERSITY HOSPITAL OF SPLIT

Objectives: The aim of this paper is to examine the incidence of microinvasive carcinoma of the uterine cervix FIGO stage IA1 treated in University Hospital of Split from 1.1.2000. to 1.1.2017., to examine the age of the patient at the diagnosis, to examine the incidence of patohistological types, to examine the incidence of lymphovascular invasion, and to examine the treatmet choice.

Methods: By retrospective analysis of histories and discharge letters and the protocol of surgeries of all patients with the CC FIGO stage IA1, assessed from the archives of the Department of Gyneacology and Obstetrics and Department of Oncology in Clinical hospital Split, we examined the following: the age of the patients at the diagnosis, pathohistological diagnosis, lymphovascular invasion and treatment choice.

Results: In total 67 women were diagnosed with and treated for the CC FIGO stage IA1 at the Deparment of Gynaecology and Obstetrics and Department of Oncology in Clinical hospital Split in period of 17 years. The highest number of diagnosed carcinomas was in year 2011 (n=8), and the lowest in year 2002 (n=1). The greatest incidence of the carcinoma was in age group 41-50 years of age (21 out of 67;31%). The youngest patient was 26 years old and the oldest was 79 years old, median age was 46 years (IQR 36-56). The most common type of carcinoma was squamous cell carcinoma (60 out of 67;90%). Most of the diagnosed carcinomas were negative for lymphovascular invasion (60 out of 67;90%). The most common surgical procedure used was conization (39 out of 73;58%). Conization was the most common surgical option used regardless of pathohistological type and LVI. Conization was the only treatment option used in age group 21-30 years (3 out of 3;100%). Conization was the most common treatment option used in age groups 31-40 years (18 out of 20;90%) and 41-50 years (10 out of 21;48%). The most common treatment option used in age group 51-60 years was hysterectomy (7 out of 9;78%). Age group 61-70 years was equally as often treated with conization (4 out of 8;50%) as it was with hysterectomy (4 out of 8;50%). The most common treatment option in age group 71-80 years of age was hysterectomy (4 out of 6;67%).

Conclusions: In the period of 17 years, in total 67 women were diagnosed with and treated for the carcinoma of the uterine cervix FIGO stage IA1 in our hospital. The median age of our patients was 46 years. The most common type of carcinoma was squamous cell carcinoma. Most carcinomas were negative for lymphovascular invasion. The most common treatment option overall and regardless of pathohistological diagnosis and lymphovascular invasion was conization. Women younger than 50 years of age were most commonly treated with conization, while women older than 51 years of age were most commonly treated with hysterectomy.

9. CROATIAN SUMMARY

Naslov:MIKROINVAZIVNI KARCINOM VRATA MATERNICE U SVEUČILIŠNOJ BOLNICI SPLIT

Ciljevi: Cilj istraživanja je ispitati pojavnost mikroinvazivnog karcinoma vrata maternice FIGO stadija IA1 liječenog u Sveučilišnoj bolnici Split od 1.1.2000. do 1.1.2017. godine, ispitati: dob pacijentica pri dijagnozi,učestalost patohistološke dijagnoze, učestalost limfokapilarne invazije i odabir liječenja.

Metode: Retrospektivnom analizom povijesti bolesti i otpusnih pisama i protokola operacija svih pacijentica s karcinomom vrata maternice FIGO stadij IA1, kojima je pristupljeno putem ulaska u arhive Odjela za Ginkologiju i Obstetriciju i Odjela za Onkologiju KBC-a Split, ispitali smo: dob pacijentica pri dijagnozi, patohistološku dijagnozu, limfokapilarnu invaziju i odabir liječenja.

Rezultati: Ukupno 67 žena liječeno je od karcinoma vrata maternice FIGO stadij IA1 na Odjelu za Ginekologiju i Obstetriciju i na Odjelu za Onkologiju KBC-a Split u periodu od 17 godina. Najveći broj dijagnosticiranih karcinoma bio je u 2011. godini (n=8), a najmanji u 2002. godini (n=1). Najveća pojavnost karcinoma bila je u dobnoj skupini 41-50 godina (21 od 67;31%). Najmlađa pacijentica imala je 26 godina, a najstarija 79 godina, srednja dob bila je 46 godina (IQR 36-56). Najčešći tip karcinoma bio je karcinom pločastih stanica (60 od 67;90%). Većina dijagnosticiranih karcinoma bila je negativna za limfokapilarnu invaziju (60 od 67;90%). Najčešći kirurški postupak bila je konizacija (39 od 73;58%). Konizacija je bila najčešći kirurški postupak bez obzira na patohistološku dijagnozu i LKI karcinoma. Konizacija je bila jedini kirurški postupak učinjen u dobnoj skupini 21-30 godina (3 od 3;100%). Konizacija je bila najčešći učinjeni kirurški postupak u dobnim skupinama 31-40 godina (18 od 20;90%) i 41-50 godina (10 od 21;48%). Najčešći kirurški postupak učinjen u dobnoj skupini 51-60 godina bila je histerektomija (7 od 9;78%). U dobnoj skupini 61-70 godina, konizacija i histerektomija učinjene su jednako mnogo puta (4 od 8;50%). Najčešća kirurška opcija u dobnoj skupini 71-80 godina bila je histerektomija (4 od 6; 67%):

Zaključci: U razdoblju od 17 godina, 67 žena je dijagnosticirano i liječeno od karcinoma vrata maternice FIGO stadij IA1 u našoj bolnici. Srednja dob naših pacijentica bila je 46 godina. Najčešći tip karcinoma je karcinom pločastih stanica. Većina karcinoma bila je negativna za limfokapilarnu invaziju. Najčešće učinjena operacija, bez obzira na

patohistološku dijagnozu i limfokapilarnu invaziju bila je konizacija. Žene mlađe od 50 godina najčešće su liječene konizacijom, dok su one starije od 51 godina najčešće liječene histerektomijom.

10. CURRICULUM VITAE

Personal Data:

Name and Surname: Anamaria Babić

Date of birth: September 21st 1993

Place of birth: Zagreb, Croatia

Citizenship: Croatian

Address: Fra Rafe Kalinića 42, 21230 Sinj

E-mail: babicanamaria@hotmail.com

Education:

2012-2018 University of Split School of Medicine, Split, Croatia

2008-2012 Opća gimnazija Dinka Šimunovića, Sinj, Croatia

2001-2007 Osnovna glazbena škola Jakova Gotovca, Sinj, Croatia

2000-2008 Osnovna škola fra Pavla Vučkovića, Sinj, Croatia

2000-2011 Centar stranih jezika, Engleski jezik, Sinj, Croatia

Languages:

Croatian (mother tongue)

English (C2)Spanish (B1) Italian (A2) German (A1) Swedish (A1)

Other activities:

2010-2016 manager of a bar/restaurant Galerija, Sinj

2009-2010 bronze medal in county competition in handball

Driving licence category B