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Should we abandon all conservative treatments for uterine fibroids? The problem with leiomyosarcomas

Fibroids are the most common tumor in women and many medical and surgical options exist for their management. The incidence of uterine sarcoma in women undergoing treatment for fibroids has previously been thought to be extremely rare, however there has been recent controversy as to whether this risk has been underestimated. This article reviews the literature investigating the incidence of leiomyosarcoma and explores how different treatment modalities may affect risk from occult malignancy. We aim to provide a tool for counseling women who are considering options for the management of their fibroids.

Keywords: fibroids • hysterectomy • laparoscopy • leiomyomosarcoma • morcellation • myomectomy

Uterine fibroids are the commonest tumor in women. By the age of 50, 80% of Afro-Caribbean and 70% of Caucasian women will have at least one fibroid [1]. It is one of the commonest clinical conditions dealt with by gynecologists.

Advances in minimally invasive surgery over recent decades have allowed the traditional surgical treatments of myomectomy or hysterectomy to be performed laparoscopically or vaginally, with their well-documented advantages over open surgery [2]. Central to the success of these minimally invasive routes is the technique of tissue morcellation, which divides the specimen into fragments enabling removal through small incisions. Although originally carried out manually, the development of electromechanical morcellation significantly improved the ease and efficiency of specimen removal. In turn this has increased the size of fibroids that can be treated using minimally invasive routes.

Leiomyosarcomas (LMS) are the most common of the uterine sarcomas and are notorious for their aggressive nature and poor prognosis. The problem of leiomyosarcoma has been brought to the forefront by the unfortunate experience of a patient in the

USA who underwent a laparoscopic myomectomy for a presumed benign fibroid which unfortunately turned out to be malignant, as highlighted in the Wall Street Journal [3], leading to the US FDA statement advising on the use of power morcellators for the management of uterine fibroids [4]. Subsequently there have been many opinion articles looking at the incidence of leiomyosarcomas and the possible association with poor outcome in women who have had morcellation of their specimen [5,6]. Many medical societies have produced statements on the interim way forward, and the need to exercise caution when using the morcellators to extract specimen from the abdominal cavity [7,8], and subsequently Ethicon, a major supplier of power morcellators, have withdrawn from the market.

The power morcellators were first introduced in 1993 and have revolutionized laparoscopic surgery for the management of uterine fibroids. It however has not been without its negative implications. Since its introduction there have been 55 reported complications with 6 deaths with most of these due to the inexperience of the surgeon using the instrument [9]. There has also been the issue

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of morcellomas due to the dissemination of benign fibroid tissue, which implants on the peritoneal surface of the abdominal cavity [10].

Traditionally hysterectomy has been the main modality of treatment of uterine fibroids, modern treatments of these tumors have diversified to include modalities that promote uterine preservation and include medical, conservative or interventional surgical procedures. These treatment modalities, due to the lack of histological specimens can lead to delay in diagnosis of malignancy and treatment and may compromise patient survival. Thus gynecologists evaluating women presenting with fibroids are faced not only with the choice of whether to offer treatment, but also the type of treatment to offer. They have the clinical challenge of deciding which patient, although rare, might have a sarcoma. Of additional concern are procedures, which disrupt and disseminate tumor cells as with morcellation. The clinician has to equally balance the need to avoid unnecessary extensive surgery, and possible complications for the purposes of avoiding a rare condition and evaluate the known benefits of minimally invasive procedures for the patient. Most of the articles published on this issue to date have looked at the effect of the morcellator on leiomyosarcoma; this article reviews the effect of conservative management of fibroids and how this affects leiomyosarcoma diagnosis, and to provide a tool for counseling women who are considering options for the management of their fibroids. Relevant articles were identified by a computerized search of the Pubmed database. The search included the following key words: 'uterine sarcoma', 'leiomyosarcoma', 'morcellation', 'morcellator', 'leiomyoma AND conservative management'. The search period covered January 1990 to July 2014.

Epidemiology of leiomyosarcoma

Uterine fibroids are one of the most commonly encountered benign gynecological conditions, affecting 40–80% of women depending on ethnicity [1,11,12]. Although the majority of fibroids remain asymptomatic, symptoms such as dysmenorrhea, menorrhagia, pelvic pain and subfertility occur in approximately 30–50% of women with fibroids.

Uterine sarcoma is rare (3-7 per 100,000 in the US population) with a poor prognosis [13]. Leiomyosarcomas are the most common of the uterine sarcomas. Brooks *et al.* reported on the surveillance, epidemiology and end results analysis of 2677 cases of uterine sarcoma between1989–1999. Racial differences in the incidence of uterine sarcoma existed for leiomyosarcoma (1.51/10⁵ for Afro-Caribbean vs 0.91/10⁵ for Caucasians, and 0.89 for women of other races, p < 0.01) [13]. The median age at presentation is

55 years, but Afro-Caribbean women have a bimodal distribution with an initial peak at 35 years of age [14].

The risk of cancer has never been an indication for prophylactic removal of fibroids as the risk of a sarcoma of the uterus is estimated at 17 in a 1,000,000 and only 1 in 1000 women treated for uterine fibroids is found to have a sarcoma. It is contentious whether the quoted incidence is accurate and also whether the incidence in women treated for uterine fibroids is accurate. Studies incorporating large series of patients have shown the incidence to be between 0.1–0.5%. Parker *et al.* found that the total incidence of uterine sarcoma (leiomyosarcoma, endometrial stromal sarcoma and mixed mesodermal tumor) among patients operated on for uterine leiomyoma is low at 0.23% [15]. An incidence of 0.1% was found by Kamikabeya *et al.*, 0.4% by Takamizawa *et al.* and 0.49% by Leibsohn *et al.* [16-18].

A recent report by the FDA reviewed all published data reporting the incidence of LMS. The primary analysis included nine studies ranging in size from 104 to 1429 patients. The prevalence of both uterine sarcoma and leiomyosarcoma ranged from 0 to 4.9 per 1000 persons [4]. They estimated the prevalence of occult uterine sarcoma in women undergoing hysterectomy or myomectomy for presumed benign leiomyomas as 1 in 354 and of leiomyosarcoma specifically as 1 in 498. However, this estimate is not without limitations and needs to be interpreted with caution. All studies involved in the recent analysis were retrospective and the overall number of sarcomas detected was low. There is potential for population bias as centers were predominantly single-center tertiary referral centers, covering a heterogeneous population and some included women of postreproductive in whom a diagnosis of benign fibroids may have been less likely.

A recent commentary highlights the difficulty in estimating risk based on the analysis of data from pooled studies as the CI of 0.07–0.3% spans a fivefold difference in incidence estimation [19].

Issues with conservative management of uterine fibroids

Risks of expectant management

Over 50% of leiomyomas are asymptomatic and many others will only be associated with mild-to-moderate symptoms which patients may wish to manage expectantly. Fibroids increase in prevalence throughout the reproductive years and usually regress after menopause, however in each individual the natural history can be unpredictable. In a multi-ethnic cohort study leiomyoma growth and shrinkage ranged from -89 to +138% both within the same uterus and between different women [20], therefore the success of expectant management can be difficult to predict, particularly as there are few long-term population studies investigating outcomes. In a retrospective longitudinal study in premenopausal women, median fibroid volume increased by 35.2% per year and fibroid size at presentation was the only independent predictor of growth [21]. However in the same study up to 20% of fibroids regressed spontaneously. In an older, nonrandomized study of women with significantly enlarged fibroid uteri (18 weeks), 77% of women choosing expectant management reported no significant changes symptoms after 1 year. 23% of those attempting expectant management subsequently underwent hysterectomy due to deteriorating symptoms [22].

As discussed above the risk of leiomyosarcoma arising from uterine fibroids is thought to be extremely rare and not usually considered a reason for surgical management of asymptomatic fibroids. The exact risk of malignant transformation in asymptomatic fibroids is difficult to establish as studies tend to women undergoing surgery for symptomatic fibroids. Current guidance suggests that expectant management of fibroids is a reasonable option, particularly if a patient is approaching menopause, but that patients should be advised to report new symptoms [23,24].

Risks of medical management

Gonadotrophin-releasing hormone agonists

Gonadotrophin-releasing hormone agonists are one of the most established therapies for medical management of fibroids. They cause amenorrhea and rapid reduction in fibroid size. However, the benefits of gonadotrophin-releasing hormone agonists as a noninvasive medical management choice are tempered by significant side effects and also the inability to obtain a tissue specimen leading to delay in diagnosis of sarcomas. Evidence is sparse and is mainly in the form of case reports. Diagnosis has been made in these reports after surgical treatment prompted by failure to respond to the medical management and also rapid growth in size [25–27]. Again there is a paucity of information as to the delay in diagnosis caused by this treatment and the effect on patient survival.

There are currently no data investigating the risk, or effect on diagnosis, of leiomyosarcoma in the other medical or hormonal treatments of fibroids such as the levonorgestrel intrauterine system and the recently approved selective progesterone receptor modulators.

Risks of nonoperative radiological techniques Focused ultrasound surgery

Focused ultrasound surgery has been widely advocated as a nonexcisional therapy for uterine leiomyomas. In 2003 treatment using a combination of MRI and ultrasonography was approved by the FDA. This treatment focuses high-intensity sound waves on selected fibroids leading to coagulation necrosis. Advantages are those of a noninvasive outpatient procedure with a short recovery time [28].

The procedure does not produce tissue for diagnosis and can lead to delayed diagnosis and suboptimal treatment of leiomyosarcomas. Accuracy of preoperative diagnosis is essential and case reports have identified MRI screening protocol as valuable in identifying women at high risk for sarcomas [29]. Thus although inadvertent treatment of malignant disease can be avoided to a degree, there have been reports of inadvertent treatment of sarcoma patients with magnetic resonance guided focused ultrasound surgery [30].

Uterine artery embolization

Uterine artery embolization aims to occlude the uterine arteries and has a proven efficacy in reduction of fibroid size [31]. The Fibroid Registry for Outcomes Data formed in 1999 collected prospective data on more than 3000 women undergoing embolization for fibroid tumors. Short-term outcomes in women included in this database show effective symptom control with a low complication rate [32]. This minimally invasive treatment, although affording all the advantages of an outpatient procedure to the patient, does not provide a tissue sample for histopathology. Diagnosis is usually made after surgical intervention due to failure of the fibroid to respond to the embolization, as evidenced by multiple case reports [33-35]. Papadia et al. reviewed the literature, comprising mainly of case reports, for the management of sarcomas in presumed benign fibroids treated by embolization. They found a diagnostic delay of 13-15 months as further surgical treatment was prompted by failure of the fibroid to respond to the embolization [36].

Risks of hysteroscopic resection

Hysteroscopic resection of fibroids is minimally invasive and provides adequate symptom relief of menorrhagia, the commonest presenting symptom of fibroids. Submucosal tumors account for approximately 15-20% of fibroids. Currently hysteroscopic resection has largely replaced hysterectomy as the treatment of choice in submucous fibroids [37]. The risk of development of uterine sarcomas after resection of endometrium or fibroids is 0.13% [38], and the risk appears to be greater in the older patient. The added advantage of hysteroscopic resection is that the procedure results in histological specimens and thus undue delay in diagnosis of sarcoma can be avoided, although the patient has to undergo further surgery to complete the treatment. The three microscopic criteria of coagulative tumor necrosis, high mitotic index and occurrence of moderate-to-severe cytological atypia in the resected specimen are indicative of a diagnosis of sarcoma [39]. Resectoscopic surgery is being replaced by endometrial ablation as this can now be performed in the outpatient and day-case setting, and the learning curve for endometrial ablation is not as steep as resection allowing for more surgeons to be able to perform the procedure. Unfortunately there is no tissue diagnosis, thus in this group of patients the risk of malignancy is unquantifiable as demonstrated in the following published series. In a series of 800 patients treated in 54 hospitals, one patient had a sarcoma at 12 month followup, however unfortunately there is no description of subsequent treatment in this patient [40]. In another study of 120 patients followed up over 5 years, one patient was found to have a sarcoma [41].

Risks of laparoscopic management Laparoscopic myomectomy

In women undergoing fertility preserving surgery, disturbance of the tumor mass may lead to dissemination and poor prognosis of an occult malignancy. Thus identification of the patient at high risk of an occult malignancy as well as adequate counseling is essential. Commonly patients undergoing surgery for fibroids are advised on a risk of underlying malignancy of 17 in 1,000,000, based on the rate of uterine malignancies in the general population. However, there is no concrete evidence to substantiate this rate in women with symptomatic uterine fibroids and patient counseling based on this rate may be prone to error. There are sensitive preoperative screening tests to detect cervical, endometrial and ovarian occult malignancies but none exists to detect uterine sarcomas. There is almost a complete lack of evidence as to the preoperative incidence of sarcomas in women undergoing myomectomies or hysterectomies. The current evidence is poor and has been acquired from small observational studies, case reports and single-center experiences. Pooling the data from such evidence may not accurately reflect the true incidence given the heterogeneity of the populations studied, variations in the methodology and reporting bias. Due to the inherent reporting bias the true incidence could be much higher. In a combined analysis of 5666 uterine procedures performed in the USA between 1983 and 2010, 13 unanticipated sarcomas were reported (0.23%). In the individual studies, incidence of leiomyosarcoma ranged from 0-0.49% [6].

Power morcellation is being used with increasing frequency since its introduction in 1993 and gives the advantage of removal of large myomas through minimally invasive procedures. There have been recent concerns raised over the ability of these instruments to disseminate tumor fragments throughout the abdominal and pelvic cavities and thus spread the disease with a perceived poor prognosis [42]. Perri et al. sought to investigate whether the initial surgery for leiomyosarcomas affected the prognosis. In patients with stage I leiomyosarcoma, primary surgery involving tumor injury seems to be associated with a worse prognosis than total hysterectomy as a primary intervention. Survival in patients who underwent primary hysterectomy was 2.8-fold better than that in those who underwent procedures such as myomectomy or subtotal hysterectomy with morcellation (95% CI: 1.02-7.67) [43]. Two other studies concluded that morcellation resulted in dissemination of the tumor and upstaging of the disease with reduced prognosis [44,45]. Oduyebo et al. analyzed the effects of morcellation in tumor dissemination and staging. Out of 12 patients with occult sarcomas who underwent re-exploration, three out of the 11 with presumed stage I disease were found to have disseminated disease [44]. Seidman et al. studied 1091 cases of uterine morcellation. Unexpected diagnoses of leiomyoma variants occurred in 1.2% of cases using power morcellation for uterine masses clinically presumed to be 'fibroids' over this period and disseminated disease occurred in 64.3% of all tumors as identified by follow-up surgery [45].

Laparoscopic supracervical hysterectomy

Morcellation is commonly used in women undergoing supracervical hysterectomy with large uteri. Similar concerns have been raised as discussed above. In contrast to the study by Perri et al. discussed previously [43], Morice et al. did not find any statistical difference in disease recurrence in patients who had morcellation/tumor injury procedures [46]. In a series by Leung et al., the authors found an incidence of leiomyosarcoma of 0.23% in women undergoing hysterectomy for fibroids and subsequently discussed the controversial issue of whether the fear of leiomvosarcoma should make us change surgical routes in a series showing [47]. However, it would not be evidence-based practice to extrapolate harm from such low numbers. In a study of 1584 patients, in which 87.4% underwent preoperative screening for occult malignancies, only four (0.25%) had occult malignancies detected postoperatively (two cases of endometrial cancer and two cases of leiomyosarcoma). This study demonstrated a low probability of unexpected malignancies even in correctly prescreened patients, but in the short term (28-52 months), patients remained recurrence free after treatment [48]. The authors concluded that supracervical hysterectomy is a good procedure for presumed benign disease. Other studies have reiterated the very low incidence of occult malignancies and the failure of preoperative detection methods [49]. Upstaging of the

malignancy in patients who have undergone morcellation is a concern [50]. Park *et al.* found that tumor morcellation during surgery increased the rate of abdominopelvic dissemination and adversely affected survival rates in patients with apparently early uterine leiomyosarcomas. Survival rates have been shown to decrease from 60% at 5 years for stage I disease, 22% for stage 3 disease and 15% for stage 4 disease [51].

It is evident that the studies so far have provided only limited numbers and experience, and as such it is difficult to extrapolate harm from minimal data. One must be cautious in assessing the harm to benefit ratio negatively considering the thousands of women who undergo minimally invasive procedures with the proven benefits in comparison with the handful of women with occult malignancies.

Reliability of preoperative diagnosis of occult malignancy

Traditionally the two symptoms of rapid growth of fibroid and postmenopausal bleeding have been used to indicate an occult malignancy. But research to date has not provided any concrete evidence to link rapid growth of fibroids with malignant change [15]. Growth spurts have been observed in benign fibroids and are accepted as part of benign tumor biology [52]. In the absence of reliable clinical markers investigations such as MRI have been widely used. Although studies have found that MRI is only moderately accurate in differentiating the subtypes of benign uterine smooth muscle tumors, signal intensities and margin characteristics are useful to distinguish benign from malignant tumors [53,54]. Several studies have reported that a combination of dynamic MRI (i.e., MRI enhanced by gadopentetate dimeglumine) and measurement of serum lactate dehydrogenase levels is useful in distinguishing leiomyosarcoma from benign fibroid tumors [55,56].

Furthermore, although endometrial sampling is commonly employed in women with abnormal bleeding to assess endometrial pathology, it does not reliably diagnose uterine sarcoma, with an estimated sensitivity of 38–62% in the limited available data [17,57]. The use of transvaginal or transparietal biopsy or intraoperative frozen section is not thought to be sufficiently reliable in the diagnosis of leiomyosarcoma [7,56].

Overall preoperative diagnosis of leiomyosarcomas are fraught with inaccuracies even with the best of investigative modalities [58]. The low incidence of the disease also contributes to the inaccuracy in diagnosis.

Discussion

A premature death for any reason is a death too many. Review of the literature shows that leiomyosarcoma is a rare and almost universally fatal disease, with no

absolute way of preoperative diagnosis, and the majority of women diagnosed on the basis of histological specimen. The traditional approach to the management of uterine fibroids has been conservative management because of the low malignant potential. Furthermore, conservative management avoids the morbidity and mortality associated with other surgical complications unrelated to malignancy such as infection, hemorrhage, visceral damage and thromboembolic disease. Although limited to a certain degree by the size and type of fibroids, laparoscopic myomectomy remains the gold standard surgical approach due to the low complication rates and faster recovery [59]. Though there has been anxiety expressed by the potential upstaging of the disease as a result of power morcellation, we have demonstrated that any conservative management of uterine fibroids runs the risk of masking or delaying the diagnosis of leiomyosarcoma. If all women expressed this anxiety should we then re-label fibroids as "tumors of unknown malignant potential" and treat all women with fibroids by excisional therapy as soon as fibroids are discovered? This approach would unfortunately add to the vast economic burden already associated with fibroids [60], and cause untold morbidity and potential mortality for women who would potentially have fibroids removed based on current available data. Based on mortality rates it has recently been estimated that the conversion of all hysterectomies using power morcellation to open procedures would result in an estimated 17 additional deaths per year as a result of surgical complications in the USA [61].

The use of contained, or 'in-bag', morcellation to reduce tissue dissemination has been described [62], but this again will need to be weighed up against being able to morcellate under direct vision at all times. Not being able to visualize the tumor being morcellated can lead to potential harm and damage to intra-abdominal organs. Also the possible advantage of the bag would be negated should it be damaged by the morcellator. A small study of 100 matched patients has demonstrated that transvaginal extraction of fibroids upholds effectiveness of electric morcellation, but larger studies are needed [63].

A further option is the use of mini-laparotomy to remove the specimen from the abdomen as demonstrated by randomized controlled trials for myomectomy [64]. Similar perioperative outcomes have been reported in comparisons of mini-laparotomy and laparoscopic myomectomy [65].

If we are to continue with morcellation, improved methods of preoperative triage are required to better identify those at high risk for malignancy and consideration given to imposing an age limit on morcellation. Future research should be directed at improving preoperative tumor identification and development of a

Executive summary

Background

- Uterine fibroids are the commonest tumor in women affecting up to 80% of women. Advances in minimally invasive surgery have allowed the traditional surgical treatments of myomectomy or hysterectomy to be performed laparoscopically. Central to the success of these minimally invasive routes is the technique of tissue morcellation.
- Concerns about the risk of dissemination of occult malignancy following morcellation have received much debate in the recent literature.

Epidemiology of leiomyosarcoma

- Uterine sarcoma is rare (3–7 per 100,000 in the US population) with a poor prognosis. Leiomyosarcomas are the most common of the uterine sarcomas.
- A US FDA report estimated the prevalence of occult uterine sarcoma in women undergoing hysterectomy or myomectomy for presumed benign leiomyomas as 1 in 354 and of leiomyosarcoma specifically as 1 in 498. These estimates are not without limitations and need to be interpreted with caution.

Issues with conservative management of uterine fibroids

- Risks of expectant management
 - The risk of leiomyosarcoma arising from uterine fibroids is thought to be extremely rare and not usually considered a reason for surgical management of asymptomatic fibroids.
 - Current guidance suggests that expectant management of fibroids is a reasonable option, particularly if a patient is approaching menopause, but that patients should be advised to report new symptoms.
- Risks of medical management
 - There is a paucity of data investigating the incidence of leiomyosarcoma in patients receiving medical treatment of fibroids, including gonadotrophin-releasing hormone agonists.
- Risks of nonoperative radiological techniques

- Focused ultrasound surgery

- Advantages of a noninvasive outpatient procedure with a short recovery time.
- Procedure does not produce tissue for diagnosis and can lead to delayed diagnosis and suboptimal treatment of leiomyosarcomas.
- Uterine artery embolization
 - Short-term outcomes show effective symptom control with a low complication rate.
 - Diagnostic delay of 13–15 months for women with sarcoma has been observed.
- Risks of hysteroscopic resection
 - Hysteroscopic resection has largely replaced hysterectomy as the treatment of choice in submucous fibroids.
 - Risk of development of uterine sarcomas after resection of endometrium or fibroids is estimated at 0.13%.
- Risks of laparoscopic management
 - Laparoscopic myomectomy
 - Power morcellation gives the advantage of removal of large myomas through minimally invasive procedures.
 - There have been recent concerns about disseminate tumor fragments and upstaging of disease.
 - Laparoscopic supracervical hysterectomy
 - Morcellation is commonly used in women undergoing supracervical hysterectomy with large uteri.
- Data is conflicting regarding the incidence of occult leiomyosarcoma and effect on prognosis associated with morcellation. **Reliability of preoperative diagnosis of occult malignancy**
- Preoperative diagnosis of leiomyosarcomas is fraught with inaccuracies even with the best of investigative modalities.
- Low incidence of the disease also contributes to the inaccuracy in diagnosis.

Discussion

- Leiomyosarcoma is a rare and almost universally fatal disease, with no absolute way of preoperative diagnosis. The majority of women are diagnosed on the basis of histological specimens.
- Laparoscopic myomectomy remains the gold standard surgical approach due to the low complication rates and faster recovery.
- In rare cases, power morcellation may be associated with upstaging of occult disease however conservative management of uterine fibroids also carries small risks of delaying the diagnosis of leiomyosarcoma.

Conclusion

- Risks from morcellation of occult malignancy may have been previously underestimated but overall risk remains low.
- This has to be balanced against the risk associated with alternative options and patients should be given the appropriate information to make informed choices.

Future perspective

- Future research should be directed at improving preoperative tumor identification and development of a screening protocol.
- Continued advances aimed at improving morcellator safety should provide further surgical options. In bag morcellation may help avoid tissue dissemination and visceral injury however further studies are needed.

screening protocol. In the interim, for practitioners who want to continue to manage fibroids, there should be a database to record outcomes of surgery for fibroids, with reporting of all leiomyosarcomas being made mandatory.

In the UK there is mandatory reporting of gestational trophoblastic disease with treatment of choriocarcinoma being confined to specialist centers, there are cervical screening programs with mandatory reporting of cervical cancer and patients treated in cancer centers. For ovarian cancer despite the absence of accurate screening investigations, women are treated in cancer centers and there is mandatory reporting. At present, even when women do develop sarcoma, treatment is ad hoc and there is no consensus on whether postoperative adjuvant therapy should be given or whether it makes a difference [51]. As with other female genital cancers, if women are unfortunate enough to suffer from leiomyosarcoma there should be a means of mandatory reporting, confining treatment to specialist centers in order to further understand the disease and monitor outcomes.

AAGL guidance supports the use of morcellation in appropriately chosen patients who have been adequately counseled [7]. They recommend that the informed consent process includes a discussion on the risks associated with morcellation such as dissemination of benign or malignant tissue, the effect of morcellation on histopathological tissue examination and the risk of visceral or vascular injury. Patients should also understand the relative risks and benefits of alternatives to morcellation.

Conclusion

The risks from morcellation of occult malignancy may have been previously underestimated but overall risk remains low. This has to be balanced against the

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

- Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am. J. Obstet. Gynecol.* 188(1), 100 (2003).
- 2 Nieboer TE, Johnson N, Lethaby A *et al*. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst. Rev.* 8(3) CD003677 (2009).
- Cochrane review of 34 studies comparing outcomes on open, vaginal and laparoscopic hysterectomy.
- 3 Levitz J, Kamp J. How morcellators simplified the hysterectomy but posed a hidden cancer risk. *Wall St. J.* (2014). www.wsj.com
- 4 US FDA. www.fda.gov

risk associated with alternative options and patients should be given the appropriate information to make informed choices. We need to develop more accurate ways of identifying those at high risk of malignancy and further data regarding the incidence of sarcoma and prognosis following morcellation is required. Due to the uncommon nature of this condition this would ideally be via a large prospective patient registry.

Future perspective

Over the next 5–10 years research needs to be directed at improving the preoperative diagnosis of malignancy, particularly of uterine sarcoma, by identifying risk factors and tumor markers. Further data regarding the incidence of leiomyosarcoma and prognosis following morcellation is required. Continued advances aimed at improving morcellator safety should provide further surgical options. Einarsson *et al.* have reported on the technique of contained electromechanical or 'in bag' morcellation which may help avoid tissue dissemination and visceral injury, however further studies are needed [62]. New devices specifically aimed at contained mechanical morcellation are in development [66].

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- US FDA review of 18 studies investigating the prevalence of occult sarcoma in women undergoing hysterectomy of myomectomy for the treatment of benign fibroids.
- 5 Hampton T. Critics of fibroid removal procedure question risks it may pose for women with undetected uterine cancer. *JAMA* 311(9), 891–893 (2014).
- 6 Kho KA, Nezhat CH. Evaluating the risks of electric uterine morcellation. JAMA 311(9), 905–906 (2014).
- 7 Hodgson B. AAGL Practice Report: morcellation during uterine tissue extraction. J. Minim. Invasive Gynecol. 21(4), 517–530 (2014).
- Comprehensive review of the literature investigating the safety of morcellation in minimally invasive gynecology and specifically the risks of leiomyosarcoma.
- Society of Gynecologic Oncology Position Statement: Morcellation.
 www.sgo.org

- Milad MP, Milad EA. Laparoscopic morcellator-related complications. J. Minim. Invasive Gynecol. 21(3), 486–491 (2014).
- Systematic review investigating the incidence of morcellator related complications over the last 15 years.
- 10 Nezhat C, Kho K. Iatrogenic myomas: new class of myomas? J. Minim. Invasive Gynecol. 17(5), 544–550 (2010).
- 11 Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil. Steril.* 36(4), 433 (1981).
- 12 Serden SP, Brooks PG. Treatment of abnormal uterine bleeding with the gynecologic resectoscope. *J. Reprod. Med.* 36(10), 697 (1991).
- 13 Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989–1999. *Gynecol. Oncol.* 93(1), 204 (2004).
- 14 Harlow BL, Weiss NS, Lotton S. The epidemiology of sarcoma in uterus. J. Natl Cancer Inst. 76, 399–402 (1986).
- 15 Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. *Obstet. Gynecol.* 83(3), 414 (1994).
- 16 Kamikabeya TS, Etchebehere RM, Nomelini RS, Murta EF. Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital. *Eur. J. Gynaecol. Oncol.* 31(6), 651–653 (2010).
- 17 Leibsohn S, d'Ablaing G, Mishell DR Jr, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. *Am. J. Obstet. Gynecol.* 162(4), 968 (1990).
- 18 Takamizawa S, Minakami H, Usui R *et al.* Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. *Gynecol. Obstet. Invest.* 48(3), 193 (1999).
- Knight J, Falcone T. Tissue extraction by morcellation: a clinical dilemma. *J Minim. Invasive Gynecol.* 21(3), 319–320 (2014).
- 20 Peddada SD, Laughlin SK, Miner K *et al.* Growth of uterine leiomyomata among premenopausal black and white women. *Proc. Natl Acad. Sci. USA* 105(50), 19887–19892 (2008).
- 21 Mavrelos D, Ben-Nagi J, Holland T, Hoo W, Naftalin J, Jurkovic D. The natural history of fibroids. *Ultrasound Obstet. Gynecol.* 35(2), 238–242 (2010).
- 22 Carlson KJ, Miller BA, Fowler FJ Jr. The Maine Women's Health Study: II. outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. *Obstet. Gynecol.* 83(4), 566–572 (1994).
- 23 Perez-Lopez FR, Ornat L, Ceausu I *et al*. EMAS position statement: management of uterine fibroids. *Maturitas* 79(1), 106–16 (2014).
- 24 Divakar H. Asymptomatic uterine fibroids. *Best. Pract. Res. Clin. Obstet. Gynecol.* 22(4), 643–654 (2008).
- 25 Loong EP, Wong FW. Uterine leiomyosarcoma diagnosed during treatment with agonist of luteinizing hormonereleasing hormone for presumed uterine fibroid. *Fertil. Steril.* 54(3), 530 (1990).

- 26 Meyer WR, Mayer AR, Diamond MP, Carcangiu ML, Schwartz PE, DeCherney AH. Unsuspected leiomyosarcoma: treatment with a gonadotropin-releasing hormone analogue. *Obstet. Gynecol.* 75(3 Pt 2), 529 (1990).
- 27 Milman D, Zalel Y, Biran H *et al.* Unsuspected uterine leiomyosarcoma discovered during treatment with a gonadotropin-releasing hormone analogue: a case report and literature review. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 76(2), 237 (1998).
- 28 Stewart EA, Gedroyc WM, Tempany CM, Quade BJ, Inbar Y, Ehrenstein T. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. *Am. J. Obstet. Gynecol.* 189, 48–54 (2003).
- 29 Samuel A, Fennessy FM, Tempany CM, Stewart EA. Avoiding treatment of leiomyosarcomas: the role of magnetic resonance in focused ultrasound surgery. *Fertil. Steril.* 90(3), 850 (2008).
- 30 Fukunishi H, Funaki K, Ikuma K *et al.* Unsuspected uterine leiomyosarcoma: magnetic resonance imaging findings before and after focused ultrasound surgery. *Int. J. Gynecol. Cancer* 17(3), 724–728 (2007).
- 31 Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K. Ontario Uterine Fibroid Embolization Collaboration Group. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. *Fertil. Steril.* 79(1), 120–127 (2003).
- 32 Worthington-Kirsch R, Spies JB, Myers ER *et al.* The Fibroid Registry for outcomes data (FIBROID) for uterine embolization: short-term outcomes [Published correction appears in Obstet Gynecol 106, 869 (2005)]. *Obstet. Gynecol.* 106, 52–59 (2005).
- 33 Common AA, Mocarski EJ, Kolin A, Pron G, Soucie J. Therapeutic failure of uterine fibroid embolization caused by underlying leiomyosarcoma. *J. Vasc. Interv. Radiol.* 12(12), 1449 (2001).
- 34 D'Angelo A, Amso NN, Wood A. Uterine leiomyosarcoma discovered after uterine artery embolisation. J. Obstet. Gynaecol. 23(6), 686 (2003).
- 35 Joyce A, Hessami S, Heller D. Leiomyosarcoma after uterine artery embolization. A case report. J. Reprod. Med. 46(3), 278 (2001).
- 36 Papadia A, Salom EM, Fulcheri E, Ragni N. Uterine sarcoma occurring in a premenopausal patient after uterine artery embolization: a case report and review of the literature. *Gynecol. Oncol.* 104(1), 260 (2007).
- 37 Lefebvre G, Vilos G, Allaire C *et al.* The management of uterine leiomyomas. Clinical Practice Gynaecology Committee, Society for Obstetricians and Gynaecologists of Canada. *Obstet. Gynaecol. Can.* 25(5), 396 (2003).
- 38 Vilos GA, Harding PG, Sugimoto AK, Ettler HC, Bernier MJ. Hysteroscopic endomyometrial resection of three uterine sarcomas. J. Am. Assoc. Gynecol. Laparosc. 8(4), 545–551 (2001).
- 39 Carta G, Palermo P, Di Ramio R, De Lellis V, Carta A, Patacchiola F. Leiomyosarcoma after hysteroscopic myomectomy: a case report. *Eur. J. Gynaecol. Oncol.* 33(6), 656–657 (2012).

- 40 Vilos GA, Vilos EC, King JH. Experience with 800 hysteroscopic endometrial ablations. J. Am. Assoc. Gynecol. Laparosc. 4(1), 33–38 (1996).
- 41 Boujida VH, Philipsen T, Pelle J, Joergensen JC. Five-year follow-up of endometrial ablation: endometrial coagulation versus endometrial resection. *Obstet. Gynecol.* 99(6), 988–992 (2002).
- 42 Heller DS, Cracchiolo B. Peritoneal nodules after laparoscopic surgery with uterine morcellation: review of a rare complication. *J. Minim. Invasive Gynecol.* 21(3), 384–388 (2014).
- 43 Perri T, Korach J, Sadetzki S, Oberman B, Fridman E, Ben-Baruch G. Uterine leiomyosarcoma: does the primary surgical procedure matter? *Int. J. Gynecol. Cancer* 19(2), 257–260 (2009).
- 44 Oduyebo T, Rauh-Hain AJ, Meserve EE *et al.* The value of reexploration in patients with inadvertently morcellated uterine sarcoma. *Gynecol. Oncol.* 132(2), 360–365 (2014).
- 45 Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. *PLoS One* 7(11), e50058 (2012).
- 46 Morice P, Rodriguez A, Rey A *et al.* Prognostic value of initial surgical procedure for patients with uterine sarcoma: analysis of 123 patients. *Eur. J. Gynaecol. Oncol.* 24(3–4), 237 (2003).
- 47 Leung F, Terzibachian JJ, Gay C *et al.* Hysterectomies performed for presumed leiomyomas: should the fear of leiomyosarcoma make us apprehend non laparotomic surgical routes? *Gynecol. Obstet. Fertil.* 37(2), 109 (2009).
- 48 Theben JU, Schellong AR, Altgassen C, Kelling K, Schneider S, Große-Drieling D. Unexpected malignancies after laparoscopic-assisted supracervical hysterectomies (LASH): an analysis of 1,584 LASH cases. *Arch. Gynecol. Obstet.* 287(3), 455–462 (2013).
- 49 Hagemann IS, Hagemann AR, LiVolsi VA, Montone KT, Chu CS. Risk of occult malignancy in morcellated hysterectomy: a case series. *Int. J. Gynecol. Pathol.* 30(5), 476–483 (2011).
- 50 Einstein MH, Barakat RR, Chi DS *et al.* Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease. *Int. J. Gynecol. Cancer.* 18(5), 1065–1070 (2008).
- 51 Park JY, Park SK, Kim DY *et al.* The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. *Gynecol. Oncol.* 122(2), 255–259 (2011).
- Observational study investigating prognosis in women with leiomyosarcoma who underwent morcellation during their initial surgery.
- 52 Baird DD, Garrett TA, Laughlin SK, Davis B, Semelka RC, Peddada SD. Short-term change in growth of uterine leiomyoma: tumor growth spurts. *Fertil. Steril.* 95(1), 242 (2011).
- 53 Schwartz LB, Zawin M, Carcangiu ML, Lange R, McCarthy S. Does pelvic magnetic resonance imaging

differentiate among the histologic subtypes of uterine leiomyomata? *Fertil. Steril.* 70(3), 580 (1998).

- 54 Sato K, Yuasa N, Fujita M, Fukushima Y. Clinical application of diffusion-weighted imaging for preoperative differentiation between uterine leiomyoma and leiomyosarcoma. *Am. J. Obstet. Gynecol.* 210(4), 368.e1–e8 (2014).
- 55 Goto A, Takeuchi S, Sugimura K, Maruo T. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. *Int. J. Gynecol. Cancer* 12(4), 354 (2002).
- 56 Schwartz PE, Kelly MG. Malignant transformation of myomas: myth or reality? *Obstet. Gynecol. Clin. North Am.* 33, 183–198 (2006).
- 57 Bansal N, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. *Gynecol. Oncol.* 110(1), 43 (2008).
- 58 Sagae S, Yamashita K, Ishioka S *et al.* Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. *Oncology* 67(1), 33 (2004).
- 59 Saccardi C, Gizzo S, Noventa M, Ancona E, Borghero A, Litta PS. Limits and complications of laparoscopic myomectomy: which are the best predictors? A large cohort single-center experience. *Arch. Gynecol. Obstet.* doi:10.1007/s00404-014-3289-2 (2014) (Epub ahead of print).
- 60 Mauskopf J, Flynn M, Thieda P, Spalding J, Duchane J. The economic impact of uterine fibroids in the United States: a summary of published estimates. J. Womens Health (Larchmt) 14(8), 692–703 (2005).
- 61 Brown J. AAGL Statement to the FDA on Power Morcellation. www.aagl.org
- 62 Einarsson JI, Cohen SL, Fuchs N, Wang KC. In bag morcellation (IBM). J. Minim. Invasive Gynecol. 21(5), 951–953 (2014).
- 63 Bogani G, Uccella S, Cromi A *et al.* Electric motorized morcellator versus trans-vaginal extraction for myomas retrieval following laparoscopic myomectomy: a propensity-matched analysis. *J. Minim. Invasive Gynecol.* pii:S1553-4650(14)00258-1 (2014) (Epub ahead of print).
- 64 Palomba S, Zupi E, Falbo A *et al.* A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. *Fertil. Steril.* 88(4), 933–941 (2007).
- 65 Fanfani F, Fagotti A, Bifulco G, Ercoli A, Malzoni M, Scambia G. A prospective study of laparoscopy versus minilaparotomy in the treatment of uterine myomas. *J. Minim. Invasive Gynecol.* 12(6), 470–474 (2005).
- 66 Isakov A, Murdaugh KM, Burke WC *et al.* A new laparoscopic morcellator using an actuated wire mesh and bag. *J. Med. Devices.* 8(1), 0110 (2014).