

Reliability of preoperative investigations in the treatment of endometrial cancer at the University Medical Centre Ljubljana

Zanesljivost preiskav, ki se izvajajo pred operacijo, za načrtovanje zdravljenja raka endometrija v UKC Ljubljana

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Abstract

Background: Slovenian recommendations for the diagnosis, treatment and follow-up of patients with endometrial carcinoma recommend a varied extent of surgical evaluation of disease progression: standard hysterectomy and adnexectomy without lymphadenectomy or with only sentinel lymph node biopsy respectively, or concomitant complete pelvic and para-aortic lymphadenectomy. Classification of patients into risk groups of disease progression outside uterus is based on histological grading and the assessment of the depth of myometrial invasion and cervical stromal invasion by image analysis, and is crucial for planning the extent of surgery. The objective of our study was to define the reliability of preoperative investigations of endometrial carcinoma treatment.

Methods: Data of 79 patients with histologically confirmed endometrial cancer, who underwent expert transvaginal ultrasound (TVUS) examination in the period between January 2016 and September 2017 at The Division of Gynaecology and Obstetrics at the University Medical Centre Ljubljana, were analysed. Preoperative histological diagnosis and TVUS evaluation of myometrial invasion and cervical stromal invasion were compared with the definite histological report.

Results: The ultrasound evaluation of myometrial invasion reached a sensitivity of 76% (95% CI, 58–89%) and specificity of 81% (95% CI, 67–91%). The sensitivity of ultrasound evaluation of cervical stromal invasion was indicated to be 54.5% (95% CI, 23–83%) and specificity 75% (95% CI, 63–85%). The histological differentiation grade was postoperatively upgraded in 11.3% and downgraded in 7.5%. Using kappa coefficient to interpret the consistency of preoperative findings with postoperative ones, the results were 0.699 for histology, 0.564 for invasion into the myometrium and 0.203 for invasion into the cervical stroma. One patient was surgically over-treated; in all others staging was adequate.

Conclusions: Preoperative histological results in our study were most reliable, while TVUS proved moderately reliable in estimating myometrial invasion and poorly reliable in estimating cervical stromal invasion.

Izvleček

Izhodišča: Slovenska priporočila za obravnavo bolnic z rakom endometrija svetujejo različnih obseg preiskav za kirurško oceno o napredovanju bolezni glede dileme, ali ob standardni odstranitvi maternice s priveski opustiti limfadenektomijo oz. opraviti zgolj biopsijo varovalne bezgavke, ali pa opraviti kompletno pelvično in paraaortno limfadenektomijo glede na stopnjo tveganja za širjenje bolezni zunaj maternice. Bolnice razvrstimo v različne skupine glede tveganja na podlagi

histološkega gradusa po biopsiji maternice ter glede na slikovno oceno razširjenosti bolezni (magnetno resonančno slikanje ali ekspertna ultrazvočna preiskava). V Univerzitetnem kliničnem centru Ljubljana smo leta 2015 uvedli ekspertno ultrazvočno preiskavo (TVUZ) za oceno razširjenosti rakavih bolezni. Naš namen je bil oceniti zanesljivost preiskav, ki jih opravimo ob diagnozi raka endometrija v UKC Ljubljana pred operacijo.

Metode: Pregledali smo dokumentacijo 79 bolnic s histološko potrjenim rakom endometrija, ki so opravile TVUZ od januarja 2016 do septembra 2017. Histološko diagnozo pred posegom in oceno razrasta (invazije) s TVUZ v miometriju in stromo materničnega vratu smo primerjali s končnim histološkim izvidom.

Rezultati: Ultrazvočna ocena razrasta (invazije) raka v miometriju je imela 76 % (95 % IZ, 58 – 89 %) občutljivost in 81 % (95 % IZ, 67 – 91 %) specifičnost. Ultrazvočna ocena razrasta raka (invazije) v stromo materničnega vratu je imela 54,5 % (95 % IZ, 23 – 83 %) občutljivost in 75 % (95 % IZ, 63 – 85 %) specifičnost. Ocena histološke stopnje diferenciacije je bila po operaciji višja (*angl.* upgrading) v 11,3 %, nižja (*angl.* downgrading) pa v 7,5 %. Ocena ujemanja preiskav pred operacijo z dokončnim izvidom z uporabo koeficienta kappa je bila za histopatološko preiskavo 0,699, za razrast v miometriju 0,564 in za razrast v stromo materničnega vratu 0,203. Ena bolnica je prestala na osnovi izvidov pred operacijo preobsežno zamejitveno operacijo; ostale pa so bile ustrezno kirurško obravnavane.

Zaključki: Kot najbolj zanesljiva se je izkazala patohistološka preiskava, sledi ji ultrazvočna ocena razrasta (invazije) v miometriju, medtem ko je bila ultrazvočna ocena razrasta (invazije) v stromo materničnega vratu manj zanesljiva.

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1 Introduction

Endometrial carcinoma—International Classification of Diseases (ICD-10) code C54—is the most common malignant tumour of the female reproductive system in the developed world, including in Slovenia, with an estimated incidence of 33.2/100,000 (1,2). The incidence rate has been increasing due to the obesity epidemic and longer life expectancy (3). Most patients (75%) are diagnosed in the early stages of the disease (FIGO stages I and II) and the 5-year survival rate is 74–91% (4). The standard treatment is with surgery – hysterectomy and adnexectomy

and includes surgical staging (5). The most important prognostic factor in endometrial carcinoma is metastasis to the regional lymph nodes. Histopathological factors in the uterus, such as the depth of myometrial invasion, histological differentiation grade, lymphovascular invasion and cervical stromal invasion, increase the risk for regional lymph node metastasis (6–9).

Patients with a preoperative estimated depth of myometrial invasion < 50% of total myometrium thickness and good (G1) or moderate (G2) histological

differentiation of endometrial carcinoma are in the low-risk group for regional lymph node metastasis. Patients with > 50% myometrial invasion and good (G1) or moderate (G2) differentiation are in the moderate-risk group for regional lymph node metastasis. According to ESGO-ESTRO-ESMO guidelines from 2015, patients with low- or moderate-risk carcinoma (endometrioid adenocarcinoma G1 and G2, without lymphovascular invasion, or myometrial invasion up to 50% or more, but limited to the uterus) have a roughly 1% risk of regional lymph node metastasis (10). Lymphadenectomy is thus not warranted as it does not have a therapeutic effect (10,11,12). In endometrial carcinoma with a high risk of regional lymph node metastasis (Slovenian recommendations: stage IA and IB endometrioid type G3, stage II, stage III – endometrioid type, without disease remnants, non-endometrioid type), surgery includes para-aortic lymphadenectomy up to the renal vasculature and infracolic resection of the omentum (in serous histopathologic type) in addition to pelvic lymphadenectomy (11,13).

Lymphadenectomy lengthens the duration of surgery and is a risk for significant bleeding. Sequelae also include lower limb lymphoedema and lymphocysts (14). As per the literature, the incidence of lymphoedema is 5–38% (15,16). The compromise between standard pelvic lymphadenectomy, which was in use until 2015, and omission of lymphadenectomy in patients with low and moderate risk, is sentinel lymph node biopsy. If it is negative, it is presumed that there are no metastases in other lymph nodes. By evaluating the presence of disease in the sentinel lymph node, we fulfil the demands of surgical staging and lower the incidence of complications associated with lymphadenectomy (17). The algorithm for

sentinel lymph node biopsy is mentioned in the National Comprehensive Cancer Network (NCCN) and ESGO-ESTRO-ESMO guidelines as a promising treatment option (5,13,17). Sentinel lymph node biopsy also enables an individualized approach to treating patients with endometrial carcinoma and increased safety if pelvic lymphadenectomy is omitted in patients with low and moderate risk for disease recurrence. Selecting the patients for such an omission is a diagnostic challenge as the histological differentiation grade can be upgraded by 19% and upstaged by 18% after hysterectomy (18,19).

Non-invasive imaging methods are used prior to surgery for local staging – MRI, expert transvaginal ultrasound (TVUS), as well as for detecting lymph node or distal metastasis (computer tomography – CT, PET-CT). TVUS is the first diagnostic method for patients with irregular or postmenopausal bleeding. It is used to evaluate the size of the tumour, the depth of myometrial invasion, and cervical stromal invasion and rule out pathology of the ovaries (20,21). In patients with histologically confirmed endometrial carcinoma, TVUS helps classify patients into risk groups of disease progression by evaluating myometrial and cervical stromal invasion, which affects surgical planning and the need for lymphadenectomy (10,11,22,23). At the University Clinical Centre Ljubljana, we started using expert transvaginal ultrasound in 2015 as part of the standard preoperative work-up of patients with gynaecological carcinomas. The method differs from a regular ultrasound in its scope and precision. A highly capable ultrasound scanner is required with a trained and experienced specialist operator as non-gynaecological tissues and organs (bowel, lymph nodes, bladder...) also need to be evaluated. As one of

the options for staging, the frozen section procedure is mentioned in the literature for use during surgery, but its use is still controversial, and it is the subject of further clinical trials (24-26).

It is important for the operating surgeon to know the reliability of preoperative diagnostic methods used in their institution. We try to reduce the number of incorrect surgical procedures in our patients—those with too extensive surgery when a less extensive one would suffice, and those who need subsequent surgery with more extensive lymphadenectomies.

2 Materials and methods

We reviewed the medical records of patients with histologically confirmed endometrial carcinoma treated at the University Clinical Centre Ljubljana between January 2016 and September 2017, who underwent expert transvaginal ultrasound examinations (TRUS) during this time. All patients gave consent for the diagnostic method and written consent for surgery. Expert TRUS was performed approximately one month prior to surgery. It was performed by only one gynaecologist with certification in gynaecological oncology scanning (International Workshop on Ultrasound in Gynecologic Oncology). It was performed using the Voluson E8 scanner and with a 5–9 MHz vaginal transducer. With 2D TVUS, we subjectively evaluated the depth of myometrial invasion (< or \geq 50%) and subjectively evaluated the cervical stromal invasion (present or absent). We obtained the endometrial biopsy histology reports. The data on lymphatic vessel invasion with a preoperative biopsy could not be obtained, so we did not include it in our study. All patients underwent a hysterectomy with adnexectomy and, depending on the preoperative evaluation, different levels of lymphadenectomy

(sentinel lymph node biopsy, standard pelvic lymphadenectomy, standard and para-aortic lymphadenectomy). The preoperative histological diagnosis and TVUS evaluation of myometrial invasion and cervical stromal invasion were compared with the definitive histology report. We used the kappa coefficient to interpret the consistency of preoperative findings with postoperative ones.

The study was approved by the Republic of Slovenia National Medical Ethics Committee (number 0120-353/2020/11), 15. 12. 2020.

3 Results

A total of 80 women were included in the data analysis. One patient was excluded because the final histology report did not confirm the carcinoma but atypical endometrial hyperplasia.

3.1 Comparing preoperative and definitive histology reports

Prior to surgery, 63 patients were histologically assessed to have endometrial carcinoma, and the remaining 16 had non-endometrioid tumours: 12 cases of serous tumours, 2 cases of carcinosarcoma, and 1 case of stromal endometrial carcinoma and dedifferentiated carcinoma. Of the 63 patients with a preoperative diagnosis of endometrial carcinoma, 40 had a histological differentiation grade 1, 19 had grade 2, and 4 patients had a grade 3.

The histological differentiation grade (G) was postoperatively upgraded in 11.3% (9/79) and downgraded in 7.5% (6/79). The consistency of histological differentiation grade before and after surgery was 0.699 (kappa coefficient).

Seven patients with preoperative endometrioid adenocarcinoma G1 were

Table 1: Consistency of preoperative histology with definitive histology, based on total patient number in %.

Preoperative biopsy	Definitive histology report			
	G1	G2	G3	
G1	33 (41.8%)	7 (8.9%)	0	40
G2	4 (5.1%)	13 (16.5%)	2 (2.5%)	19
G3	0	2 (2.5%)	18 (22.8%)	4+16*

Legend: * Non-endometrioid carcinoma types.

upgraded to G2 with the final histological report, and 4 patients with G2 were downgraded to G1. Two patients with endometrioid adenocarcinoma G2 were upgraded to G3, and 2 patients with G3 were downgraded to G2. There were no upgrades from G1 to G3 or downgrades from G3 to G1 in the final histology reports (Table 1).

If we took into account the percentage in which such changes were clinically significant (transitioning from the endometrioid adenocarcinoma G1 and G2 groups to groups with more aggressive types – endometrioid carcinoma G3 and non-endometrioid carcinoma), the grade was 3.3% higher in the definitive histology report (2/59 of patients who were previously in groups with low and moderate risk for lymph node metastasis). Both patients had adequate staging operations based on higher disease stages found by imaging. Clinically significant changes from more aggressive preoperative histology to less invasive after surgery were present in 10% (2/20). In one patient, the disease was of higher grade, so the more extensive surgery was appropriate, and only one patient could have had less extensive surgery without lymphadenectomy.

3.2 Comparing the TVUS evaluation of myometrial invasion and cervical stromal invasion evaluation with a definitive histology report

After comparing histology results, the expert TVUS evaluation of myometrial invasion reached a specificity of 81% (95% confidence interval (CI), 67–91%) and sensitivity of 76% (95% CI, 58–99%); for cervical stromal invasion, the specificity was 75% (95% CI, 63–85%) and sensitivity 54.5% (95% CI, 23–83%). Using the kappa coefficient to interpret the consistency of preoperative findings with postoperative ones, the results were 0.564 for invasion into the myometrium and 0.203 for cervical stromal invasion.

Here we also tried to find differences that would significantly influence decision making. Endometrioid adenocarcinomas, especially of grade 1 and G2, are usually hormone-dependent, are formed from precancerous lesions and grow more slowly (27). They are more hyperechoic on ultrasound, so they are easier to demarcate from the rest of the myometrium. The other histological types of carcinomas are less hormone-dependent, grow faster, are more aggressive and are iso- or hypoechoic on ultrasound (28–30). Some types invade the myometrium earlier with a microcystic, elongated and fragmented (MELF) invasion pattern, which ultrasonographically resembles a very thin endometrium despite numerous micrometastases in the myometrium (31). Ultrasound evaluation of myometrial invasion depth is less reliable with these carcinomas due to their ultrasonographic characteristics (32).

Comparing the depth of myometrial invasion in endometrioid adenocarcinomas G1 and G2 and other histological

types with definitive histology reports, the myometrial invasion depth matches in 84.1% with low-risk carcinomas (endometrioid adenocarcinoma G1 and G2), and only in 56% with others (endometrioid adenocarcinoma G3 and non-endometrioid carcinomas).

4 Discussion

The degree of consistency of endometrial biopsy results with the definitive histology report was good at our centre (upgrade of histological grade in 11.3%, downgrade in 7.5%) compared to foreign studies (19% histological upgrade) (19). Clinically, it is better to sort patients into two groups – those with low and moderate risk (endometrioid adenocarcinoma G1 and G2) and those with other histological types (endometrioid adenocarcinoma G3, serous, clear-cell, neuroendocrine, mixed-cell, undifferentiated and dedifferentiated, carcinosarcomas). In this case, the change of histological grade was significant in 5% (4/79) of all patients (in 2.5%, it was a clinically significant upgrade and a clinically significant downgrade in 2.5%). Taking into account the imaging methods, only one patient was overtreated, and the rest received appropriate treatment. Other Slovenian authors have discussed the importance of consistency of histology reports in a review article (33), but they cited a higher consistency in high-risk types. Our results do not confirm this; looking at the group with a preoperative high histological risk, there was a significant downgrade in 10% (2/20) of patients. Different types of sampling (fractionated abrasion, endometrial biopsy, outpatient or surgical hysteroscopy) also affect the consistency of results (33). Our patient group has already been included in a more extensive study, where the most reliable method was found to be

fractionated abrasion (kappa coefficient 0.84), followed by outpatient hysteroscopy (kappa coefficient 0.77), aspiration biopsy (kappa coefficient 0.71), and surgical hysteroscopy (kappa coefficient 0.68) (34). Close cooperation between the gynaecologist and pathologist is key to avoiding wrong results.

In our study, the sensitivity of the ultrasound evaluation of myometrial invasion was 76% and the specificity was 81%. The sensitivity and specificity of cervical stroma invasion were 54.5% and 75%, respectively. As per the literature, the subjective evaluation of myometrial invasion has a sensitivity of 61–93% and specificity of 71.92% (32,35–38), and cervical stroma invasion has a sensitivity of 25–93% and a specificity of 85–99% (32,33,37). Comparing the TVUS evaluation of myometrial invasion in the low- or moderate-risk groups and the high-risk group with the definitive histology results, the results match in 84.1% in the first two risk groups and in 56% in the high-risk group. This confirms that non-endometrioid tumours are poorly visible on ultrasound, which does not change subsequent treatment, however (32,39).

With TVUS and MRI, we can also evaluate the local extent of the disease. TVUS has its advantages and limits. Pelvic organs are only visible to a certain depth, and the whole female reproductive system cannot be seen with changed anatomies as they lie outside the view range of the transvaginal transducer (32). According to the European Society of Urogenital Radiology guidelines from 2009, MRI is the best imaging option for preoperative evaluation of myometrial invasion. However, expert TRUS, which is gaining ground, also reaches comparable accuracy and, in the hands of an experienced operator, is an effective diagnostic method (20,21,32,40). In 2008, Savelli et

al. published the results of a prospective study in which they compared the preoperative accuracy of an MRI and TVUS in 74 patients with endometrial carcinoma. The diagnostic methods proved comparable. The sensitivity and specificity of myometrial invasion evaluation were 84% and 83% with TVUS, respectively, and 84% and 81% with an MRI (32). It would be interesting to compare the results of MRI and TVUS in our environment, especially in patients with high-risk tumours, which are more difficult to visualize with ultrasound.

Ultrasound is widely available, fast and also cheaper than MRI in our environment. Highly capable scanners are a requirement, and the method is also dependent on the operator and their experience. All patients at our centre underwent an ultrasound prior to surgery, but this was different from an expert TVUS. The results of our study, poorer though still comparable to foreign studies, could be attributed to the learning curve because of limited experience with expert TVUS.

Numerous studies of predictive models and 3D ultrasound are ongoing, but so far, the subjective assessment of an experienced operator has proved to be more accurate (30).

There is a great need for a highly sensitive and specific diagnostic method for planning the extent of surgery and informing the patient of it. Good preoperative histopathologic and imaging diagnostics lead to a more appropriate selection of patients in whom omission of lymphadenectomy or at least a sentinel lymph node biopsy could be performed. Between 2016 and 2017, a study was conducted at the Division of Gynaecology and Obstetrics in Ljubljana, in which the degree of success of surgical detection of the sentinel lymph node with intracervical administration of indocyanine green

dye in 32 patients with histologically confirmed G1 and G2 endometrioid carcinoma was noted. The unilateral success rate was 85.7% and bilateral 80%, which is comparable to the rate of sentinel lymph node detection success in the literature – 80–90% (41). Sentinel lymph node biopsy is a promising method as per the ESGO-ESMO-ESTRO guidelines, but it is still only used for research purposes. At University Clinical Centre Ljubljana, it is the method of choice in patients with estimated low- and moderate-risk endometrial carcinoma in which lymphadenectomy would otherwise be omitted.

Taking into account the preoperative histological differentiation grade, staging, based on the expert TVUS, and the sentinel lymph node biopsy protocol (unilateral/bilateral pelvic lymphadenectomy only in cases where a sentinel lymph node biopsy is not feasible, removal of macroscopically suspicious lymph nodes regardless of preoperative results), one patient underwent too extensive staging surgery, and all other patients had appropriate surgery.

5 Conclusion

Based on our preoperative results, only one patient underwent too extensive surgery, and all other patients had appropriate staging surgery. The most reliable method proved to be preoperative histology (consistency of preoperative findings with postoperative ones with a kappa coefficient 0.699), followed by ultrasound evaluation of myometrial invasion (kappa coefficient 0.564), while the ultrasound evaluation of cervical stromal invasion was poorly reliable (kappa coefficient 0.203).

Expert TVUS use could be improved with highly capable ultrasound scanners and a suitably qualified and experienced

operator with certification in gynaecological oncology scanning. Preoperative diagnostics are crucial in deciding on a surgical treatment plan. We must be aware, however, that this is not perfect. In centres where patients with endometrial carcinoma are treated surgically, accurate recording and evaluation of own results with comparison to other centres are required, alongside the search for improvements for an individualized treatment approach.

References

- Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al.; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. *Radiother Oncol.* 2015;117(3):559-81. DOI: [10.1016/j.radonc.2015.11.013](https://doi.org/10.1016/j.radonc.2015.11.013) PMID: 26683800
- Šegedin B, Merlo S, Smrkolj Š, 1971, Bebar S, Blatnik A, Cerar O, et al. Priporočila za obravnavo bolnic z rakom materničnega telesa. Ljubljana: Onkološki inštitut; 2018.
- Register raka Republike Slovenije. Slora: Slovenija in rak. Ljubljana: Onkološki inštitut; 2019 [cited 2019 Nov 23]. Available from: http://www.slora.si/c/document_library/get_file?uuid=2ddea78e-6a5e-4ccc-8edc-df0c4cfabd49&groupId=11561.
- Svetovna zdravstvena organizacija. Mednarodna klasifikacija bolezni in sorodnih zdravstvenih problemov za statistične namene, Avstralska modifikacija (MKB-10-AM). Verzija 6. Ljubljana: Inštitut za varovanje zdravja RS; 2008 [cited 2019 Nov 23]. Available from: https://www.nijz.si/files/uploaded/ks_mkb10-am-v6_v02_splet.pdf.
- Fischerova D. Ultrasound scanning of the pelvis and abdomen for staging of gynecological tumors: a review. *Ultrasound Obstet Gynecol.* 2011;38(3):246-66. DOI: [10.1002/uog.10054](https://doi.org/10.1002/uog.10054) PMID: 21898632
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29. DOI: [10.3322/caac.21254](https://doi.org/10.3322/caac.21254) PMID: 25559415
- National Comprehensive Cancer Network. Uterine Neoplasms. Endometrial carcinoma. Philadelphia: NCCN; 2019 [cited 2019 Nov 23]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
- Wright JD, Barrena Medel NI, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management of endometrial cancer. *Lancet.* 2012;379(9823):1352-60. DOI: [10.1016/S0140-6736\(12\)60442-5](https://doi.org/10.1016/S0140-6736(12)60442-5) PMID: 22444602
- Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* 1987;60(8):2035-41. DOI: [10.1002/1097-0142\(19901015\)60:8+<2035::AID-CNCR2820601515>3.0.CO;2-8](https://doi.org/10.1002/1097-0142(19901015)60:8+<2035::AID-CNCR2820601515>3.0.CO;2-8) PMID: 3652025
- Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstet Gynecol.* 1984;63(6):825-32. PMID: 6728365
- Mariani A, Webb MJ, Keeney GL, Lesnick TG, Podratz KC. Surgical stage I endometrial cancer: predictors of distant failure and death. *Gynecol Oncol.* 2002;87(3):274-80. DOI: [10.1006/gyno.2002.6836](https://doi.org/10.1006/gyno.2002.6836) PMID: 12468325
- Vargas R, Rauh-Hain JA, Clemmer J, Clark RM, Goodman A, Growdon WB, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. *Gynecol Oncol.* 2014;133(2):216-20. DOI: [10.1016/j.ygyno.2014.02.011](https://doi.org/10.1016/j.ygyno.2014.02.011) PMID: 24548726
- Jakopič K, Smrkolj Š, Kobal B, Brič Š, Krajec M. Ultrazvočna preiskava pri odkrivanju in zdravljenju raka na maternični sluznici. In: Merlo S, Smrkolj Š, Šegedin B. Šola o ginekološkem raku. Rak materičnega telesa. Zbornik. 11. november 2016; Ljubljana, Slovenija. Ljubljana: Združenje za radioterapijo in onkologijo SZD; 2016.
- Abu-Rustum NR. Update on sentinel node mapping in uterine cancer: 10-year experience at Memorial Sloan-Kettering Cancer Center. *J Obstet Gynaecol Res.* 2014;40(2):327-34. DOI: [10.1111/jog.12227](https://doi.org/10.1111/jog.12227) PMID: 24620369
- Abu-Rustum NR, Alektiar K, Iasonos A, Lev G, Sonoda Y, Aghajanian C, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. *Gynecol Oncol.* 2006;103(2):714-8. DOI: [10.1016/j.ygyno.2006.03.055](https://doi.org/10.1016/j.ygyno.2006.03.055) PMID: 16740298

16. Tada H, Teramukai S, Fukushima M, Sasaki H. Risk factors for lower limb lymphedema after lymph node dissection in patients with ovarian and uterine carcinoma. *BMC Cancer*. 2009;9(1):47. DOI: [10.1186/1471-2407-9-47](https://doi.org/10.1186/1471-2407-9-47) PMID: [19193243](https://pubmed.ncbi.nlm.nih.gov/19193243/)
17. Kobal B, Cvjetičanin B. Kirurško zdravljenje nizko in srednje rizičnega raka materničnega telesa - endometrija. In: Merlo S, Smrkolj Š, Šegedin B. Šola o ginekološkem raku. Rak materničnega telesa: zbornik. 11. november 2016; Ljubljana, Slovenija. Ljubljana: Združenje za radioterapijo in onkologijo SZD; 2016.
18. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, Soslow RA, Dao F, Sonoda Y, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? *Gynecol Oncol*. 2009;113(2):163-9. DOI: [10.1016/j.ygyno.2009.01.003](https://doi.org/10.1016/j.ygyno.2009.01.003) PMID: [19232699](https://pubmed.ncbi.nlm.nih.gov/19232699/)
19. Ben-Shachar I, Pavelka J, Cohn DE, Copeland LJ, Ramirez N, Manolitsas T, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol*. 2005;105(3):487-93. DOI: [10.1097/01.AOG.0000149151.74863.c4](https://doi.org/10.1097/01.AOG.0000149151.74863.c4) PMID: [15738013](https://pubmed.ncbi.nlm.nih.gov/15738013/)
20. Antonsen SL, Jensen LN, Loft A, Berthelsen AK, Costa J, Tabor A, et al. MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - a multicenter prospective comparative study. *Gynecol Oncol*. 2013;128(2):300-8. DOI: [10.1016/j.ygyno.2012.11.025](https://doi.org/10.1016/j.ygyno.2012.11.025) PMID: [23200916](https://pubmed.ncbi.nlm.nih.gov/23200916/)
21. Lin MY, Dobrotwir A, McNally O, Abu-Rustum NR, Narayan K. Role of imaging in the routine management of endometrial cancer. *Int J Gynaecol Obstet*. 2018;143(2):109-17. DOI: [10.1002/ijgo.12618](https://doi.org/10.1002/ijgo.12618) PMID: [30306593](https://pubmed.ncbi.nlm.nih.gov/30306593/)
22. Akbayir O, Corbacioglu A, Numanoglu C, Guleroglu FY, Ulker V, Akyol A, et al. Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. *Gynecol Oncol*. 2011;122(3):600-3. DOI: [10.1016/j.ygyno.2011.05.041](https://doi.org/10.1016/j.ygyno.2011.05.041) PMID: [21700322](https://pubmed.ncbi.nlm.nih.gov/21700322/)
23. Kinkel K, Forster R, Danza FM, Oleaga L, Cunha TM, Bergman A, et al. Staging of endometrial cancer with MRI: guidelines of the European Society of Urogenital Imaging. *Eur Radiol*. 2009;19(7):1565-74. DOI: [10.1007/s00330-009-1309-6](https://doi.org/10.1007/s00330-009-1309-6) PMID: [19194709](https://pubmed.ncbi.nlm.nih.gov/19194709/)
24. Stephan JM, Hansen J, Samuelson M, McDonald M, Chin Y, Bender D, et al. Intra-operative frozen section results reliably predict final pathology in endometrial cancer. *Gynecol Oncol*. 2014;133(3):499-505. DOI: [10.1016/j.ygyno.2014.03.569](https://doi.org/10.1016/j.ygyno.2014.03.569) PMID: [24699308](https://pubmed.ncbi.nlm.nih.gov/24699308/)
25. Kumar S, Medeiros F, Dowdy SC, Keeney GL, Bakkum-Gamez JN, Podratz KC, et al. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. *Gynecol Oncol*. 2012;127(3):525-31. DOI: [10.1016/j.ygyno.2012.08.024](https://doi.org/10.1016/j.ygyno.2012.08.024) PMID: [22940491](https://pubmed.ncbi.nlm.nih.gov/22940491/)
26. Kumar S, Bandyopadhyay S, Semaan A, Shah JP, Mahdi H, Morris R, et al. The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS One*. 2011;6(9):e21912. DOI: [10.1371/journal.pone.0021912](https://doi.org/10.1371/journal.pone.0021912) PMID: [21912633](https://pubmed.ncbi.nlm.nih.gov/21912633/)
27. Sawicki W, Śpiewankiewicz B, Stelmachów J, Cendrowski K. The value of ultrasonography in preoperative assessment of selected prognostic factors in endometrial cancer. *Eur J Gynaecol Oncol*. 2003;24(3-4):293-8. PMID: [12807243](https://pubmed.ncbi.nlm.nih.gov/12807243/)
28. Mascilini F, Testa AC, Van Holsbeke C, Ameye L, Timmerman D, Epstein E. Evaluating myometrial and cervical invasion in women with endometrial cancer: comparing subjective assessment with objective measurement techniques. *Ultrasound Obstet Gynecol*. 2013;42(3):353-8. DOI: [10.1002/uog.12499](https://doi.org/10.1002/uog.12499) PMID: [23640790](https://pubmed.ncbi.nlm.nih.gov/23640790/)
29. Alcázar JL, Galván R, Albela S, Martínez S, Pahisa J, Jurado M, et al. Assessing myometrial infiltration by endometrial cancer: uterine virtual navigation with three-dimensional US. *Radiology*. 2009;250(3):776-83. DOI: [10.1148/radiol.2503080877](https://doi.org/10.1148/radiol.2503080877) PMID: [19164122](https://pubmed.ncbi.nlm.nih.gov/19164122/)
30. Alcazar JL, Pineda L, Martinez-Astorquiza Corral T, Orozco R, Utrilla-Layna J, Juez L, et al. Transvaginal/transrectal ultrasound for assessing myometrial invasion in endometrial cancer: a comparison of six different approaches. *J Gynecol Oncol*. 2015;26(3):201-7. DOI: [10.3802/jgo.2015.26.3.201](https://doi.org/10.3802/jgo.2015.26.3.201) PMID: [26197857](https://pubmed.ncbi.nlm.nih.gov/26197857/)
31. Stewart CJ, Little L. Immunophenotypic features of MELF pattern invasion in endometrial adenocarcinoma: evidence for epithelial-mesenchymal transition. *Histopathology*. 2009;55(1):91-101. DOI: [10.1111/j.1365-2559.2009.03327.x](https://doi.org/10.1111/j.1365-2559.2009.03327.x) PMID: [19614771](https://pubmed.ncbi.nlm.nih.gov/19614771/)
32. Savelli L, Ceccarini M, Ludovisi M, Fruscella E, De Iaco PA, Salizzoni E, et al. Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. *Ultrasound Obstet Gynecol*. 2008;31(5):560-6. DOI: [10.1002/uog.5295](https://doi.org/10.1002/uog.5295) PMID: [18398926](https://pubmed.ncbi.nlm.nih.gov/18398926/)
33. Arko D, Kozar N, Rmuš M, Takač I. Zanesljivost določitve stopnje diferenciacije raka endometrija pred operacijo. *Zdrav Vestn*. 2018;87(3-4):167-75.
34. Kukovič N, Maček Jakopič K, Kobal B, Blaganje M, Drusany Starič K, Kenda Šuster N. Stopnja ujemanja histoloških izvidov predoperativnih preiskav (frakcionirana abrazija, ambulantna in operativna histeroskopija, aspiracijska biopsija) s končno histologijo pri bolnicah z rakom endometrija: [Specialistična naloga]. Ljubljana: UKC Ljubljana, Ginekološka klinika; 2018.

35. Arko D, Takač I. High frequency transvaginal ultrasonography in preoperative assessment of myometrial invasion in endometrial cancer. *J Ultrasound Med.* 2000;19(9):639-43. DOI: [10.7863/jum.2000.19.9.639](https://doi.org/10.7863/jum.2000.19.9.639) PMID: [10972561](https://pubmed.ncbi.nlm.nih.gov/10972561/)
36. Takač I. Transvaginal ultrasonography with and without saline infusion in assessment of myometrial invasion of endometrial cancer. *J Ultrasound Med.* 2007;26(7):949-55. DOI: [10.7863/jum.2007.26.7.949](https://doi.org/10.7863/jum.2007.26.7.949) PMID: [17592058](https://pubmed.ncbi.nlm.nih.gov/17592058/)
37. Frühauf F, Zikan M, Semeradova I, Dunder P, Nemejcova K, Dusek L, et al. The Diagnostic Accuracy of Ultrasound in Assessment of Myometrial Invasion in Endometrial Cancer: Subjective Assessment versus Objective Techniques. *BioMed Res Int.* 2017;2017:1318203. DOI: [10.1155/2017/1318203](https://doi.org/10.1155/2017/1318203) PMID: [28812010](https://pubmed.ncbi.nlm.nih.gov/28812010/)
38. Šumak R, Pakiž M. Transvaginal sonography in endometrial carcinoma: preoperative assessment of deep myometrial invasion and its impact on surgical planning. *Eur J Obstet Gynecol Reprod Biol.* 2019;234(11):e21. DOI: [10.1016/j.ejogrb.2018.08.197](https://doi.org/10.1016/j.ejogrb.2018.08.197)
39. Seracchioli R, Solfrini S, Mabrouk M, Facchini C, Di Donato N, Manuzzi L, et al. Controversis in Surgical Staging of Endometrial Cancer. Review article. *Obstet Gynecol Int.* 2010;181963:1-8. DOI: [10.1155/2010/181963](https://doi.org/10.1155/2010/181963)
40. Haldorsen IS, Salvesen HB, Salvesen HB. What Is the Best Preoperative Imaging for Endometrial Cancer? *Curr Oncol Rep.* 2016;18(4):25. DOI: [10.1007/s11912-016-0506-0](https://doi.org/10.1007/s11912-016-0506-0) PMID: [26922331](https://pubmed.ncbi.nlm.nih.gov/26922331/)
41. Čas S, Jakopič Maček K, Kobal B, Drusany Starič K, Meglič L, Barbič M, et al. Začetni rezultati odstranjevanja varovalnih bezgavk pri kirurškem zdravljenju raka endometrija. *Zdrav Vestn.* 2019;88(11-12):509-16. DOI: [10.6016/ZdravVestn.2875](https://doi.org/10.6016/ZdravVestn.2875)