Role of preoperative imaging in the diagnosis and planning of surgical radicality of endometrial and cervical cancer

Summary of Ph.D. Thesis

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LIST OF PUBLICATIONS related to the subject of the dissertation

I. Bús D, Nagy G, Póka R and Vajda G. Clinical Impact of Preoperative Magnetic Resonance Imaging in the Evaluation of Myometrial Infiltration and Lymph-Node Metastases in Stage I Endometrial Cancer. Pathology and Oncology Research 2021, 27:1-8. **IF: 2,826**.

II. Bús D, Nagy G, Vajda G. A preoperatív mágnesesrezonanciavizsgálat klinikai jelentősége az I. stádiumú endometriumcarcinoma myometrialis infiltrációjának és nyirokcsomó-státuszának megítélésében. Magyar Nőorvosok Lapja. 2021, 84:37-41.

LIST OF PUBLICATIONS not related to the subject of the dissertation

III. Bús D, Buzogány M, Nagy G, Vajda G. Rare virilizing granulosa cell tumor in an adolescent. Molecular and Clinical Oncology. 2017; 6:88-90.

IV. Husz V, Bús D, Vajda Gy. Extremely large epithelial ovarian cancer associated with pregnancy: A case report. Molecular and Clinical Oncology. 2018, 8:103-106

V. Bús D, Buzogány M, Nagy Gy, Vajda Gy. Menarchét követő, amenorrheát okozó ritka virilizáló granulosasejtes tumor (diagnosztikus és terápiás konzekvenciák). Interdiszciplináris Magyar Egészségügy. 2017, 7: 41-43. 3.

VI. Husz V, Bús D, Vajda Gy. Subpubicus képlet diagnózisának és terápiájának határterületi kérdései. Interdiszciplináris Magyar Egészségügy. 2017, 7: 47-50. 4.

VII. Goldfinger J, Bús D, Husz V, Nagy Gy, Tóth Z, Vernarelli F, Vajda Gy. Terhességet komplikáló kiterjedt petefészektumor. Interdiszciplináris Magyar Egészségügy. 2017, 7: 44-46. 5.

1. Abbrevations

BMI	Body mass index
CT	Computer tomography
DNS	Deoxyribonucleic acid
FIGO	International Federation of Gynecology and Obstetrics
HPV	Humán papillomavírus
IARC	International Agency for Research on Cancer
ICC	Intraclass correlation coefficient
MRI	Magnetic resonance imaging
SEER	Surveillance, Epidemiology and End Results Program
TNM	Tumor, nodes and metastasis System

2. Introduction

Gynecological cancers are the most common malignancies among women in industrialized countries. Due to a more excessive screening of cervical cancer, diagnosis is available at an early stage leading to decreased mortality, which is estimated to be 0.7% both in all cancer cases and all cancer-related deaths in 2019 in the US.

Advanced diagnostic methods and imaging modalities, such as the worldwide available MRI and CT technology, allow staging and treatment to be based on histopathological and magnetic resonance findings. Therefore, the specificity and sensitivity of these diagnostic methods is of great importance in making an appropriate diagnostic choice and in determining the radicality of the treatment.

2.1 Endometrial cancer

Endometrial cancer is the 9th most common cancer among women in developing countries. According to the National Cancer Institute SEER, IARC and the Hungarian National Cancer databases, the incidence and mortality of uterine cancer is increasing, however the 5-year relative survival rate is still around 81.2% overall, with a 95% survival rate in localized tumors – based on data from SEER 18 2009-2015.

Most cases of endometrial cancer are diagnosed in women aged between 45 and 74. Risk factors include extended hyperestrogenism (due to anovulation, nulliparity, polycystic ovarian syndrome or tamoxifen therapy), obesity (BMI>30), diabetes and hypertension. In rare cases, tumors are associated with Lynch-syndrome type II. Symptoms of the cancer are postmenopausal bleeding and premenopausal menstrual disorder.

Diagnosis is based on dilatation and curettage, minimally invasive methods (endometrial biopsy, hysteroscopy) and vaginal ultrasound scan. MR imaging is the modality of choice for staging, with CT having relatively low specificity, especially for myometrial invasion).

Endometrial cancer is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO) and TNM system which is based on histopathological characteristics, tumor grade, rate of myometrial invasion, the presence or absence of lymph-

node and distant metastases, which further determine the radicality of surgery and the required neoadjuvant and adjuvant oncologic treatment.

2.2 Cervical cancer

Cervical cancer is still the 2nd most frequently diagnosed cancer, and the 3rd cause of cancerrelated mortality among women in developing countries. However, due to specific screening methods and their increasing availability, a decreasing rate of incidence and mortality is seen in both developing and developed countries. The 5-year relative survival rate in the US is 65.8% overall, with a 91.8% survival rate in localized tumors – based on data from SEER 18 2009-2015.

Cervical cancer is usually diagnosed in women aged between 35 and 74, with a median age of 50. Its main risk factor is human papilloma virus (HPV) infection, with an increased prevalence in groups with certain epidemiologic risk factors, including first intercourse at a young age, sexually transmitted diseases, promiscuity, smoking, multiparity and chronic immunosuppression. The cancer is often asymptomatic in the early stages. The leading symptoms of an advanced cervical cancer are menstrual disorders, abnormal vaginal bleeding or discharge, postcoital contact bleeding or pain, abdominal pain and uraemia.

Diagnosis is based on cervical cytology, colposcopy guided cervical biopsy and HPV DNA testing.

The clinical staging of cervical cancer is determined by tumor size, vaginal/parametrial involvement, or distant metastasis (based on physical examination, histopathology, colposcopy, cystoscopy and MR imaging results of the uterus, kidneys, lung and skeleton. Interpretation is based on FIGO or TNM staging, which further determine the radicality of surgery and the required neoadjuvant and adjuvant oncologic treatment.

3. Material and methods

3.1 Design

In the period between 2010 and 2019, 254 radical hysterectomies and lymphadenectomies were performed at the Obstetrics and Gynecology Department of Zala County Saint Rafael Hospital due to endometrial or cervical cancer of the uterus.

Eligibility criteria included: 1. evidence of endometrial or cervical cancer of any type, grade or stage, confirmed by a preoperative endometrial or cervical sample, 2. available documentation on preoperative and postoperative cancer treatment stored in the Medical Network System database of the hospital, 3. achievable information of the preoperative clinical and imaging findings, 4. histological evaluation of endometrial or cervical cancer, 5. intraoperative findings, 6. postoperative histopathological staging and 7. data upon follow-up and treatment until the end of 2019.

Six patients were excluded from data collection due to the lack of preoperative MRI or CT findings, and 12 patients due to their missing data on follow-up.

Data collection was approved by the Ethics Committee of the Hospital.

3.2 Diagnostic algorithm

On all patients with abnormal vaginal bleeding or positive Papanicolau-smear dilatation and curettage, cervical biopsy or conization was performed. Based on a positive histopathological result of endometrial or cervical cancer, a preoperative radiological investigation was performed for local and distant cancer staging. Modalities involved magnetic resonance imaging, chest X-ray, transvaginal ultrasound and computer tomography, when necessary.

Based on radiologic staging, a multidisciplinary tumor board, consisting of an oncologist, a pathologist, a radiologist and a gynecologist, decided on the necessity of neoadjuvant oncological therapy and the radicality of hysterectomy with the possibility of involving a multidisciplinary surgical team in case local intestinal or urological metastases are found.

Staging was re-evaluated by the tumor board postoperatively, based on intraoperative and histopathological findings. A postoperative oncological therapy was designed individually for each patient.

Follow-up visits, conducted in the Department of Oncology and the Department of Gynecology, included routine physical and radiological check-ups.

3.3 Data collection

The following data were obtained from the Medical Network System database of the Hospital:

The age of the patient at the time of surgery, the surgical diagnostic methods (conization, curettage, biopsy), preoperative MRI, ultrasound or CT findings and staging, the surgical description of the radical hysterectomy and lymphadenectomy, the histopathological type and stage of the tumor, postoperative treatment (irradiation, chemotherapy), recurrence of tumor or metastases in the follow-up period, 1- and 5-year mortality.

3.3.1 Radiology findings

The preoperative MRI was performed using a Siemens Magnetom Area 1.5 Tesla device. Data required for FIGO 2009 staging were collected: the degree of myometrial, cervical, serosal, adnexal and parametrial invasion, as well as metastases of pelvic or para-aortic lymph nodes.

Preoperative CT was performed in patients with contraindications for MRI or with extreme obesity using a Siemens Somatom Definition Edge device, with iobitridol as contrast medium. Osseal and pulmonal metastases were evaluated preoperatively for staging of distant tumor-spread.

Transvaginal ultrasound was performed using a GE Voluson E6 device with a multifrequency endovaginal probe (5-8 MHz); it had a role in evaluating cervical stroma infiltration, endometrial thickness and structure, adnexal and parametrial invasion, endometrial color-flow index and vascularization of the masses.

3.3.2 Surgical treatment

Indication for surgery was based upon preoperative histological and radiological findings, indicated by the Multidisciplinary Tumor Board of the institution, which involves specialists of radiology, oncology, pathology and gynecology.

Abdominal, laterally extended radical hysterectomy was in all cases performed by a gynecologist and a urologist specialist trained in oncosurgery.

Radical hysterectomy involved the removal of cervix, uterus, Falloppian tubes and ovaries, together with the parametria and upper vagina, followed by parailiacal and pelvic/obturator lymphadenectomy in the pelvic retroperitoneal space.

3.3.3 Histopathological evaluation

Macroscopic and microscopic histopathological evaluation of the surgical specimen was performed. Findings included the description of the type of tumor, differentiation, TNM and FIGO

staging based on the extent of infiltration, and the presence or absence of parametrial, cervical, adnexal, rectal and cystic involvement, lymph-node and pelvic wall invasion.

3.4 Statistical analysis

The age at the time of surgery, prevalence of different tumor histological subtypes, tumor grades and differentiation were taken into account at analysis. The 1- and 5-year survival rates were calculated accounting for deaths occurring before December 2019.

The results of the preoperative radiology staging were compared with the final histological analysis of the surgical specimen, using $\chi 2$ or Fisher's exact test to compare variables. P-values < 0.05 were considered to be significant. The sensitivity, specificity, positive- and negative predictive values of the preoperative assessment were calculated for each endpoint, together with 95 % confidence intervals (95 % CI). The percentage of the underdiagnosed or overdiagnosed cases and accuracy rate in terms of stage, local invasion and lymph-node metastases were also calculated.

All data were collected in an Excel database, and they were analyzed using SPSS statistical software. The intraclass correlation coefficient (ICC) and Cohen's kappa value was used to determine the inter-rater agreement of the overall results concerning myometrial invasion and lymph-node metastases, and to evaluate the role of experience between radiologic evaluators. ICC and Cohen's kappa below 0.50 was considered as poor, between 0.50 and 0.75 as moderate, between 0.75 and 0.90 as good, and above 0.90 ICC it was considered as excellent inter-rater reliability. SPSS software (ver. 25; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses, and p-values < 0.05 were considered to be significant.

4. Results

4.1 Endometrial cancer

A total of 148 patients with a final histopathological diagnosis of endometrial cancer were enrolled in this study. All patients have undergone dilatation and curettage for endometrial sampling, those with a positive result were followed by MRI staging of the tumor. Based on the decision of a multidisciplinary tumor board, radical hysterectomy with paraaortic and pelvic lymph-node dissection was performed. Pathologists used macroscopic and microscopic evaluations on hysterectomy, tumor histologic subtype, grade, depth of myometrial invasion and lymph-node

positivity were examined. The tumor board evaluated the postoperative results and final stages, according to the FIGO 2009 classification, to determine the optimal treatment for the patient.

The age, menopausal status, body mass index and mortality of the patients were collected and postoperative histologic findings were analyzed.

The overall accuracy of MRI evaluating the correct staging was 75%, with good interrater reliability. Rates of overdiagnosis were 10.8% and underdiagnosis 14.3% of the cases. The accuracy of MRI for the detection of lymph-node in all stages status was 74.3%, and its sensitivity, specificity, PPV, and NPV were 53.8%, 78.7%, 35%, and 88.9%, respectively, with poor inter-rater reliability. False negative results were 8.1%, false positive were 17.6% of the cases.

In stage I cancers, the accuracy of MRI regarding stage was 93.8%, with an underestimation in 6.2% of the cases. The accuracy of MRI for the detection of myometrial invasion in stage I cancers was 70.1%, and its sensitivity, specificity, PPV, and NPV were 80.0%, 61.5%, 64.3%, and 78%, respectively, with moderate inter-rater reliability. The rates of overdiagnosis were 20.61%, underdiagnosis were 9.27%. The accuracy of MRI for the detection of lymph-node in stage I cases was 77.3%, and its sensitivity, specificity, PPV, and NPV were 28.6%, 81.1%, 10.5%, and 93.6%, respectively, with poor inter-rater reliability. False negative results were 5.2%, false positive were 17.5% of the cases.

In stage II cancers, the accuracy of MRI regarding stage was 32.1%. The MRI staging was underestimated in 11 and overestimated in 8 of the cases. The accuracy of MRI for the detection of lymph-node in stage II cases was 60.7%, and its sensitivity, specificity, PPV, and NPV were 44.4%, 68.4%, 40%, and 72.2%, respectively with poor inter-rater reliability. There were 6 false positive and 5 false negative lymphnode status.

In advanced, stage III and IV cancers, the accuracy of MRI regarding stage was 52.38. The MRI staging was underestimated in 47,61% of the cases.

The accuracy of MRI for the detection of lymph-node in advanced stages cases was 80.95%, and its sensitivity, specificity, PPV, and NPV were 80%, 81.8%, 80%, and 81.8%, respectively, with good inter-rater reliability. There were 2 false positive and false negative cases as well.

In order to analyze the role of the rater evaluating the MRI findings, we divided the specialists into two groups: a radiologist specialized in imaging of gynecological tumors and a subgroup of nonspecialized evaluators.

A radiologist specialized in the evaluation of gynecological imaging staged 94 of the cases. The accuracy of overall staging was 75.5%, with good inter-rater reliability.

In the second rater group, four radiologist of average experience in the evaluation of gynecological imaging staged 54 of the cases. The accuracy of overall staging was 74.07%, with moderate inter-rater reliability. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated for the assessment of myometrial invasion and for the detection of lymphnode metastases, with evaluation of the corresponding inter-rater reliability for each sub-group.

4.2 Cervical cancer

A total of 88 patients with a final histopathological diagnosis of cervical cancer were enrolled in this study. Patients have undergone conization due to abnormal citology result, or were diagnosed by dilatation and curettage. The positive result was followed by MRI staging of the tumor. Based on the decision of a multidisciplinary tumor board, radical hysterectomy with paraaortic and pelvic lymph-node dissection was performed. Pathologists used macroscopic and microscopic evaluations on hysterectomy specimen, tumor histologic subtype, grade,

depth of stromal and parametrial invasion as well as lymph-node positivity were examined. The tumor board evaluated the postoperative results and final stages according to the FIGO 2009 classification to determine the optimal treatment for the patient.

The age, menopausal status, body mass index and mortality of the patients were collected and postoperative histologic findings were analyzed.

The overall accuracy of MRI evaluating the correct staging was 61.4%, with the rates of overdiagnosis in 28 and underdiagnosis in 6 of the cases, with poor inter-rater reliability Sensitivity, specificity, PPV, and NPV were 87.5%, 68.6%, 70% and 86.8%, respectively. The accuracy of MRI for the detection of lymph-node status was 67%, and its sensitivity, specificity, PPV, and NPV were 58,6%, 71,2%, 50%, and 77.8%, respectively, with good inter-rater reliability. False negative results were 13.6%, false positive were 19.3% of the cases.

In stage I cancers, the accuracy of MRI regarding stage was 61.8%, with an underestimation in 13 cases (38.2%). The accuracy of MRI for the detection of stromal invasion was 79.4%, and its sensitivity, specificity, PPV, and NPV were 80%, 75%, 96%, and 33.3%, respectively, with moderate interrater reliability. The rates of overdiagnosis were 2.9%, underdiagnosis were 17.6%. The accuracy of MRI for the detection of lymph-node in stage I cases was 70.6%, and its sensitivity, specificity, PPV, and NPV were 66.7%, 71.4%, 33.3%, and 90.9%, respectively, with poor inter-rater reliability. False negative results were 5.9%, false positive were 23.5% of the cases.

In stage II cancers, the accuracy of MRI regarding stage was 72.7%. MRI staging was underestimated in 15.1% and overestimated in 12.2% of the cases. The accuracy of MRI for the detection of lymph-node in stage II cases was 54.5%, and its sensitivity, specificity, PPV, and NPV were 58.8%, 50%, 55.6%, and 53.3%, respectively, with poor inter-rater reliability. False negative results were detected in 21.2%, false positive in 24.2% of the cases.

In advanced, stage III and IV cancers, the accuracy of MRI regarding stage was 85.7%. The MRI staging was underestimated in 14.3% of the cases. The accuracy of MRI for the detection of lymph-node in advanced stages was 50%, and its sensitivity, specificity, PPV, and NPV were 60%, 50%, 75%, and 33.3%, respectively, with poor inter-rater reliability There were 2 false negative and 1 false positive lymph-node detection.

In order to analyze the role of the rater evaluating the MRI findings, we divided the specialists into two groups: a radiologist specialized in imaging of gynecological tumors and a subgroup of nonspecialized evaluators.

A radiologist specialized in the evaluation of gynecological imaging staged 55 of the cases. The accuracy of overall staging was 60%, with good inter-rater reliability.

In the second rater group, four radiologist of average experience in the evaluation of gynecological imaging staged 33 of the cases. The accuracy of overall staging was 63.6%, with also with good inter-rater reliability. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated for the assessment of myometrial invasion and for the detection of lymph-node metastases, with evaluation of the corresponding inter-rater reliability for each subgroup.

5. Discussion and conclusion

Gynecological cancers are the most common tumors among women in the developed world. Due to a more excessive screening, diagnosis is available at an early stage. Furthermore, advanced diagnostic imaging methods allow appropriate preoperative staging, therefore the radicality of surgery and adjuvant therapy can be more tailored to the patient and the tumor-spread.

In this study we analyzed the reliability of preoperative MRI findings in the staging of endometrial and cervical cancer, as well as the clinical characteristics of patients underwent radical hysterectomy and the histopathologic evaluation of their tumor.

The results of the preoperative radiology staging were compared with the final histological analysis of the surgical specimen. The sensitivity, specificity, positive- and negative predictive values of the preoperative assessment were calculated for each endpoint. The percentage of the underdiagnosed or overdiagnosed cases and accuracy rate in terms of stage, local invasion and lymph-node metastases were also evaluated.

In order to analyze the role of the rater's expertise assessing the MRI findings, we divided the specialists into two groups: a radiologist specialized in imaging of gynecological tumors and a

subgroup of non-specialized evaluators. Inter-rater agreement was calculated to determine the conformity of pre- and postoperative staging.

Based on our results, we report similar findings as found in international literature. MRI is the method of choice in the terms of evaluating overall staging, as well as myometrial and stromal invasion, as its specificity and negative predictive value is rather high. Our studies showed that the diagnosis of lymph node metastases is difficult with MRI modality, since hyperplastic and metastatic nodes cannot be easily differentiate leading to high percentage of false positive results, therefore other imaging modalities can be used for more accurate evaluation.

We have also found that raters with more expertise in gynecological imaging provide a more consistent evaluations of staging, local invasion and finding lymph node metastases, however the difference between inter-rater agreements was not significant between the groups.