

Clinical and surgical staging in patients with cervical cancer – a retrospective study regarding correlations between initial diagnosis, treatment options and histopathological results

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Abstract

According to the International Federation of Gynecology and Obstetrics (FIGO), cervical cancer staging is realized through clinical examination. The imaging and subsequent surgical findings come in addition to the first staging. Although in the incipient stages surgery is the first step in treatment, in advanced stages the treatment options are based on the clinical staging in corroboration with imaging techniques. The recognition of the prognostic factors, such as lymph node metastasis and distant metastasis, represents a key element for the proper diagnosis and treatment. In this paper, we present a retrospective study that included patients with cervical cancer for which imaging evaluation of the lymph nodes was performed and was compared with post-surgery histopathological results.

Keywords: cervical cancer, staging, lymph nodes, imaging

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Stadializarea clinică și chirurgicală a pacientelor cu cancer de col uterin – studiu retrospectiv privind corelațiile dintre diagnosticul inițial, opțiunile de tratament și rezultatele histopatologice

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Rezumat

Conform Federației Internaționale de Ginecologie și Obstetrică (FIGO), stadializarea cancerului de col uterin se realizează prin examinare clinică. Imagistica și constatările chirurgicale ulterioare au rolul de a îmbunătăți precizia diagnosticului față de prima stadializare. Deși în stadiile incipiente intervenția chirurgicală este primul pas în tratament, în stadii avansate opțiunile de tratament se bazează pe stadializarea clinică, în coroborare cu tehnicile imagistice. Recunoașterea factorilor de prognostic, precum metastazele ganglionilor limfatici și metastazele la distanță, reprezintă un element-cheie în diagnosticul și tratamentul adecvat. Această lucrare prezintă un studiu retrospectiv ce a inclus paciente cu cancer de col uterin pentru care s-a realizat evaluarea imagistică a ganglionilor limfatici, iar rezultatele au fost comparate cu rezultatele histopatologice postoperatorii.

Cuvinte-cheie: cancer de col uterin, stadializare, ganglioni limfatici, imagistică

Introduction

Cervical cancer represents a common public health-care issue. Worldwide, it is on the fourth place in the list of common cancers in patients regarding age, and 85% of them are in regions with restricted resources⁽¹⁾. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) updated the 2009 recommendations. The new guideline takes into consideration the day-to-day clinical practice and the needs for treatment stratification. The stage of the cervical cancer determines the treatment options. Surgical treatment and chemoradiotherapy represent the management alternatives.

According to FIGO, the staging for cervical cancer is currently made clinical. There is a strong recommendation that imaging techniques should be used to offer a more accurate staging⁽²⁾. It is considered that the staging for cervical carcinoma can be imprecise in a significant number of patients with both early and advanced stages⁽³⁾. The 2018 staging aimed at reducing the rate of error by increasing the importance of imaging. Two main changes were represented by redefining stage IA (removing lateral extension) and stage IB (introducing the 2-4 cm group). For stage III, the presence of lymph node involvement can be indicated

by imaging or pathology (notations ‘r’ and ‘p’ should be mentioned)⁽⁴⁾.

The correct assessment of lymph nodules is important for proper staging and treatment, as lymph node metastasis, parametrial involvement, stromal infiltration and metastasis in other organs are negative prognostic factors⁽⁵⁻⁷⁾. Failure to evaluate the extent of the disease can lead to suboptimal treatment and to disease recurrence⁽⁸⁾. The presence of paraaortic lymph node metastases is correlated with poor prognosis and with risk for disease recurrence^(8,9), and it is encountered in up to 16% of the cases⁽¹⁰⁾. As a solution, the surgical evaluation of nodules in advanced cancer was assessed. Laparoscopic paraaortic lymphadenectomy for advanced cases could help adjust radiotherapy⁽¹¹⁾. The involvement of other lymph nodes can be present in up to 44% of cases and require adequate chemoradiotherapy in order to obtain a proper response⁽¹⁰⁾.

Although the most precise evaluation is realized by surgical staging, the procedure can be correlated with increased morbidity and mortality when radiotherapy is needed⁽⁸⁾. Laparoscopy and robotic surgery can be options to reduce complications^(12,13). Surgical evaluation is associated with considerable rates of upstaging⁽¹⁴⁾. There is a potential benefit from surgery that is represented by the metastatic lymph node debulking prior to the other treatments and thus obtaining higher control⁽⁶⁾.

As an alternative, imaging assessment of the lymph nodules is encouraged to be made. Computed tomography, magnetic resonance imaging and positron emission tomography can be used in all stages of cancers. When compared with surgical staging, these techniques have lower sensitivity and specificity. There is a false-negative rate regarding the imaging method used for evaluation^(9,11,15,16), but it seems that it is no difference between surgical and clinical staging regarding recurrence rate in women with advanced cervical cancer⁽⁶⁾.

For every patient, it is important to determine the most favorable management, including diagnosis and treatment. The proper evaluation using adequate imaging can contribute to a more precise staging and adapted medical and surgical treatment. The aim of this paper is to highlight the correlation between imaging aspects and surgical aspects in patients with various stages of cervical cancer.

Materials and method

We performed a retrospective analysis of the patients with cervical malignant tumors investigated in the University Emergency Hospital Bucharest in the last five years (between January 2017 and December 2022). We analyzed the database of the Obstetrics-Gynecology Clinic to obtain information regarding clinical staging of patient, post-surgery staging, and the relevance of imaging in these cases. The aim of this study was to compare the clinical staging and imaging findings with the histopathological forms and lymph node implications. This analysis was part of the national, single-center, investigational, retrospective clinical research

study entitled “Surgical treatment methods in cervical cancer” (study number 74825/07.12.2021), carried out in the Obstetrics-Gynecology Clinic of the Emergency University Hospital Bucharest, for a period of five years. The purpose of this project was to study different types of surgical interventions, including lymphadenectomy and new diagnostic procedures, monitoring human papillomavirus (HPV) infection and evaluating lymphedema of the lower limbs after lymph node dissection.

Results

During the studied period, 826 patients were reported with gynecological cancers, and 746 interventions were performed for malignant tumors. There were performed 50 loop diathermy excision of the cervix, 437 conizations and 259 radical hysterectomies with lymph node dissection (Figure 1). In the last category, there were included operations performed for uterine cancer and ovarian cancer as well.

The distribution by year is showing the impact of the COVID-19 pandemic. The lowest number of surgeries were performed in 2020 – a total of 56 procedures (four loop diathermy excision, 27 conizations and 25 radical hysterectomies). As presented in Figure 2, in 2017 there were performed the most procedures (117). The total number started to increase after lifting restrictions, as seen in 2021 (83 procedures) and 2022 (118 procedures).

Analyzing the data, we observed that the number of radical hysterectomies with lymphadenectomy dropped during the pandemic but, at the same time, the percentage from the total number of interventions was significantly increased (25 radical hysterectomy with lymphadenectomy, representing 44.6% from all surgeries, compared with a median of 55 radical hysterectomy with lymphadenectomy a year in the previous three years, representing 33%) – Figure 3. These data can be correlated with the diagnosis in advanced forms of cancer rather than the diagnosis of preneoplasia lesions due to delayed presentation. The patients who underwent radical hysterectomy with lymphadenectomy were mostly from urban areas (161 women versus 71 women from rural areas). In this lot of patients, there

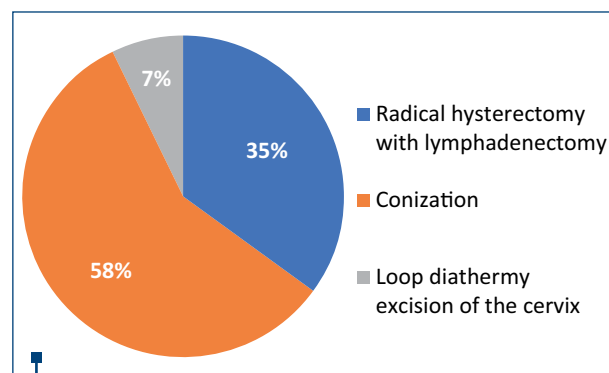


Figure 1. Surgeries performed for gynecological tumors

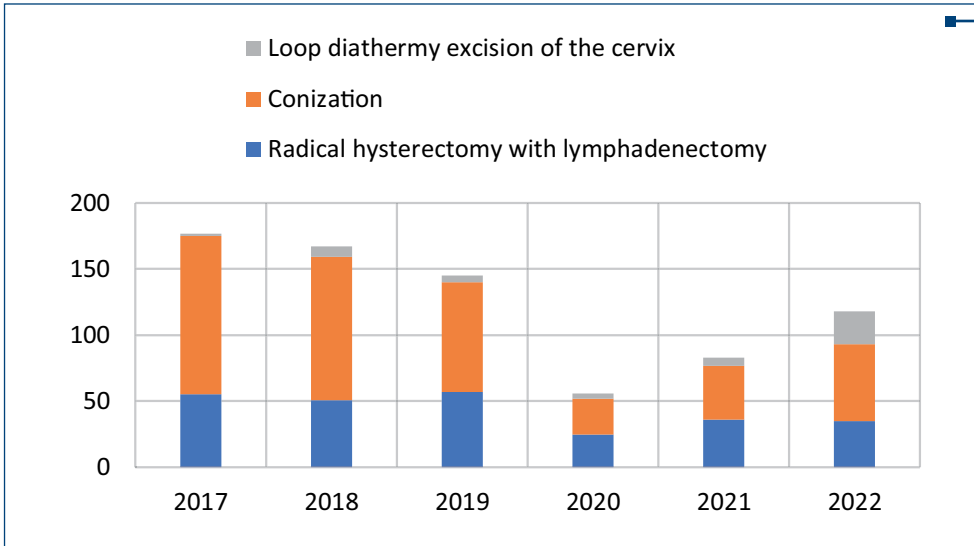


Figure 2. Distribution of loop diathermy excision, conization and radical hysterectomy with lymphadenectomy, by years

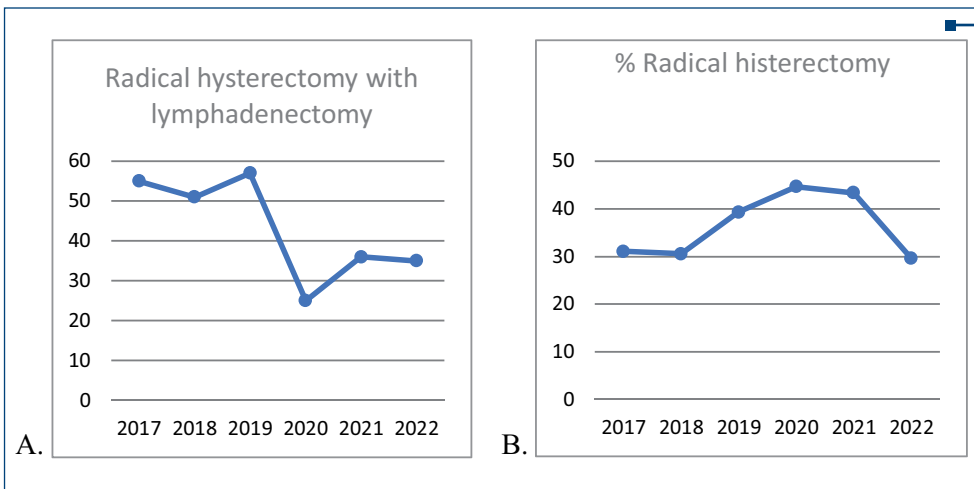


Figure 3. A) Number of radical hysterectomies with lymphadenectomy, by year; **B)** Percentage from all surgeries for radical hysterectomies with lymphadenectomy, by year

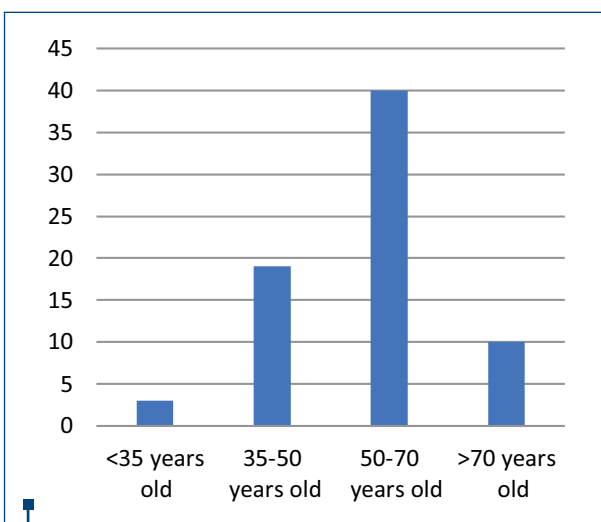


Figure 4. Patients' distribution by age group

was one person older than 80 years of age, with 42.67% of patients between 40 and 59 years old, and 51.72% between 60 and 79 years old.

Out of these women who underwent surgical procedures in our clinic, we selected 72 patients who had radical hysterectomy with lymphadenectomy for cervical cancer of different stages. The median age was 58.5 years old and the medium age was 55.8 years old, with the youngest women of 26 years old and the oldest patient of 75 years old. The distribution by age groups is presented in Figure 4. The majority of women came from urban areas (56 patients).

The histological types of cancer encountered were represented by keratinized squamous cell carcinoma (26 patients), nonkeratinized squamous cell carcinoma (40 patients) and endocervical adenocarcinoma (six patients) – Figure 5. One particular case was represented by a 50-year-old patient diagnosed with endocervical adenocarcinoma G3 associated with stratified

mucin-producing intraepithelial lesion (SMILE). WHO classifies SMILE as a rare high-grade cervical precancerous lesion and a variant of adenocarcinoma *in situ*. Figure 6 reveals the histopathological aspects of this particular tumor.

The clinical staging was assessed with the clinical evaluation of the patient and with imaging techniques (CT and MRI). In our studied group, there were 20 patients with stage IA, 23 patients with stage IB, seven patients with stage IIA, 16 patients with stage IIB, two patients with stage IIIA and four patients with stage IIIB. There were no patients with stage IIIC or IV. The distribution of cervical cancer staging by age can be seen in Figure 6. In this analysis, patients with *in situ* cervical carcinoma or with stage IV were not included.

In order to evaluate properly the patient, the MRI and CT protocols were followed. The patients were required to present with bladder and rectum emptied with 30-60 minutes before the procedure. The purpose was to obtain a partial distention of the bladder and a favorable uterine position. The typical MRI image of cervical tumors reveals intermediate T2-weighted signal intensity and enhanced T1-weighted signal for small tumors.

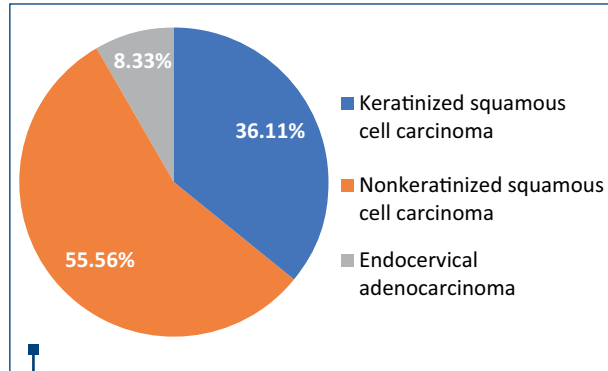


Figure 5. Histopathological types of cervical cancer in our patients (percentage of total cases)

Out of a total of 72 patients, 44 women (61.11%) underwent chemoradiotherapy, of which 29 patients had no residual tumor at surgery. For 28 patients (38.89%), radical hysterectomy with lymphadenectomy was the first line of treatment. There were four patients who were subdiagnosed and the clinical staging was lower than the surgical staging, although the imaging did not show lymph node implication, parametrial invasion or

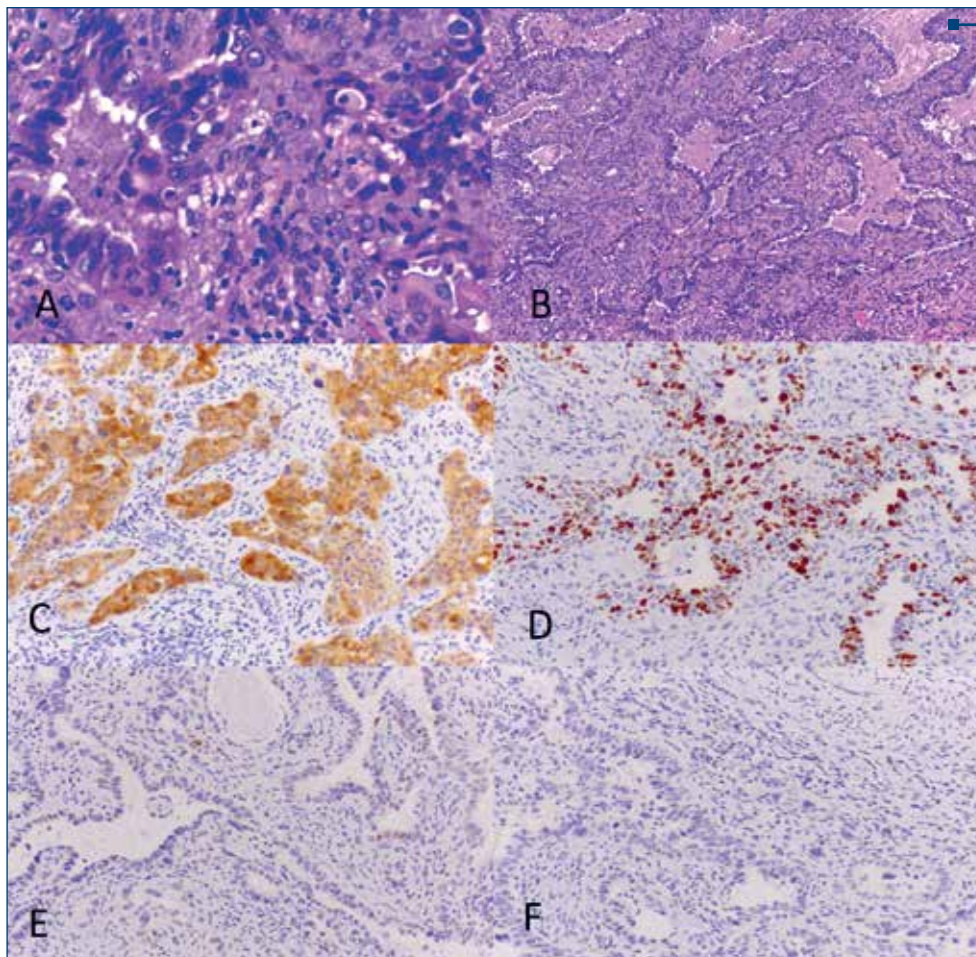


Figure 6. **A)** Epithelial malignant tumor proliferation with an infiltrative characteristic, with pseudoglandular and papillary structures covered by neoplastic epithelium – HE, ob. 100X; **B)** Large tumor cells are observed, with eosinophilic cytoplasm and marked cytonuclear pleomorphism – vHE, ob. 200X; **C)** Intense nuclear and cytoplasmic expression of p16 protein in tumor cells – IHC p16, ob. 200X; **D)** Expression of the proliferation marker Ki67 in 60% of tumor cells – IHC Ki67, ob. 200X. **E)** “Wild-type” expression pattern of the TP53 protein in the context of malignant neoplastic proliferation – IHC p53, ob. 200X; **F)** NapsinA negative in tumor cells – IHC Napsin A, ob. 200X (NapsinA – clone TMU-Ad 02 Biocare – mouse monoclonal)

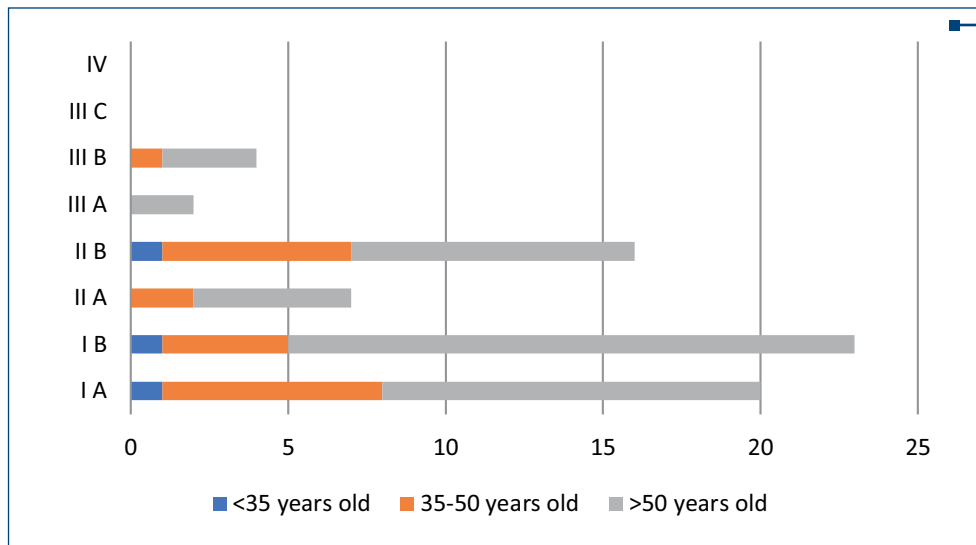


Figure 7. Clinical staging of patients at diagnosis, by age

extension to vagina or uterus. There were six cases with stages IA, IB or IIB in which the recommendation for chemoradiotherapy and not surgery was made, taking into consideration the aspect of the lymph nodes at CT or MRI. In five cases, positive lymph nodes were identified at post-chemoradiotherapy surgery.

To better evaluate the patient, in all patients it was performed lymphadenectomy that included iliac, crural and obturator nodes. Lymph node dissection is realized in the first surgical steps. The first nodes evaluated are the ones located on the opposite site of the surgeon, near the iliac vessels, followed by the dissection of the

retrocrual lymph nodes. After removing this lymph nodes groups, the obturator lymph nodes are removed. The next step is represented by evaluating and removing this groups of nodes from the side of the main surgeon. Figures 11 and 12 show the macroscopic aspects of the pelvic lymph nodes and the skeletonized vessels after lymph node dissection.

The median number of dissected lymph nodes was 17.5, with a total number of 1206 sampled lymph nodes and 31 nodes with present metastasis. In 22 women, the lymph node aspect was of reactive histiocytosis. For the 28 patients who had primary surgery, a total of

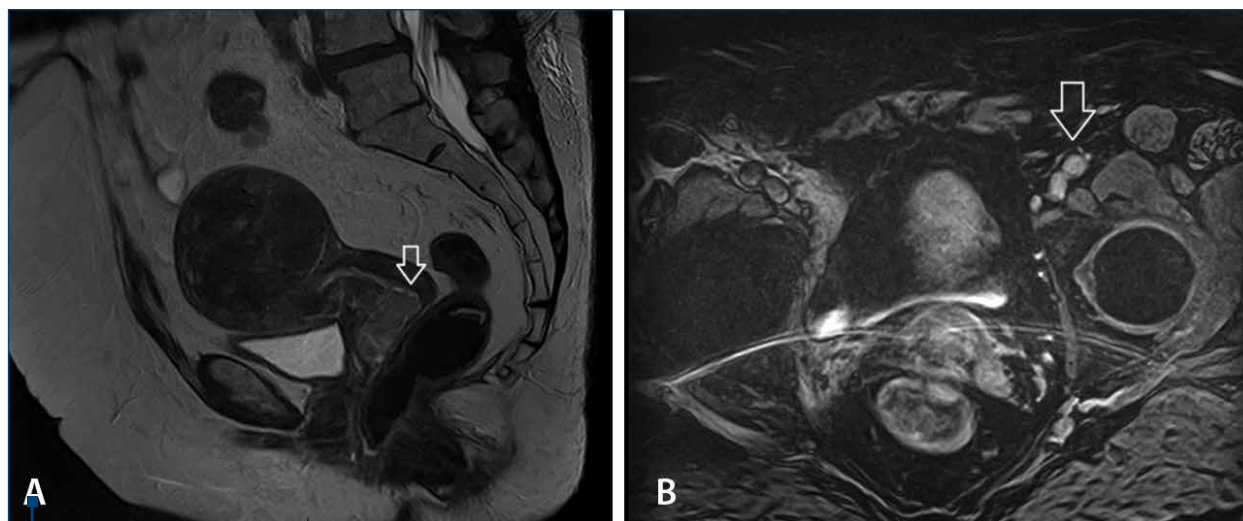


Figure 8. (A) Space-replacing process with intermediate signal, tissue located on the anterior and left lateral wall of the cervix and extension into the vaginal cavity, with an irregular outline and dimensions of 3.6/2/4.8 cm; the expansive process determines the partial occupation of the cervical groove, the anterior vaginal recess, as well as the occupation of the proximal portion of the vaginal cavity. Also, the expansive process presents important diffusion restriction with low ADC, heterogeneous gadolinophilia through mixed tissue and pseudocystic components. (B) Images of two left external iliacs in the plane of the lesion, showing a low subunit ADC signal, which can be classified in a malignant context

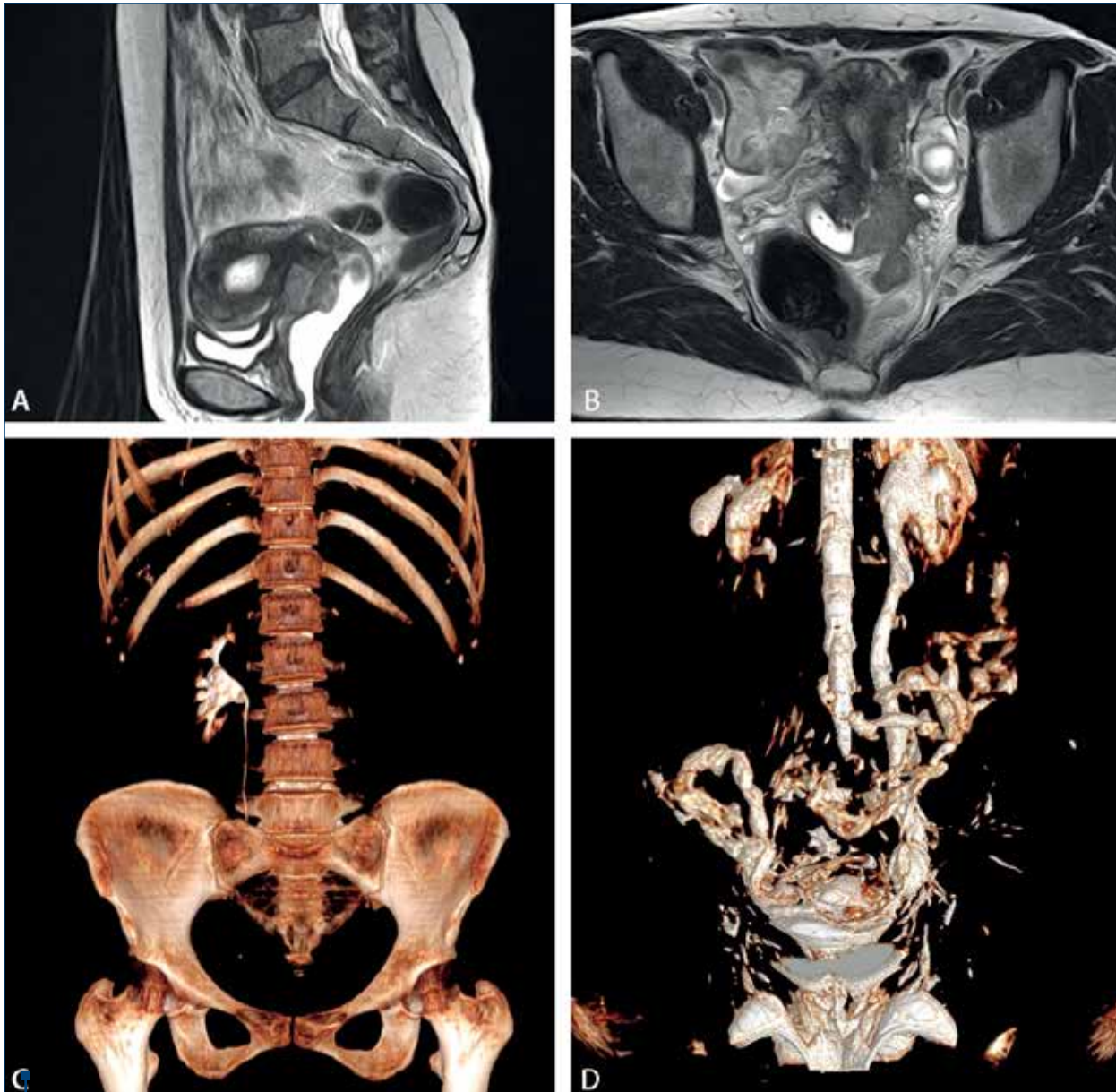


Figure 9. A, B) Polylobate tissue mass, developed exophytically at the level of the anterior cervix and the one-half of the left side, with diameters of 51/47/36 mm, in T1 hyposignal, moderately T2 hypersignal, which associates restriction on the diffusion sequence with low ADC, without interesting internal cervical ostium, with caudal extension at the level of the vagina 1/2 upper anterior contour, with invasion through the left antero-lateral slope at the level of the ureter on the same side in the juxtavesical portion, determining the overlying ureterohydronephrosis, and through the left posterolateral slope coming into intimate contact with the anterior wall and the left side of the middle rectum, but presenting a line of demarcation in front of it; necrotic adenopathic mass located in the sacral fat of 16 mm; **C)** CT image with normal renal filtration at examination in the right side; **D)** MRI image of left ureter invasion during tardive renal filtration and ureterohydronephrosis

446 nodes were evaluated and the median number of lymph nodes was 14.5. The increased number of lymph node dissection was not associated with higher rates of metastatic lymph node detection. In our group, we encountered two patients who presented lymph node invasion at the histopathological evaluation. Twenty-six patients (92.86%) had no metastatic nodes.

Figure 13 shows the ROC curve for the overall discriminatory power of pelvic lymph node dissection in predicting nodal status with corresponding AUC of 0.615. This value was observed when the lymph node examination was categorized using 15 lymph nodes as cut-off points. The number of lymph nodes was not associated with the pathologic finding of metastatic lymph nodes.

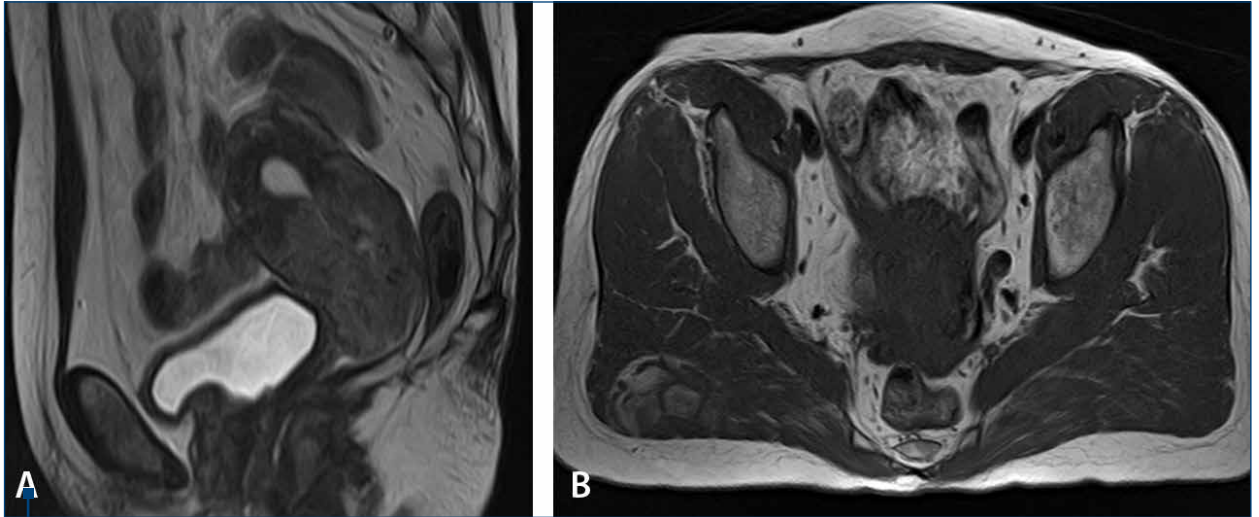


Figure 10. (A) Uterus in anteflexed lateral deviated to the right with increased dimensions, sagittal diameter of 90/55 mm, homogeneous myometrium, enlarged cervix (43/37 mm transaxial) with inhomogeneous structure due to the endoluminal presence of a tissue mass, in hyposignal T2/T1, in restriction of diffusion and with a low ADC coefficient (malignant characteristics), gadolinophilic, with a heterogeneous tissue/liquid structure, dimensions of 49/35 mm transaxial, respectively 45 mm cranio-caudal, with polylobed external contours, without invasion at the level of the vagina but with cranial extension in the lower two-thirds of the uterine body with obstruction of the internal cervical opening and slight distension of the uterine cavity, with a maximum thickness of 15 mm and serous content, without changes in the paracolp fat, the fatty demarcation line is preserved from the posterior wall of the urinary bladder and the anterior wall of the rectum. (B) Isolated pelvic adenopathies in diffusion restriction, but with normal ADC coefficient, without malignant features, bilateral internal obturators of 5 mm on the right side, 4 mm on the left side, bilateral deep inguinal 5 mm right/7 mm left, bilateral superficial inguinal 10 mm on the right side, respectively 9 mm from the left side

Discussion

Cervical cancer is one of the most prevalent forms of cancer in developing countries and has one of the highest mortality rates worldwide⁽¹⁷⁾. Unfortunately, Romania occupies the first place in Europe regarding mortality in cervical cancer⁽¹⁸⁾. Its prevalence is correlated with low socioeconomic status, low education level and with poor addressability to healthcare. It is considered that the difference between the high-income and low-income



Figure 11. Macroscopic aspect of pelvic lymph node

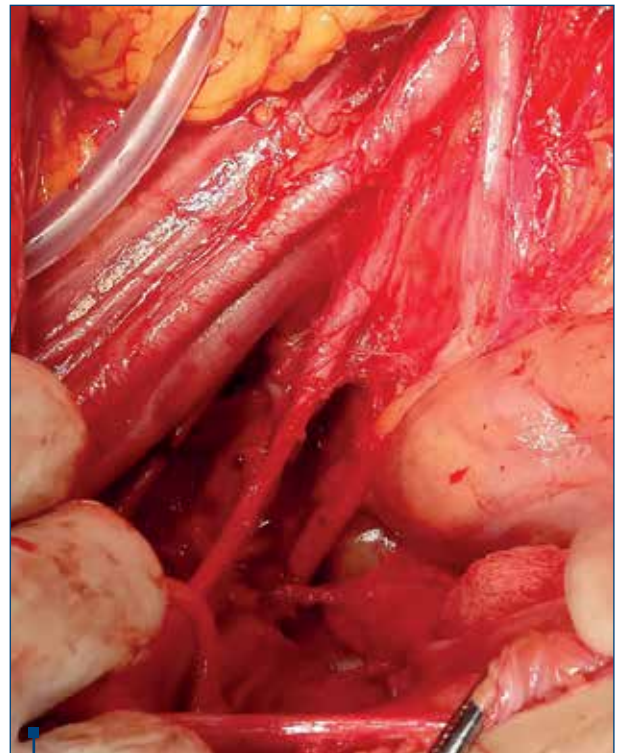


Figure 12. Skeletonized vessels after lymph node dissection

regions prevalence is due to the difference in access to screening⁽¹⁷⁾.

After the 2018 FIGO review of cervical cancer staging, a better classification that reflects the clinical practice entered the daily use. The changes helped to estimate in which survival category the patients fit and which is the optimal treatment pathway. Multiple validation studies have shown a statistically significant improvement of five-year survival and disease-free period when the 2018 staging is applied⁽¹⁹⁻²¹⁾. In our analysis, the patients included were staged both with 2009 FIGO staging (patients from 2017 and 2018) and the 2018 FIGO staging (patients from 2019-2022). The management of the patients from the first two years of the study with suspicion of lymph node invasion or extension of the neoplasia was similar to that of patients who were staged according to 2018 FIGO staging. In further studies, we aim to re-stage the patients and report the follow-up according to the new stage.

Squamous cell carcinoma of the cervix is the most prevalent tumor and sums up to 80% of the total cervical malignancies⁽²²⁾. A lower percentage of the patients are diagnosed with adenocarcinoma, clear cell carcinoma or serous carcinoma. Although the majority of histopathological types are associated with the HPV infection, adenocarcinomas have been evaluated as non-HPV related cervical cancers⁽²³⁾. In our studied group, 79.17% of women had squamous cell carcinoma and 8.3% of women had adenocarcinoma. In one case, the histopathological diagnosis was endocervical adenocarcinoma with HPV-associated and SMILE (stratified mucin-producing intraepithelial lesion) of the uterine cervix. SMILE is classified as a rare high-grade precancerous lesion⁽²⁴⁾. The histopathological aspects include cellular stratification the same as in squamous intraepithelial lesions. In the literature, SMILE is associated with invasive squamous carcinoma or adenocarcinoma^(25,26) and has been correlated with high-risk genotypes^(26,27). In our case, the patient had high-grade endocervical adenocarcinoma, and HPV 16 and 62 were present.

One important aspect in staging and management is represented by the identification of the lymph node involvement. The classic criteria of suspicion of lymph node involvement included the dimension (larger than 10 mm – long axis, or 8 mm – short axis) and shape (round)⁽²⁸⁾. The imaging techniques can present capsular breach, lymph node necrosis or signal intensity similar to the primary tumor. This are signs of lymph node involvement with high predictive value both in MRI and CT⁽²⁹⁾. The 2018 FIGO staging increased the relevance of MRI as assessing the main tumor characteristics, parametrial and the lymph node involvement. In the meantime, CT is more frequently used in lower income countries. Although it can be used with high accuracy for advanced stages, it is not accurate without evident parametrial invasion or cervical stroma integrity⁽³⁰⁾. In our study, the clinical staging was made

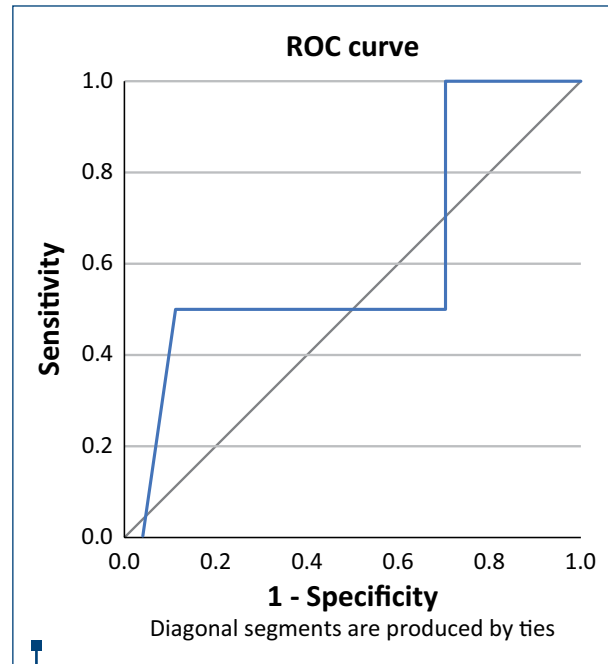


Figure 13. ROC curve for the overall discriminatory power of number of pelvic lymph node dissected in predicting nodal status (AUC=0.615)

by correlating the clinical findings with the imaging characteristics of the tumor. In our clinic, the implementation of routine MRI for cervical cancer patients was realized simultaneously with using the new FIGO staging.

The dissection of the lymph nodes is realized by removing the baring fat tissue that is adjacent to the vessels. In the literature, the median number of lymph node dissected varies from 9 to 48 nodes⁽³¹⁻³³⁾, decreasing in time⁽³⁴⁾. In low stages (IA or IB), lymph node involvement is encountered in 3.7% up to 21.7% of the patients⁽³¹⁾. In our study, in the group with primary surgery with stages IA or IB, the percentage of lymph node implication was 7.14% out of 28 women. The multidisciplinary evaluation committee recommended chemoradiotherapy followed by surgery for the women with imaging suspicion of ganglion invasion.

We consider that the multidisciplinary team and all-in-one centers can improve the patients' outcome. Bringing together all the qualified members on the medical team allows to have a panoramic view on the women's treatment path. Corroborating clinical information, ultrasound, CT, MRI, histopathology, surgical aspects, and oncological approach is in the beneficence of the patient with gynecological oncological pathology⁽³⁵⁾. Managing the potential complication that derive from the ability of the malignant disease to metastasize⁽³⁶⁾, the side effects of aggressive chemotherapy⁽³⁷⁾, the impact of extensive surgical dissection and subsequent lymphedema and maintaining the compliance of the women are all objectives of an patient-centered healthcare system.

Conclusions

Our study presents a six-year retrospective analysis that included the clinical staging, lymph node imaging evaluation, histopathological particularities, and surgical staging. The data obtained is consistent with the current literature. The analysis reveals the modification

in addressability during the COVID-19 pandemic and the change in management approach. The study of the dissection of the lymph nodes in early stages shows that an increased number of lymph nodes does not associate with an increased pathologic finding of metastatic lymph nodes. ■

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