

The benefits and limitations of modern imaging methods (CT, MRI, PET/CT) in gynecologic oncology

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Review article

Abstract

The aim of this review is to demonstrate the optimal use of modern imaging methods (CT, MRI and PET/CT) in the preoperative staging, therapeutic management and follow-up of gynecological cancer patients (neoplasm of cervix, uterus and ovary). We present an overview of the advantages and limitations of modern imaging modalities that are complementary to ultrasound, which remains the first choice in gynecology. The review should be used as a guide for gynecologists and oncologists on how to use the methods effectively.

Key words: CT, MRI, PET/CT, cervical carcinoma, endometrial carcinoma, ovarian carcinoma

PŘÍNOS A LIMITY MODERNÍCH ZOBRAZOVACÍCH METOD (CT, MR, PET/CT) V ONKOGYNEKOLOGII

Přehledový článek

Abstrakt

Cílem je ukázat optimální využití počítačové tomografie (CT), magnetické rezonance (MR) a PET/CT (fúze počítačové emisní tomografie a CT) v předoperačním (klinickém) stagingu, plánování léčby a dispenzarizaci onkogynekologických pacientek se zhoubnými nádory děložního hrdla, těla a ovarií. Podáváme přehled o možnostech a limitech jednotlivých zobrazovacích modalit komplementárních k ultrazvukovému vyšetření, které zůstává metodou první volby v zobrazování v gynekologii. Práce by měla být vodítkem pro kliniky, jak využívat dané techniky efektivně.

Klíčová slova: CT, MR, PET/CT, karcinom děložního hrdla, karcinom endometria, karcinom ovaria

Introduction

Ultrasound examination (US) remains the first choice method in examination of the pelvis and diagnostics of gynecological cancer. Its advantage lies in wide accessibility, good tolerance by the patient without known risks or contraindications, and – last but not least – high tissue resolution in imaging gynecological pelvic organs. Other modern imaging techniques are indicated as complementary methods to ultrasound where their findings would have an effect on the therapy. This review deals with choosing the appropriate complementary imaging method.

Magnetic resonance (MRI) provides detailed information on the anatomy of pelvic organs. It is a method of choice where the ultrasound examination of the pelvis is suboptimal or non-diagnostic, namely in detecting relapses after radiation therapy and in assessing postoperative complications. In the staging in gynecological oncology, MRI is most frequently used for cervical carcinoma, in particular where an experienced sonographer is not available to carry out the imaging of the affected cervix, parametria and closest nodes. In the staging of malignant tumors of the uterus, MRI is used in the event of suboptimal acoustic conditions, mostly where acoustic shadowing of myomas makes it impossible to image the junction zone optimally and determine the invasion of the tumor into myometrium or cervix. Also, a complementary MRI of uterus is often carried out before a fertility-preserving treatment of cervical carcinoma to exclude the invasion in myometrium. In imaging and diagnosing ovarian carcinoma, ultrasound examination by an experienced sonographer is the most exact modern imaging method (1). Only in exceptional cases is it complemented by MRI examination in differential diagnostics to distinguish endometrial cysts from dermoids or mucinous cystadenomas, as these tumors are usually easily and correctly assessed within an ultrasound examination. Furthermore, MRI is indicated where the origin of pelvic tumors is unclear. It is also necessary to mention contraindication of MRI for patients with a cardio stimu-

lator, cochlear implant or magnetic metal implants in the body.

Computer tomography (CT) is not a suitable technique for imaging early-stage gynecological tumors due to its low tissue resolution (2). On the other hand, it has a place in the clinical staging of advanced gynecological tumors and in monitoring the response to their treatment. Importantly, compared to ultrasound and MRI, with CT there is a higher radiation dosage, which is associated with certain risk of origination of malignity. Therefore each CT examination must be justified by the expected benefit for the patient, since the number of CT scans carried out generally grows and these are often carried out without a substantiated indication (3). CT and MRI scans are also used to plan radiotherapy, providing a visual basis for delineation of the target volume for external radiotherapy as well as brachytherapy. The limitations of MRI and CT scans in diagnosing relapses lie in their inability to distinguish adequately between viable tumor tissue and postoperative and postradiation changes connected with oncology therapy.

Positron emission tomography as a functional method, combined with CT as a morphological method (**PET/CT**), is an optimum method in diagnostics and the therapeutic management of relapses of gynecological tumors, as it makes it possible to find a viable tumor tissue, and – unlike PET by itself – to exactly specify its localization. It may also be beneficial in finding the primary source of the disease for disseminated tumors or where duplicity of the tumor is detected. PET/CT is also used in clinical staging and restaging of gynecological tumors, particular where the conclusions of the other imaging techniques are ambiguous. It should be noted that PET/CT is not a suitable staging method for early stages of the disease and may lead to false positive findings during physiological changes to uterus and ovaries in fertile women (4). A precondition of correct interpretation of PET/CT is main-

Tab. 1 Summary of optimum use of imaging methods in gynecologic oncology

Ultrasonography (TVUS, TRUS, TAS)	Magnetic Resonance Imaging (MRI)	Computer Tomography (CT)	Positron Emission Tomography/Computer Tomography (PET/CT)
Assessment of early and advanced stages of the disease, lymph glands, presence of metastases. Navigation in biopsy procedures.	Assessment of early stages of the disease for tumors of the cervix and uterus, local spreading of tumors into surrounding organs and closest lymph nodes, detection of metastatic lesions. Diagnostic of unclear adnexal lesions. Endometriosis. Planning of radiotherapy. Diagnostics of relapse.	Assessment of advanced disease, affected lymph nodes, metastases. Planning of radiotherapy. Monitoring response to therapy. Diagnostics of relapse. Navigation in biopsy procedures and radiofrequency ablation (RFA).	Determining relapse. Staging of gynecological tumors, especially detection of infiltrated nodes and other metastases. Complementary method in the event of ambiguous conclusions of other imaging techniques (distinguishing between benign and malignant lesions). Assessment of response to therapy. Detection of occult primary tumor where metastases are known.

(TVUS – transvaginal ultrasound examination, TRUS – transrectal ultrasound examination, TAS – transabdominal ultrasound examination)

taining a sufficient time interval between previous therapy and the examination. The recommended interval for PET/CT is at least 6 weeks after the operation and 3 months after completing radiation therapy. Generally, the longer the time interval between previous therapy and the examination, the higher the reliability; otherwise, positive artefacts may originate at the places of radiation or operation. Chemotherapy generally reduces the cancer cells' ability to utilize glucose ("stunning effect"), and the minimum delay after completing chemotherapy is 2 weeks. **Tab. 1** shows a brief summary of optimum use of modern imaging methods in gynecological oncology.

Tumors of the cervix

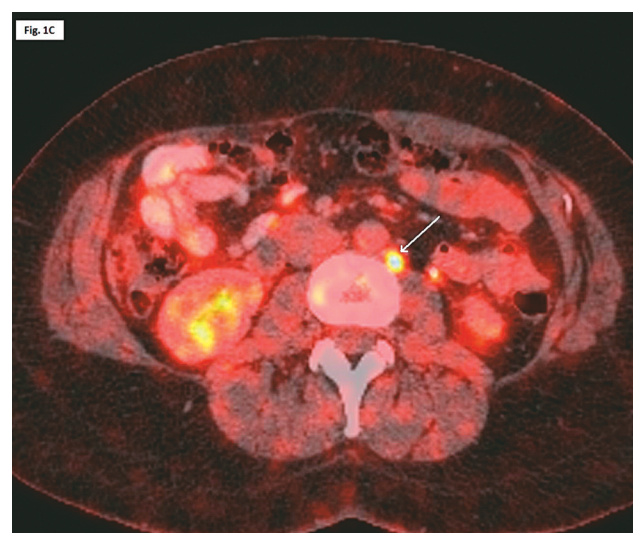
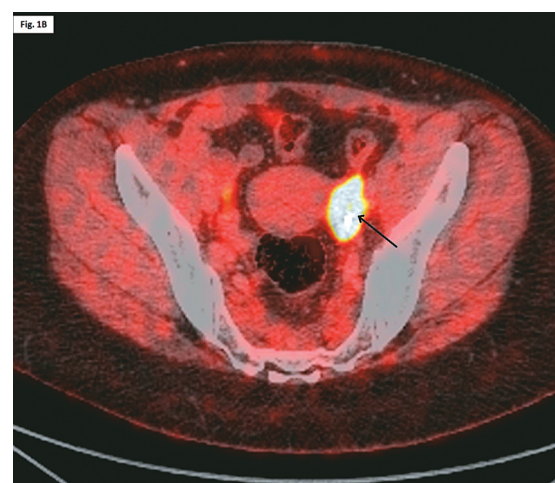
Cervical cancers are the largest group indicated in gynecology for MRI examination. MRI is suitable for staging of malignant tumors verified by biopsy, rather than for primary diagnostics. The more advanced the stage of the disease, the more reliable the MRI diagnostic. Similarly as in the initial staging by ultrasound examination, magnetic resonance determines the volume of the tumor, its distance from the internal orifice in fertility preserving operations, assesses the depth of stromal tumor invasion and its distance from pericervical fascia. The most common indication for MRI is to determine parametrial invasion. However, a recent prospective multicentric study by Epstein E et al. proved that US is significantly better than MRI in recognizing parametrial invasion (5). Compared with the final histology results, US showed significantly higher accuracy in determining parametrial invasion (accuracy 97%, sensitivity 77%, specificity 98%); MRI achieved accuracy of 90% (sensitivity 69%, specificity 92%). US was also significantly better in detecting a residual tumor: compared with the final pathology finding, its accuracy was 96% (sensitivity 90%, specificity 97%), while MRI achieved accuracy of 86% (sensitivity 67%, specificity 89%). The accuracy of MRI diagnostics could be increased by applying a contrast substance i.v. and a dynamic post-contrast technique (6), using 3T equipment (Tesla), and also by using diffusion weighted imaging (DWI). DWI assessment is based on the fact that malignant tumors are highly cellular and have a small extracellular space; therefore diffusion is restricted in the tumor and DWI signal is increased, while the signal in ADC (apparent diffusion coefficient) maps is low. DWI may contribute to determining the grade of differentiation of the tumor (grading) and to assessing the effect of therapy (7,8). In FIGO stages III and IV, MRI is very good in imaging propagation to the surrounding organs, vagina and posterior bladder wall, anterior rectum wall or pelvic floor. It also images regional lymph nodes. A diagnostic criterion for a pathological node is 10 mm in the short axis, long to short ratio (L/S ratio) ≤ 2 (9), which causes lower sensitivity in the examination due to the presence of malignant cells even in nodes that are not enlarged. A relatively new method PET/MRI – Positron Emission Tomography combined with Magnetic Resonance Imaging seems rather promising.

Compared to MRI, the significance of CT scan is substantially lower for cervical cancer. The limitation of CT is its lower tissue contrast and difficult assessing of local spreading of the tumor; most studies show that US and MRI are more accurate than CT in assessing local spread-

ing of the tumor. In practice, CT is only used for locally very advanced tumors of the cervix – with propagation to the bladder, rectum and vaginal wall.

It is, however, highly beneficial in diagnostics of affected retroperitoneal and distant (mediastinal) nodes and other metastases. For cervical cancer patients, PET/CT has higher ability than CT and MRI to detect spreading into

Fig. 1 Recurrence of cervical tumor in left iliac region. **A)** MRI axial plane, **B)** PET/CT axial plane, **C)** infiltrated left paraaortal node at the level of L2 PET/CT, axial plane



lymph nodes (most often pelvic, paraaortic and supraclavicular) and distant metastases (10,11). Loft A et al. in their study comparing PET/CT with histopathology results and/or a follow-up determined sensitivity and specificity of PET/CT at 75% and 96% respectively, a negative predictive value of 96%, positive predictive value of 75% (12). False negativity of results is mainly due to micrometastases, which are beyond the distinguishing ability of today's scanners; false positivity is caused mostly by inflammatory lymphadenopathy (13). Because of the particular clinical importance of detecting infiltrated nodes, PET/CT is now recommended for cervical tumors as a standard method for staging of the disease for patients planned for primary treatment by chemo-radiotherapy where no diagnostic staging laparoscopy with histology of closest nodes was carried out (recommendation of the National Comprehensive Cancer Network, NCCN). Another indication for PET/CT is diagnostics of relapse. In diagnosing the recurrent disease, FDG-PET achieves higher sensitivity and specificity (96% and 95%) than CT and MRI (14). False positive FDG-PET findings are mostly caused by incorrect interpretation of inflammatory complications of the therapy.

Tumors of the uterus

Due to the high tissue resolution of ultrasound, MRI is indicated on an exceptional basis, as a facultative examination to exclude myometrial invasion, for instance before initiating fertility preserving treatment of endometrial carcinoma or in suboptimal acoustic conditions. It is indicated to assess the depth of the invasion to the myometrium of the uterus (disruption of junction zone), propagation of the tumor into the stroma of the cervix, and also to assess extrauterine invasion. It also assesses possible metastases in the vagina and infiltration of the bladder wall and rectum. MRI also detects infiltrated regional/pelvic, paraaortic and inguinal nodes. For endometrial cancer, application of a paramagnetic contrast substance makes the diagnostics significantly more accurate, as it increases the contrast between the uterine muscles and the infiltrating tumor tissue, making the assessment in the terrain of myomatosis or adenomyosis easier. Dynamic post-contrast MRI has an accuracy of 85 – 95% in predicting myometrial invasion, and 82 – 91% in predicting affectation of the cervix (16). In determining the depth of the invasion, the issues are: natural involution of the uterus in post-menopause followed by atrophy of myometrium, myometrial thinning on the basis of distension of uterine cavity by a large exophytic tumor, location of the tumor in uterine corners, pyo- or hematometra, adenomyosis or myomatosis (17–19). Similarly, it is difficult to distinguish a simple protrusion of the tumor into the cervical canal without invading the mucosa from stromal infiltration of the cervix (18). Similarly as with tumor infiltration of the cervix, CT is not a method of choice for early stages of the disease (20,21). In gynecologic oncology, it is used primarily for advanced tumors, to determine the local spreading of the tumor, affectation of retroperitoneal nodes and parenchymatous organs (liver, lungs). Neither CT nor PET/CT have as much significance for clinical staging before the therapy for malignant tumors of the uterus as they do for malignant tumors of the cervix

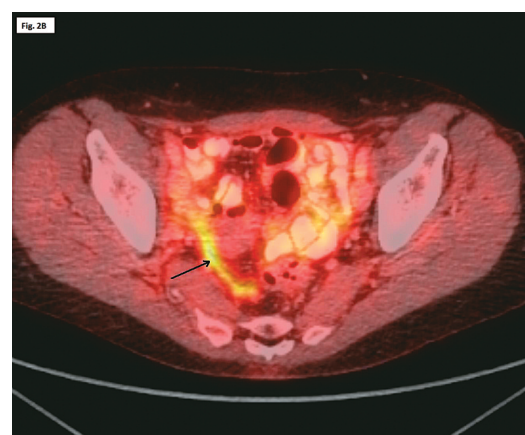
and ovaries. For endometrial carcinoma, imaging methods have rather low sensitivity in detecting metastatic affectation of nodes, as at the time of the first diagnosis of the disease the affectation of nodes is often micrometastatic. Therefore, based on the FIGO recommendation from 1988, staging of the malignant tumors of the uterus is based on surgical staging (22). Selection of patients for the more or less extensive surgical staging is based on preoperative prediction of the risk of affectation of lymph nodes. The risk of lymph nodes being affected is influenced by the depth of the tumor invasion into the myometrium, cervix, histological grading, and histotype of the disease.

The main task of imaging methods therefore remains to determine the depth of the invasion in the myometrium and stroma of the cervix, where ultrasound or MRI remain methods of choice

Tumors of the ovaries

Presently we have sufficient data confirming ultrasound examination as the ideal imaging method in diagnosing benign and malignant tumors of ovaries (4,23). MRI is a method of choice for unclear adnexal lesions, where it may enable identification of the origin of the lesion (for instance, distinguishing subserosal myoma from ovarian fibroma), contributing to specific diagnostics (endometrial or dermoid cyst) and differential diagnostics of benign and malignant lesions (cystic, cystic-solid, solid). In the hands of an experienced radiodiagnostician, MRI has high

Fig. 2 Relapse of ovarian carcinoma in the area of mesocolon sigmoideum. **A)** CT axial plane, **B)** PET/CT axial plane



accuracy in determining benign and malignant ovarian tumors (83–93%) (24).

CT is indicated for staging, assessing the effect of neo-adjuvant therapy, and diagnostic of relapse of the disease. CT may also be indicated for suspected dermoid cysts, where it reliably images fat, teeth or bones. It is used for navigating in biopsy procedures. CT is most frequently used for advanced ovarian tumors, to determine the extent of the disease.

In the study by Forstner R et al., CT achieved sensitivity and specificity of 50% and 92% in preoperative staging of ovarian cancer (25). The possibilities of CT are limited especially in detecting small deposits of cancer in the small intestine; due to low tissue resolution, CT is not a suitable method for differential diagnostic of pelvic tumors.

PET/CT is nowadays considered the optimum method in the diagnostics of relapse of ovarian carcinoma. It is indicated in particular for patients with dynamically growing levels of CA-125 tumor marker where the results of other imaging methods were negative. For patients with clinical suspicion of relapse, PET/CT shows accuracy and sensitivity of 81.8% and 83.3% in detecting relapse > 1 cm (26). In meta-analytical comparison of the benefits of PET/CT, MRI and CT in detecting tumor relapse, PET/CT had the best results (sensitivity 91%, specificity 88%); CT and MRI showed sensitivity of 79% and 75% and specificity of 84% and 78% (27). PET/CT is better at imaging peritoneal implantation metastases based on accumulation of FDG in subdiaphragmatic and subhepatic region, or small infiltrations in the node; the method is also better at distinguishing possible postoperative changes (seromas). Another possible use of PET/CT is in preoperative staging of ovarian tumors, in particular in detecting extraabdominal metastases. Castelluci et al. compared PET/CT and CT: PET/CT staging agreed with the final pathological finding in 69% of cases, CT in 53% (28). A limitation of a wider use of PET/CT is the cost of the examination, worse accessibility and considerable radiation stress.

Another possibility of using PET/CT is to monitor early response to therapy. Standard Utilization Values (SUV) are used as an indicator, calculated from radioactivity of the tumor after injection of fluor isotope (18F-FDG, 2-deoxy-2-[fluorine-18] fluoro-D-glucose), depending on body mass and physical condition. CT and MRI have a lower utilization in early assessment of therapy, as anatomical diminution takes time (29).

PET/CT is not an ideal method in differential diagnostic of ovarian tumors. The imaging of lesions with less cells and a higher cystic component or with presence of necrosis is problematic. Due to the prevalence of the cystic component in borderline tumors or well-differentiated ovarian carcinomas, these may be incorrectly interpreted as benign and may be the cause of false negative findings (30,31). Another cause of false negative findings are micro-metastases in lymph nodes and the small size of the lesion; diagnostic of small peritoneal tumor implantations on intestines is especially difficult. Reliable detection may be expected for accumulating tumors up from the size of 10 mm (literature mentions ≥ 5 mm). False positive findings are mainly due to inflammations (tubo-ovarian abscess) and inflammatory response after therapy. False positivity may also be caused by some be-

nign affectations, such as cystadenomas, endometrial or dermoid cysts, pedunculated myomas, etc. In healthy women, findings may be falsely positive for instance in uterine lining at the time of ovulation or menstruation, or in ovaries during ovulation. Local findings therefore always have to be correlated with the menstrual cycle. An ideal time for the examination is either before or after the menstruation phase. An alarming sign of possible malignity is the accumulation of radio-pharmaceuticals in postmenopausal women (4).

Conclusion

Modern imaging methods have become an inseparable part of gynecological oncology, as timely diagnostics and exact preoperative staging are a precondition of optimal treatment of malignant tumors. They are also significant in monitoring the response to therapy, follow-up of gynecological cancer patients, and navigation in minimally invasive diagnostic and therapeutic procedures. Imaging methods should be indicated rationally, considering whether the examination will be beneficial for the patient and whether it may have an effect on the treatment procedure. In many cases, unnecessary engagement of numerous diagnostic methods leads to delays, stress for the patient and extra financial costs. **MRI** is the method of choice for examinations of the pelvis where ultrasound is suboptimal or non-diagnostic; it is also indicated where the origin of the pelvic tumor is unclear and before planning fertility-preserving therapy for malignant tumors of the uterus. **CT** is suitable mainly for staging and assessing the effect of therapy. **PET/CT** is the optimum method in the diagnostics of relapses of gynecological tumors. For cervical cancer, PET/CT is recommended for staging of the disease, because of the clinical importance of detecting infiltration of nodes.

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