

## Peer Review File

Article information: <http://dx.doi.org/10.21037/gpm-21-20>

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### Comment 1:

It is a nice paper, however the part 3,1 is more like a text book and could be condensed

Blood flow seems to be important in diagnosis of malignant fibroids and I miss a section about ultrasound contrast like SonoVue which has increased sensitivity in endometrial carcinoma

#Flow differences between endometrial polyps and cancer: a prospective study using intravenous contrast-enhanced transvaginal color flow Doppler and three-dimensional power Doppler ultrasound  
Ultrasound ObstetGynecol . 2008 Dec;32(7):935-40.#

The authors conclusion, all large inhomogeneous uterine lesions with irregular cystic areas, without shadows and calcification in symptomatic patients especially with abnormal vaginal bleeding suggests malignancy. All mesenchymal lesions resenting dubious ultrasound features and clinical symptoms should be evaluated in a referral center, these statements should be modified. The diagnosis is usually established with pathology examination after a simple hysterectomy. Biopsies should not be performed due to spillage. Fibroids is very common and compromise almost 50% of all hysterectomies performed and many shows a blizzard ultrasound feature, and in case of sarcoma: no morcellation and a total hysterectomy procedure should be performed, which after all is done in most cases. It would be a burden for referral centers to receive all of these cases. Pet scan to detect metastasis is performed postoperatively. Furthermore, the correct ultrasound diagnosis or MRI of benign and malignant lesions of myometrial tumors would bevery interesting and important.

**Reply 1:** Thanks for the observations made to our work. The part 3.1 can be condensed.

The work cited: #Flow differences between endometrial polyps and cancer: a prospective study using intravenous contrast enhanced transvaginal color flow Doppler and three-dimensional power Doppler ultrasound Ultrasound ObstetGynecol. 2008 Dec;32(7):935-40.# is very interesting and the application of SonoVue to evaluate the vascularization of mesenchymal lesions of the uterus could be a subject of study. However, to our knowledge, there are few publications dealing with this topic, which present preliminary data.

In the conclusions, we wanted to emphasize that only doubtful cases, therefore, few and selected cases should be evaluated in reference centers

Following the reviewer's suggestion, we modified the manuscript underlining the new words and sentences:

#### **- Part 3.1; lines 110-111 in the revised version:**

~~Leiomyosarcomas have a poor prognosis even when diagnosed in the early stages (4,23,24). In a large study published in 2009, patients had a five-year survival of 51% at Stage I and 25% at Stage II. All patients with tumor spread outside the pelvis died within 5 years~~

#### **- Part 3.1; lines 114-120 in the revised version:**

~~Leiomyosarcomas arise from a myometrial cell. The cut surface is typically soft, bulging, fleshy, necrotic, hemorrhagic, and lacks the prominent whorled appearance of leiomyomas (4). Pathological diagnosis of leiomyosarcomas is difficult because the differential diagnosis includes all leiomyoma variants, that may mimic malignant lesions, atypical smooth muscle tumors (STUMPs). Furthermore, the histopathologic diagnosis of uterine leiomyosarcoma is based upon mitotic count and the mitotic index is usually high (15 mitotic figures per 10 high power fields (MF/10 HPF), cellular atypia, and the presence of coagulative necrosis. Infiltrating borders large size, extrauterine extension are frequently present. cellular pleomorphism of epithelioid and myxoid leiomyosarcomas, two rare variants, makes microscopic diagnosis difficult. In both tumors, nuclear atypia and mitotic rate are often low, moreover, myxoid leiomyosarcoma present often hypocellularity, while in epithelioid leiomyosarcoma, necrosis is rarely found (4,25,26).~~

#### **- Part 3; lines 167-173 in the revised version:**

Intravenous contrast-enhanced color flow Doppler is an emerging technique in gynecological ultrasound. A prospective study by Lieng suggest that intravenous contrast may help to discriminate between benign endometrial polyps and cancer (35). A recent pilot study on a small cohort of patients (36) investigated the

use of contrast-enhanced ultrasound for the differential diagnosis of uterine leiomyoma subtype and sarcoma. This study describes an uneven high enhancement without regular border associated with large areas of non-enhancement for sarcomas.

**- Part 4; lines 222-227 in the revised version:**

In conclusion, all large inhomogeneous uterine lesions with irregular cystic areas, without shadows and calcification in symptomatic patients especially with abnormal vaginal bleeding suggests malignancy. Preoperative diagnosis of sarcomas remains difficult. The correct preoperative diagnosis is essential for correct treatment. All mesenchymal lesions presenting dubious ultrasound features and clinical symptoms should be evaluated by experienced staff and only selected mesenchymal lesions should be sent to the reference centers.

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**Comment 2:**

The authors aims to provide a narrative review of sonographic imaging in uterine sarcomas. However, I failed to see what NEW or CUTTING-EDGE information does it add to our knowledge compared to other similar review.

**Reply 2:** The differential diagnosis between benign and malignant lesions remains difficult despite the publication of papers researching significant ultrasound parameters. Recent publications reiterate that sarcomas are large heterogeneous masses with irregular cystic areas and rich vascularization, rapidly growing. However, these features are not sufficient for a correct diagnosis, because some sarcomas are poorly vascularized, others have no areas of necrosis and sometimes mimic benign myomas. We think that a new feature is the absence of shadow cones especially those defined as fan shaped shadowing.

Following the reviewer's suggestion, we modified the manuscript underlining the new words and sentences:

**Part 4 lines 218-221 in the revised version:**

Fan shading is a constant feature of leiomyomas. In our opinion, the most important aspect that emerges in the series published by Ludovisi et al. is the absence of the shadow cones in particular the absence of fan shaped shadowing in all types of sarcomas, especially in leiomyosarcomas, in according to Bonneau et al.

**Part 4 lines 228-230 in the revised version:**

The correct ultrasound diagnosis of benign and malignant lesions of myometrial tumors would be very interesting to evaluate with a prospective study especially stressing the evaluation of the shadow cones however, the rarity of these tumors makes it difficult to carry out this project.