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Adenomyosis As a Confounder to Accurate Endometrial Cancer Staging

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The coexistence of endometrial adenocarcinoma and adenomyosis in the same uterus is a common phenomenon. In many of such affected patients foci of adenomyosis could also be colonized by adenocarcinoma. The various permutations arising from these scenarios pose preoperative imaging and postoperative pathologic staging challenges. This article aims to raise awareness of these staging issues and lists some of the relevant practical approaches. Adenomyosis reduces the accuracy of magnetic resonance imaging in assessing the depth of invasion as it reduces the contrast between the endometrial cancer adenomyosis-involved myometrium. The article also offers an alternate argument for staging cancers where myoinvasion is found deep in the myometrium, arising from cancer-positive adenomyotic foci when the surface tumor is either limited to the endometrium or to the inner half of myometrium.

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Introduction

Endometrial adenocarcinoma is the most common invasive malignancy of the female genital tract in North America.[1] Most cases are of the endometrioid cell type (or type I), and since the disease commonly presents by abnormal uterine bleeding, patients tend to seek medical care relatively early when the tumor is still confined to the uterine corpus (Stage 1) at the time of diagnosis. The depth of myometrial invasion by endometrial adenocarcinoma, as determined in the subsequent hysterectomy specimen, closely correlates with lymph node metastasis and is a documented predictor of hematogenous spread and recurrence.[2-4] Subsequently, the depth on myometrial invasion relevant to the full myometrial thickness is the sole subclassification determinant of endometrial cancer staging when the tumor is limited to the uterus. These tumors are assigned a pT1a vs a pT1b stage according to whether they are limited to the inner myometrial half or invade into the outer half respectively. The ability of malignant cells to invade into the underlying myometrium and to exist in its outer layers is believed to be influenced by several intrinsic tumor factors as well as suspected extrinsic topographic factors. Intrinsic tumor factors, which have been documented to influence myometrial invasion are its histologic Federation of Gynecology and Obstetrics (FIGO) grade,[3] the nonendometrioid histology,[4] oncogene overexpression,[5,6] ploidy,[7,8] and proliferative activity.[8,9] Among the extrinsic topographic factors suspected to affect positioning of malignant cells in the myometrium is pre-existing adenomyosis and its involvement by endometrial adenocarcinoma.[10-12] Studies have shown that involvement of pre-existing adenomyosis by endometrial adenocarcinoma represents an increased risk for myometrial invasion in patients with FIGO grade 1 adenocarcinomas and is typically associated with outer half myometrial invasion.[10,11] Other investigators have confirmed that adenomyosis is associated with deep myometrial invasion by endometrial endometrioid adenocarcinoma but could not confirm its risk for recurrence or increased mortality.[12]

Adenomyosis, or the presence of endometrial glands and stroma, disconnected from the native endometrium, within the myometrium deeper than one low-powered microscopic field (approximately 2.1 mm), is a common condition that is reported in 15%-30% of hysterectomy specimens.[13] Foci of adenomyosis are confirmed in hysterectomy specimens performed for the management of endometrial adenocarcinoma with incidences ranging from 9% to 34%.[14-19] Similarly, a recent study of patients with adenomyosis, found endometrial

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adenocarcinoma in 5.5% of uteri examined.[20] With this relatively high likelihood of encountering these 2 conditions in the same patient, it becomes prudent to address the challenges that could be posed by adenomyosis on staging endometrial adenocarcinoma. This discussion will cover both aspects of preoperative imaging and postoperative pathologic staging.

Preoperative Imaging Staging Challenges

Magnetic resonance imaging (MRI) is currently the cross-sectional modality of choice to determine depth of myometrial invasion as well as extension of the disease to the cervix. The standard MRI sequences that delineate endometrial cancer include T2-weighted, dynamic T1-weighted gadolinium (early and late) sequences, and diffusion-weighted imaging including apparent diffusion coefficient map. Diffusion-weighted imaging (DWI) increases the accuracy of conventional sequences. Endometrial cancer is low to more frequently intermediate signal intensity on T2-weighted sequence and hypoenhancing on the gadolinium sequence. Interruption of the enhancing subendometrial stripe of the junctional zone at the endomyometrial junction in the arterial phase and low T2 signal of the more compact junctional zone determine superficial invasion.[21] In a recent meta-analysis, sensitivity and specificity of MRI to determine depth of invasion was 82% and 83%, respectively.[22]

Adenomyosis manifests as thickening with or without poor definition of the junctional zone, and areas of poorly defined low T2 signal in the myometrium, representing smooth muscle hyperplasia.[23] In addition, high T2 signal areas corresponding to endometrial glands may be present.[23] It may also result in heterogenous enhancement of myometrium on the gadolinium sequenced.[23] Presence of adenomyosis reduces the accuracy of MRI to assess depth of invasion by reducing the contrast between the endometrial cancer and adenomyosis-involved myometrium[21] (Fig. 1). Early T1-weighted gadolinium sequence appears to be superior to T2-weighted and late postgadolinium sequences to assess for depth of invasion in adenomyosis (Fig. 1).[21] The addition of diffusion-weighted sequence appears to improve the accuracy of MRI for depth assessment when there is underlying adenomyosis.[24] Tumors appear high signal on the high B value DWI sequence and hypointense on the corresponding apparent diffusion coefficient map, distinguishing it from adenomyosis (Fig. 2). Recent literature suggests inclusion of a reduced field of view DWI further enhances the accuracy of MRI.[25] Nonoperative treatment of endometrial cancer in young women to preserve fertility would require the absence of myometrial invasion. This is confirmed by the presence of a continuous subendometrial enhancement in the arterial phase of gadolinium sequence and sharp demarcation of the endomyometrial junction at the junctional zone on T2-weighted imaging; both are disturbed by the presence of adenomyosis.[26]

Postoperative Pathologic Staging Challenges

In patients with pre-existent adenomyosis, hysterectomies performed for endometrial adenocarcinoma may show tumor coexistence in the adenomyotic foci without true myometrial invasion. This finding is not considered as true myometrial invasion and does not influence, by itself, the assigned tumor stage. When the 2 conditions coexist, involvement of adenomyosis by adenocarcinoma is seen in

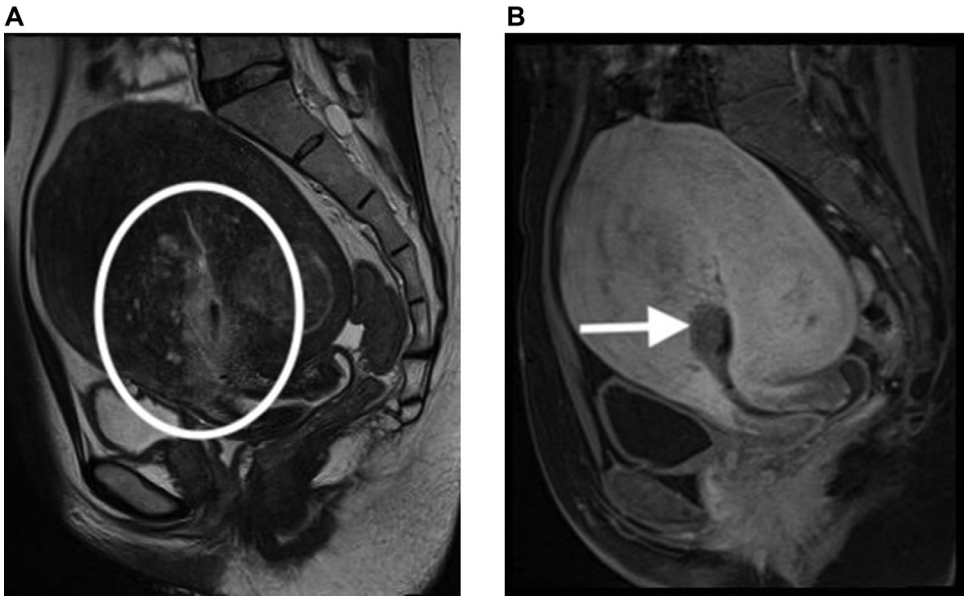

Figure 1 50-year-old woman. Hysterectomy showed Stage 1A endometrioid cancer limited to the endometrium and adenomyosis. (A) Sagittal T2-weighted sequence shows poorly defined high signal thickening of the endometrium in the body and lower uterine segment surrounded by adenomyosis. (B) Sagittal T1-weighted + gadolinium sequence shows hypovascular well-defined focal thickening (arrow) of the endometrium in the lower uterine segment.

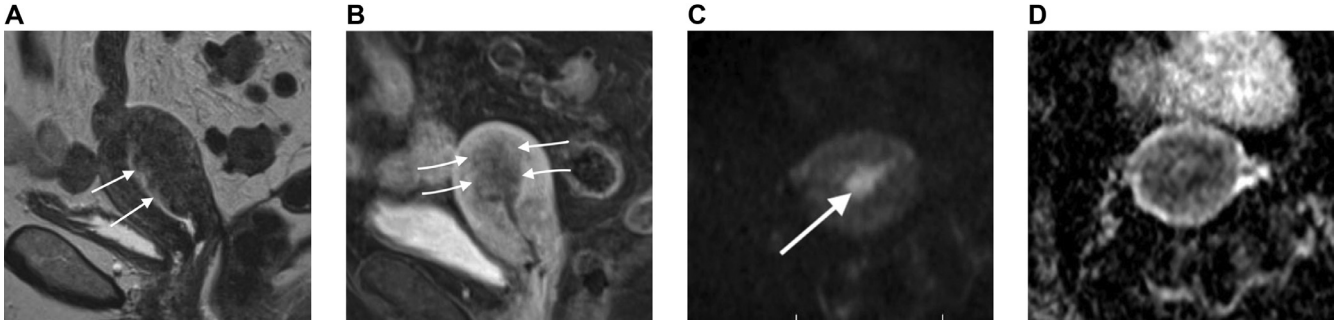

Figure 2 35-year-old woman. Hysterectomy showed Stage 1A endometrioid cancer limited to the endometrium and adenomyosis. (A) Sagittal T2-weighted sequence shows irregular mixed signal thickening (arrows) of the dorsal endometrium in the body and lower uterine segment in a patient with history of trachelectomy. There is poor definition of the junctional zone with thick dorsal myometrium; (B) Sagittal T1-weighted + gadolinium sequence shows poor definition of the endometrium in the upper body of the uterus (arrows) in a patient with history of trachelectomy; (C) Axial DWI sequence (B value 1000) shows focal high signal thickening (arrow) of the endometrium; (D) Axial ADC map shows no diffusion restriction corresponding to the high signal area on DWI sequence due to the low grade of the cancer.

49.5%[11] to 53.6%[27] of all hysterectomy specimens, depending on the uterine grossing and sampling protocols used by the respective laboratories. It was suggested that this phenomenon could simply occur as a result of the low resistance of these areas compared to the remainder of the endometrial-myometrial junction.[28] This low resistance was proposed to allow the adenocarcinoma of the native and/or surface endometrial lining to spread downward directly to colonize pre-existing adenomyosis. However, findings of other studied have suggested a "*field effect*" mechanism rather than a "*direct extension*" one. In this model, endometrial adenocarcinoma is proposed to arise de novo as neoplastic transformation in adenomyosis.[29,30] Irrespective of the mechanism of development, coexistent tumors of the endometrium and adenomyosis are frequently preceded by estrogen therapy, are of low histologic grades, and have excellent prognosis.[31] Cancer-positive adenomyotic foci without myometrial invasion would typically have round smooth contour and residual endometrial stroma or benign endometrial glands surrounding malignant cells (Fig. 3). These foci would appear microscopically as areas of adenocarcinoma surrounded by myometrium which could represent some diagnostic difficulties during intraoperative consultation by frozen section examination. However, distinguishing them from true myometrial invasion by malignant cells is relatively straightforward on permanent sections and, in most cases, is not significantly challenging for the experienced pathologist. It is established that the presence of these foci should not affect tumor stage or outcome.[15] Some researches even suggested that pre-existing adenomyosis may offer a preventive mechanism against myometrial invasion by adenocarcinoma. It is suggested that the microenvironment changes surrounding the deep cancer-positive adenomyotic foci induce an inflammatory response against tissue injury and myometrial hyperplasia mediated by the secreted growth factors could restrict further tumor myoinvasion.[32]

However, in some patients with coexistent tumors in the endometrium and adenomyosis, true myometrial invasion takes place from areas of cancer-positive adenomyosis. This phenomenon is marked by the presence of irregular clusters or malignant glands with ragged outlines extended out of the adenomyotic foci and into adjacent myometrium (Fig. 4). They typically are surrounded by desmoplastic stromal response, edema, and chronic inflammatory changes, in the absence of endometrial stroma. These microscopic features are used reliably by pathologists to distinguish between cases where adenocarcinoma is confined to adenomyosis, and should not count as true myometrial invasion, from the other, less common, examples where true myometrial invasion has taken place from cancer-positive adenomyotic foci.

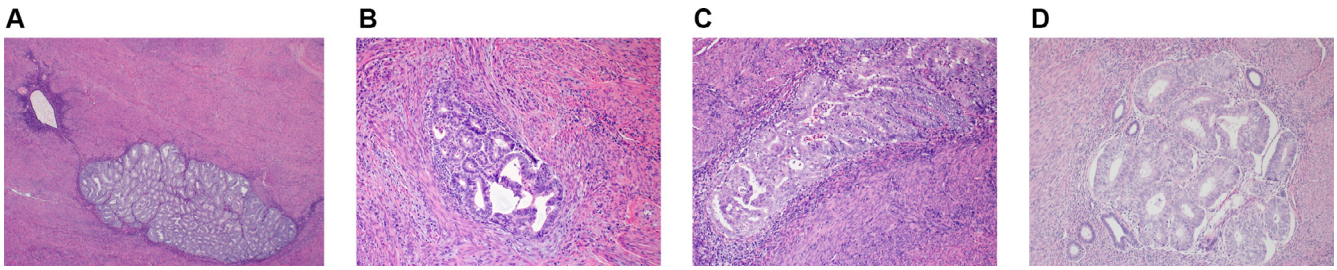

Figure 3 Cancer-positive adenomyosis without myometrial invasion. (A) Low power depicting the round smooth contour of the lesion; (B) Cancer-positive foci appear as areas of adenocarcinoma surrounded by myometrium which could represent a challenge during frozen section examination; (C) High power depicting the round smooth contour and the preservation of benign endometrial stroma; (D) Benign endometrial glands located at the periphery of adenocarcinoma are help exclude myometrial invasion.

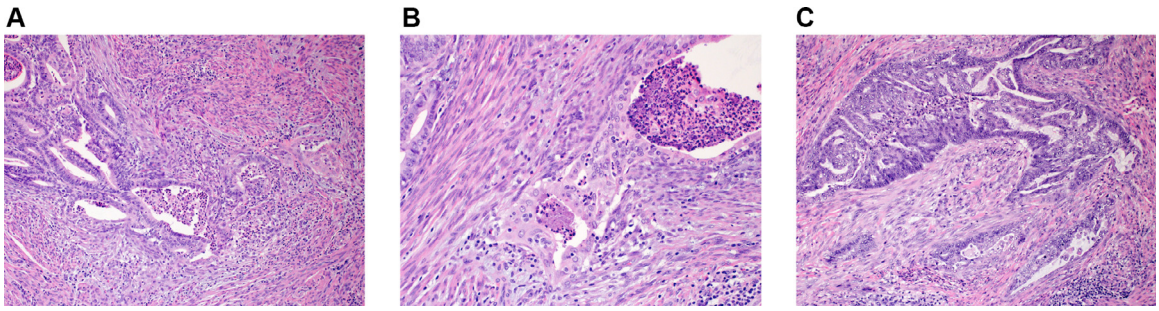

Figure 4 Cancer-positive adenomyosis with invasion of adjacent myometrium. (A) The focus has ragged outlines extending out of the adenomyosis and into adjacent myometrium. Stroma is desmoplastic and edematous; (B) The invasive focus shows inflammation and absent endometrial stroma; (C) In addition to the ragged outlines, some malignant glands broke off the main focus and traveled into the adjacent myometrium for a short distance.

Extension of adenocarcinoma of the native endometrium and colonizing underlying adenomyosis, or the concomitant de novo adenocarcinoma in both locations with subsequent invasion into the adjacent myometrium from cancer-positive adenomyotic foci is an uncommon phenomenon.[27] The degree of subjectivity involved in confidently making this diagnosis and the variability introduced by the local grossing and sampling protocols in various laboratories is well-acknowledged. This has led to the view proposed by some researchers to limit staging of endometrial adenocarcinoma to myometrial invasion noted at the native endomyometrial junction. On the other hand, since the depth of myometrial invasion remains as an important indicator for recurrence, overall survival, lymph node metastasis and the only independent predictor of hematogenous dissemination in patients with endometrial adenocarcinoma, accurate measurement of myoinvasion stands as a significant task for the pathologist postoperatively.[2-4] Myometrial invasion arising from cancer-positive adenomyosis located in the outer myometrium is conceptually challenging to pathologists since, on one hand, malignant cells in these cases invade for a short distance of only few millimeters, but on the other hand, are present in the outer myometrium which is often considered as a marker for poorer outcome. Native endometrial cancer that invades the underlying myometrium for only few millimeters is usually classified as pT1a (limited to inner myometrial half) whereas more advanced examples where malignant cells reach the outer myometrial half are classified as pT1b. Currently, there are no guidelines for staging endometrial adenocarcinoma in which myoinvasion is found deep in the myometrium and is arising from cancer-positive adenomyotic foci when the surface tumor is either limited to the endometrium or to the inner half of myometrium. This particular scenario has not been addressed by the FIGO system. To address this issue, Ali et al[33] proposed measuring the distance between the adenomyosis and/or myometrial interface and the deepest extent of invasive tumor as the depth of myometrial invasion. Acknowledging that this approach has not been validated specifically, Soslow[34] supported it and suggested that few cells of myometrial-invasive carcinoma deep in the myometrium will not have the same clinical implication as a mass of millions of tumor cells arranged contiguously from the overlying native endomyometrial junction to the deepest focus.

While this logic could be true, we argue that the outcome of endometrial adenocarcinoma in this particular scenario is not solely dependent on the number of malignant cells and the mere distance they travel. The size of endometrial adenocarcinoma, as a proxy of the total number of malignant cells for example, is not part of the American Joint Commission on Cancer or the International FIGO staging systems. Tumor size is incorporated for risk stratification in an intraoperative algorithm regarding staging procedure but is still not considered as a hallmark for endometrial cancer staging.[35,36] The physical presence of the invasive malignant cells in close proximity to the Arcuate Vascular Plexus (AVP) located in the outer myometrium,[37] irrespective of their true biologic malignant potential, offers them a distinct advantageous access to the vascular bed and metastasis. The fact that the pT1b classification of endometrial adenocarcinoma implies a worse prognosis than that of a pT1a class could partly be because of the bulk of tumor required to invade into the outer myometrial half, but could also be due to the accessibility to the AVP malignant cell gain by being in this location.

Soslow's approach[33,34] has been endorsed by the College of American Pathologists (CAP) in the current version of Cancer Protocol Template for endometrial adenocarcinoma published in 2018.[38] The protocol referenced Ali et al[33] work as the suggested approach to reporting these cases which would classify them with few millimeters myometrial invasion from cancer-positive adenomyotic foci as pT1a adenocarcinomas even though malignant cells are present in the outer myometrium. It is of note that the same CAP protocol has introduced, for the first time, the presence of adenomyosis in the hysterectomy specimen and its status as whether it is involved by adenocarcinoma as a nonrequired checklist entry.[38] This development highlights concerns of the impact adenomyosis could have on accurate endometrial cancer staging without outlining its practical application at the current time. It is hoped that the adoption of this new CAP protocol and the consistent reporting on the status of adenomyosis will help accumulate the data needed to objectively address staging issues of endometrial adenocarcinoma when invasion into the outer myometrium occurs from cancer-positive adenomyotic foci when the surface tumor is either limited to the endometrium or the inner half of myometrium. A counter-logic suggesting the alternate classification of these tumors as pT1b carcinomas is presented in the following discussion emphasizing the role of physical proximity of invasive malignant cells to the AVP in the outer myometrium.

Tumor-Free Distance from Serosa

Tumor-free distance (TFD) from uterine serosa is the distance from the deepest myometrial invasion by adenocarcinoma to the serosal surface. While this is a single measurement that is easier and more practical for the pathologist to perform as it does not take in account measurement of the myometrial thickness, it has not been widely adopted by North American gynecologic oncologists or staging systems. Compared to the depth of myometrial invasion, TFD has been shown in multivariant analyses to be a more superior predictor for recurrence, death of disease, lymph node involvement.[39-42] Studies that have validated TFD as a superior outcome predictor add evidence to the hypothesis that the mere location of malignant cells and their physical proximity to the AVP in the outer myometrium is an important factor that needs to be taken in consideration. The closer malignant cells are to the uterine serosa, the worse is the prognosis. This approach, which has already been validated, does not incorporate the bulk of tumor or the distance malignant cells travel. Rather, it simply highlights the topographic role and metastatic advantage for cancer cells when they are present in the outer myometrium, closer to uterine serosa.

Primary Adenocarcinoma Arising Within Adenomyosis

Primary endometrioid adenocarcinoma arising within adenomyosis diagnosed in hysterectomy specimens with normal, non-neoplastic native endometrium is a rare event that is mostly documented in case reports and small case series.[43-47] While the tumor could be confined to adenomyosis[47] a pathologist would most likely diagnose these rare tumors that showed invasion into adjacent myometrium of the outer half as stage pT1b tumors.[43-46] Two of these rare examples are of particular interest. The case reported by Puppa et al[44] was a moderately differentiated endometrioid adenocarcinoma limited to a focus of adenomyosis reported in a hysterectomy with unilateral salpingo-oophorectomy specimen. The patient developed recurrence to her pelvic lymph nodes, confirmed by cytologic examination, 4 months postoperatively. The other patient received modified radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy for a pT1b, FIGO 1 endometrioid adenocarcinoma limited to foci of adenomyosis. This was followed by 5 cycles of adjuvant chemotherapy. Five years later, the patient developed right lung metastasis and right para-aortic and pelvic lymph node metastases.[45] These 2 cases may point to the metastatic advantage gained by malignant cells when physically located in the outer myometrium and justify classifying them as pT1b tumors. By extrapolation, malignant cells invading deep myometrium, even when they travel for few millimeters from foci of cancer-positive adenomyosis could impart a similar adverse outcome.

Conclusion

MRI continues to be the modality of choice for preoperative staging of endometrial cancer. It provides clinically actionable information regarding the depth of myometrial invasion (Stage 1A vs 1B) as well as extension of the disease to the cervix (Stage 1 vs 2). Interpreting radiologists are becoming increasingly aware of the effect of adenomyosis in reducing the accuracy of MRI to assess depth of invasion as it reduces the contrast between the endometrial cancer and adenomyosis-involved myometrium.

Myometrial invasion arising from cancer-positive adenomyosis located in the outer myometrium is conceptually challenging to pathologists, especially when the surface tumor is either limited to the endometrium or to the inner half of myometrium. On one hand, malignant cells in these cases invade for only few millimeters, but on the other hand, are present in the outer myometrium which is often considered as a marker for poorer outcome because of their proximity to large vascular channels. Currently, there are suggested approaches but no guidelines for staging endometrial adenocarcinoma with this scenario. Until guidelines are validated and published, it is recommended that pathologists, when faced with this unusual situation, elaborate in their report and offer the background reasoning for their reported tumor stage.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65:5-29, 2015
2. Mariani A, Dowdy SC, Keeney GL, et al: High-risk endometrial cancer subgroups: Candidates for target-based adjuvant therapy. Gynecol Oncol 95:120-126, 2004
3. Nofech-Mozes S, Ghorab Z, Ismiil N, et al: Endometrial endometrioid adenocarcinoma: A pathologic analysis of 827 consecutive cases. Am J Clin Pathol 129:110-114, 2008
4. Prat J: Prognostic parameters of endometrial carcinoma. Hum Pathol 35:649-662, 2004
5. Khalifa MA, Mannel RS, Haraway SD, et al: Expression of EGFR, Her-2/neu, p53, and PCNA in endometrioid, serous papillary and clear cell endometrial adenocarcinomas. Gynecol Oncol 53:8-92, 1994
6. Khalifa MA, Abdoh AA, Mannel RS, et al: Prognostic utility of epidermal growth factor receptor overexpression in endometrial adenocarcinoma. Cancer 73:370-376, 1994
7. Stendhal U, Strang P, Wagenius G, et al: Prognostic significance of proliferation in endometrial adenocarcinomas: A multivariate analysis of clinical and flow cytometric variables. Int J Gynecol Pathol 10:271-284, 1991
8. Pfisterer J, Kommoss F, Sauerbrei W, et al: Prognostic value of DNA ploidy and S-phase fraction in stage I endometrial carcinoma. Gynecol Oncol 58:149-156, 1995
9. Lax SF, Pizer ES, Ronnett BM, et al: Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. Hum Pathol 29:551-558, 1998
10. Ismiil ND, Rasty G, Ghorab Z, et al: Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. Int J Gynecol Pathol 26:278-283, 2007
11. Ismiil N, Rasty G, Ghorab Z, et al: Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. Ann Diag Pathol 11:252-257, 2007
12. Taneichi A, Fujiwara H, Takahashi Y, et al: Influences of uterine adenomyosis on muscle invasion and prognosis of endometrioid adenocarcinoma. Int J Gynecol Cancer 24:1429-1433, 2014
13. Seidman JD, Kjerulff KH: Pathologic findings from Maryland Women's Health Study: Practice patterns in the diagnosis of adenomyosis. Int J Gynecol Pathol 15:217-221, 1996
14. Winkelman J, Robinson R: Adenocarcinoma of endometrium involving adenomyosis. Cancer 19:901-908, 1966
15. Hall JB, Young RH, Nelson Jr JH: The prognostic significance of adenomyosis in endometrial carcinoma. Gynecol Oncol 17:32-40, 1984

16. Hayata T, Kawashima Y: Clinicopathologic study of eight cases of uterine body cancers associated with endometriosis interna (uterine adenomyosis). Am J Obstet Gynecol 156:663-666, 1987
17. Taskin M, Lallas TA, Shevchuk M, et al: P53 expression in adenomyosis in endometrial carcinoma patients. Gynecol Oncol 62:241-246, 1996
18. Koshiyama M, Okamoto T, Ueta M: The relationship between endometrial adenocarcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. Cancer Detect Prev 28:94-98, 2004
19. Zhang Z, Yang B, Zhang W, et al: Clinicopathological characteristics and survival outcomes of patients with coexistence of adenomyosis and endometrial adenocarcinoma. Int J Clin Exp Pathol 11:956-962, 2018
20. Ferraz Z, Mogueira-Martins N, Mogueira-Martins F: Adenomyosis: Back to the future? Facts Views Vis Obgyn 9:15-20, 2017
21. Utsunomiya D, Notsute S, Hayashida Y, et al: Endometrial carcinoma in adenomyosis: Assessment of myometrial invasion on T2-weighted spin-echo and gadolinium-enhanced T1- weighted images. AJR Am J Roentgenol 182:399-404, 2004
22. Alcázar JL, Gastón B, Navarro B, et al: Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: A systematic review and meta-analysis. J Gynecol Oncol 28:e86, 2017
23. Reinhold C, Tafazoli F, Mehio A, et al: Uterine adenomyosis: Endovaginal US and MR imaging features with histopathologic correlation. Radiographics 19, 1999. Spec No:S147-60
24. Deng L, Wang QP, Chen X, et al: The combination of diffusion- and t2-weighted imaging in predicting deep myometrial invasion of endometrial cancer: A systematic review and meta- analysis. J Comput Assist Tomogr 39:661-673, 2015
25. Takeuchi M, Matsuzaki K, Harada M: Evaluating myometrial invasion in endometrial Cancer: Comparison of reduced field-of-view diffusion-weighted imaging and dynamic contrast- enhanced MR Imaging. Magn Reson Med Sci 17:28-34, 2018 10
26. Fujii S, Kido A, Baba T, et al: Subendometrial enhancement and peritumoral enhancement for assessing endometrial cancer on dynamic contrast enhanced MR imaging. Eur J Radiol 84:581-589, 2015
27. Hanley KZ, Dustin SM, Stoler MH, et al: The significance of tumor involved adenomyosis in otherwise low-stage endometrioid adenocarcinoma. Int J Gynecol Pathol 29:445-451, 2010
28. Colman H, Rosenthal AH: Carcinoma developing in areas of adenomyosis. Obstet. Gynecol 14:342-348, 1959
29. Giammalvo JT, Kaplan K: The incidence of endometriosis interna in 120 cases of carcinoma of the endometrium. Am J Obstet Gynecol 75:161-165, 1958
30. Marcus CC: Relationship of adenomyosis uteri to endometrial hyperplasia and endometrial carcinoma. Am J Obstet Gynecol 82:408-416, 1961
31. Mittal KR, Barwick KW: Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. Gynecol Oncol 49:197-201, 1993
32. Tetikkurt S, Çelik E, Taş H, et al: Coexistence of adenomyosis, adenocarcinoma, endometrial and myometrial lesions in resected uterine specimens. Mol Clin Oncol 9:231-237, 2018
33. Ali A, Black D, Soslow RA: Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. Int J Gynecol Pathol 26:115-123, 2007
34. Soslow RA: Practical issues related to uterine pathology: Staging, frozen section, artefacts, and Lynch syndrome. Modern Pathol 29:S59-S77, 2016
35. Mariani A, Webb MJ, Keeney GL, et al: Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 182: 1506-1519, 2000
36. Khalifa MA, Salama S, Vogel RI, et al: Assessment of the intraoperative consultation service rendered by general pathologists in a scenario where a well-defined decision algorithm is followed. Am J Clin Pathol 147:322-326, 2017
37. Williams JW, Hirschowitz L: Assessment of uterine wall thickness and position of the vascular plexus in the deep myometrium: Implications for the measurement of depth of myometrial invasion of endometrial carcinomas. Int J Gynecol Pathol 25:59-64, 2006
38. College of American Pathologists. Protocol for the examination of specimens from patients with carcinoma and carcinosarcoma of the endometrium. Endometrium 4.1.0.0, posting date August 2018. https://documents.cap.org/protocols/cp-femalereproductive-endometrium-18protocol- 4100.pdf. Last accessed February 16, 2019.
38. Lindauer J, Fowler J, Manolitsas TP, et al: Is there a prognostic difference between depth of myometrial invasion and the tumor-free distance from the uterine serosa in endometrial cancer? Gynecol Oncol 91:547-551, 2003
40. Kondalsamy-Chennakesavan S, van Vugt S, Sanday K, et al: Evaluation of tumor-free distance and depth of myometrial invasion as prognostic factors for lymph node metastases in endometrial cancer. Int J Gynecol Cancer 20:1217-1221, 2010
41. Chattopadhyay S, Galaal KA, Patel A, et al: Tumour-free distance from serosa is a better prognostic indicator than depth of invasion and percentage myometrial invasion in endometrioid endometrial cancer. BJOG 119:1162-1170, 2012
42. Ozbilen O, Sakarya DK, Bezircioglu I, et al: Comparison of myometrial invasion and tumor free distance from uterine serosa in endometrial cancer. Asian Pac J Cancer Prev 16:519-522, 2015
43. Hsu M-I, Chou S-Y, Lin S-E, et al: Very early stage adenocarcinoma arising from adenomyosis in the uterus. Taiwanese J Obstet Gynecol 45:346-349, 2006
44. Puppa G, Shozu M, Perin T, et al: Small primary adenocarcinoma in adenomyosis with nodal metastasis: a case report. BMC Cancer 7:103, 2007
45. Taga S, Sawada M, Nagai A, et al: A case of endometrioid adenocarcinoma arising from adenomyosis. Case Rep Obstet Gynecol 2014:569295
46. Mao X, Zheng W, Mao W: Malignant changes in adenomyosis in patients with endometrial adenocarcinoma: A case series. Medicine (Baltimore) 96:e8336, 2017
47. Antovska VS, Krstevska I, Trajanova M, et al: Endometrioid adenocarcinoma arising in adenomyoma in a woman with a genital prolapse - case report. Open Access Maced J med Sci 20:1091-1094, 2018