Review

Reasons to Reconsider Risk Associated With Power Morcellation of Uterine Fibroids

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Abstract. *Our insights into the molecular pathogenesis of uterine smooth muscle tumors have improved significantly. Accordingly, in the present review, we advocate a more refined risk assessment for patients considering surgical removal of fibroids or hysterectomy, respectively, requiring morcellation. For this procedure, the risk estimates given for the iatrogenic spread of a previously unexpected malignancy considerably vary among different studies. Nearly all previous studies conducted retrospectively refer to the risk of a patient having an unexpected malignancy at the time of surgery. We feel that, more appropriately, risk should refer to the number of tumors because, as a rule, every single nodule arises independently and, thus, carries an independent risk of being malignant or not. Furthermore, whether so-called parasitic fibroids carry an underestimated risk of stepwise malignant transformation is discussed.*

The risk of spreading a malignancy which is associated with power morcellation during laparoscopic hysterectomy or myomectomy is a matter of an ongoing medical, scientific, and even legal discussion. A thorough review addressing different issues of power morcellation and its risks was published recently in this journal (1). The present review addresses an

aspect that was not covered in that review, namely implications related to the genetic basis of fibroid development. We feel that this point should be taken into account when considering the pros and cons of procedures requiring power morcellation and thus warrants an additional review.

As a main part of the discussion on the risks of power morcellation, increased mortality following open procedures compared to laparoscopic approaches requiring morcellation is weighed against a lower risk of iatrogenic spread of an unexpected malignancy such as in leiomyosarcoma (LMS). Base-case estimates for procedure-related deaths led Siedhoff and co-workers to the conclusion that at a hypothetical LMS incidence of 0.0015, mortality for both groups, *i.e.* laparoscopic *versus* abdominal hysterectomy, is equivalent (2). This appears to be close to but higher than the incidence of LMS among women undergoing hysterectomy due to presumed fibroids which the same authors estimate to be around 0.0013. According to these minor differences that have been observed between the two different types of risk, laparoscopic hysterectomy was calculated to result in slightly more quality-adjusted life years than abdominal hysterectomy (499,171 *vs.* 490,711 over 5 years). This prompted us briefly to review the tumor genetics point of view because we feel that in the past three topics which are covered in this review have received only little or no attention at all but should encourage re-reconsideration of risk figures and further studies. Before going into the details of these three topics, we briefly review the genetic alterations found in benign, borderline, and malignant smooth muscle tumors of the uterus.

The Genetic Background of Uterine Fibroid Development

Molecular studies have revealed that, like other benign and malignant tumors, fibroids, in the majority of cases, are of

monoclonal origin with nearly every individual nodule having its own independent history and pathogenesis. This independent monoclonal origin of the single fibroids of individual patients was pointed out already in early studies based on the inactivation patterns of the two alleles of genes mapping to the X chromosome and later confirmed by a variety of independent studies (3-6). In contrast to multiple uterine fibroids, multiple lesions found in benign metastasizing leiomyoma disease apparently often share the same genetic alterations, indicating their origin from a monoclonal lesion, presumably a single benign uterine fibroid (7, 8). More recently, impressive studies on the heterogeneity of driver mutations among multiple fibroids of the same patient have been presented, the results of which confirm the independent origin of nearly every single lesion (9-12).

Alterations of the genes encoding the two DNA-binding proteins mediator complex subunit 12 (*MED12*) and high-mobility group protein AT-hook 2 (*HMGA2)* seem to drive tumorigenesis mutually exclusively in single tumors (13-15) and constitute the two most frequent types of driver mutations in fibroids (9, 10, 14, 15) with those of *MED12* being highly predominant in women with multiple fibroids (13, 16, 17). Accordingly, both types of mutations characterize independent tumor entities that can also be distinguished based on certain clinical and histological parameters *e.g.* their size and stromal content (18, 19), their gene-expression patterns (20), and metabolome (21), and may even differ with respect to their cellular growth capacity *in vitro* (22). Moreover, they even very rarely coexist among the individual tumors of single patients (23). Interestingly, both main genetic alterations seen in subsets of uterine fibroids are also found in separate subgroups of fibroadenomas of the breast (24-26) and, akin to the situation in smooth muscle tumors of uncertain malignant potential (STUMP) and uterine leiomyosarcomas, *MED12* mutations are also a frequent finding in benign as well as in malignant phyllodes tumors (27-29).

Besides these two frequent genetic subgroups, other less frequent genetic alterations are found in double-negative (lacking *MED12* mutations as well as *HMGA2* rearrangements) fibroids (30, 31) that also present with a higher percentage of histological variants. Nevertheless, it has been demonstrated that in these cases as well, single fibroids usually can be distinguished based on the individual mutations they carry (9). Some of these latter genetic alterations, *e.g.* full or partial monosomy of chromosome 22, may endow tumors with a higher risk of malignant transformation (32, 33).

Malignant Transformation of Uterine Fibroids – Fact or Fiction?

The question as to whether uterine fibroids may (rarely) undergo malignant transformation has been a matter of debate for many years. Recently, the results of genetic analyses have offered additional evidence for such a transformation. Regarding uterine leiomyosarcomas and STUMP, a subset of these shares genetic alterations occurring in fibroids, in particular mutations of *MED12* (34-41). This suggests an albeit very low probability of malignant transformation within pre-existing fibroids, in particular with cellular or symplastic areas (42) leading to STUMP and leiomyosarcomas. This is in accordance with previous studies demonstrating the presence of morphologically benign tumoral areas in a considerably high percentage of leiomyosarcomas (42, 43), as well as common genetic alterations as outlined above and summarized by Mittal *et al.* (42). In addition, patients apparently experiencing malignant transformation of leiomyomas, atypical leiomyomas, benign metastasizing leiomyomas or STUMP to leiomyosarcomas (33, 44-47) have been described repeatedly. In contrast, evidence for the existence of a considerable percentage of STUMP or leiomyosarcomas with *HMGA2* rearrangement is lacking.

In summary, genetic studies on benign, borderline, and malignant smooth muscle tumors of uterine origin suggest a very low but existent probability of malignant transformation of initially benign tumors. A genetic classification of these lesions may be not only of diagnostic but also of predictive relevance (48-52) and should be mandatory for future clinical studies.

The Number of Tumors as a Potential Independent Risk Factor

Lessons from tumor genetics in general make it highly reasonable to assume that due to their independent molecular origin, every nodule carries its own and independent risk of being malignant. *Vice versa*, it is tempting to assume that with an increasing number of nodules, a linear increase of the risk of morcellating a malignant tumor is likely to be expected. Accordingly, for future studies the number of fibroids examined should be given in addition to the mere number of patients.

Actually, the number of tumors can be expected to act as an independent risk modifier. For example, if a study with adequate sampling has revealed a risk of having *de novo* LMS at the time of surgery of about 1/1,000 patients and if in the study population, the average number of tumors is three, a patient with just one tumor has a risk of malignancy of 1/3,000, whereas a patient with three nodules has a risk of 3/3,000 and a patient with six tumors of 6/3,000.

Because we have to consider not only *de novo* LMS but also eutopic malignant transformation of uterine leiomyoma (UL) which seems to be likely *e.g.* for the group with *MED12* mutations (34-36, 38), these considerations fit with a well-documented higher incidence of LMS in populations having a higher number of fibroids. A study by Laughlin *et al.* revealed that during pregnancy leiomyomas occurred

more often in Black than in White women (18% in Blacks, 8% in Whites, and 10% in Hispanics). In addition, the proportion of women with leiomyomas was found to increase much more steeply with age for Blacks than Whites (53). In another study on 18- to 30-year-old women, the prevalence of ultrasound-diagnosed fibroids was 15% overall, again with a clearly higher prevalence among Black women (26% in Black women and 7% in White women) (54). This has been reported by a number of other articles [see *e.g*. (55-57), reviewed by (58, 59)]. An association between age at menarche and fibroid development apparently was observed in several studies both for Black and White women (60, 61).

Of note, a number of older studies also revealed a clearly higher incidence of uterine LMS in Black patients of Afro-American origin than in White Americans (62, 63). In order to determine the association of race with incidence, histology, treatment, and survival in women with uterine sarcoma, Brooks *et al*. analyzed the data of 2,677 patients from the Surveillance, Epidemiology, and End Results program. All patients had been diagnosed with a uterine sarcoma within a 10-year period, including 300 who had leiomyosarcoma. Compared to White women, a significantly higher incidence of LMS was found in Black women ($1.5/10^5$ for Blacks *vs*. $0.9/10^5$ for Whites, $p<0.01$) (64). More recently, in a series of 984 patients with uterine cancer from one institution (Montefiore Medical Center, NY, USA), Smotkin *et al*. found a significantly higher incidence of uterine leiomyosarcomas in Black than in White patients [5.2% (16/308)] compared to 1.0% (4/382) of uterine cancer (65). *Vice versa*, in line with these considerations, power morcellation in case of patients of ethnicities showing a higher number of fibroids can be assumed to carry a higher risk of iatrogenic spreading of malignant and premalignant tumors. Accordingly, the risk of occult uterine cancer seems to be significantly associated with race/ethnicity (66).

In summary, in the case of multiple fibroids, preoperatively, patients should be aware of the higher risk associated with minimally invasive removal of these fibroids compared with hysterectomy.

Follow-up of the Patients: Which Groups and Why?

Without any doubt, women undergoing minimally invasive surgery requiring morcellation should know about the risk of spread of an occult malignancy by the procedure. Nevertheless, all studies addressing this point consider the risk of a malignant tumor already existing at the time of surgery. A more sophisticated question is if the risk of peritoneal implantation followed by secondary malignant transformation warrants additional attention. Besides malignant tumors, as in particular leiomyosarcomas, there are apparently other tumor entities prone to be spread by morcellation, *i.e*. particular subsets of STUMP, as well as

atypical leiomyomas. There might be a high risk for some of these latter lesions giving rise to the so-called parasitic tumors characterized by their ability for peritoneal spread.

The recent WHO nomenclature refers to STUMP as to smooth-muscle tumors "with features that preclude an unequivocal diagnosis of leiomyosarcoma, but do not fulfil the criteria for a benign leiomyoma, or its variants, and raise concern that the neoplasm may behave in a malignant fashion" (67). Certainly, it is questionable whether these STUMPs constitute a separate clear-cut entity of tumors or rather represent different steps of a dynamic process of potentially malignant transformation. However, Croce *et al*. used comparative genomic hybridization to investigate a series of 29 patients with uterine STUMP with a follow-up period ranging between 12 and 156 months. By introducing a scoring system to evaluate genomic abnormalities, the tumors were split into two groups with different outcomes: A group comparable to leiomyomas and another similar to leiomyosarcomas, but more indolent (50). Heterogeneity and ongoing karyotypic evolution also detected by comparative genomic hybridization may be other genetic criteria assisting the differential diagnosis of STUMP *versus* leiomyosarcoma (51). The results of an attempt to differentiate between benign and malignant uterine smooth muscle tumors based on integrated comparative genomic and transcriptomic approach were published recently (68). Nevertheless, these methods all require available tumor tissue, whereas to the best of our knowledge, clear preoperative biomarker- or image-based assessment tools to recognize STUMP as well as atypical leiomyomas with sufficient specificity and sensitivity are lacking. Overall, the International Society for Gynecologic Endoscopy (ISGE) Task Force for Estimation of the Risk in Endoscopic Morcellation stated recently that in general, further studies and prospective data collection are greatly needed to improve sarcoma risk assessment (69).

In addition, unfortunately, most studies on the risk of spreading a malignancy do not address the problem of STUMP and neither do they give information on the prevalence of STUMP in their series nor address the problem of follow-up of these patients (70). Of note, once morcellated, peritoneal dissemination of STUMP does not seem to be an infrequent outcome. For example, dissemination without definite infiltration or invasion of adjacent tissue was noted in all four patients with STUMP undergoing follow-up exploratory laparotomy reported by Seidman *et al*. (71). Mowers *et al*. performed a retrospective chart review on six patients who underwent morcellation and were subsequently found to have a STUMP. Of these, five patients were found to have benign implants after surgical re-exploration (median time to re-exploration-7 weeks, range=6-19.2 weeks) (72). A trend towards an increased risk of recurrence was also noted by Raspagliesi *et al*. for patients undergoing morcellation of a STUMP (73) and Oduyebo *et al*. detected disseminated

intraperitoneal disease in one out of four patients with presumed stage I STUMP even at immediate surgical re-exploration (74). In line with these findings, Bogani *et al*. reported a case of a (morcellator) port-site implantation of a smooth muscle tumor seen 6 years after laparoscopic morcellation of a STUMP (75), thus also pointing to the significance of a relatively long follow-up period.

From the latter studies on the risk of power morcellation, sparse information is also available about the prevalence of so-called parasitic leiomyomas at the time of initial surgery. Parasitic leiomyomas lead to benign implants outside the uterus and are thought to be of iatrogenic origin in the majority of cases. Their presumable incidence among patients undergoing laparoscopic surgery including power morcellation is clearly higher than that of unexpected malignancies and is estimated to be in the range of 0.12-0.95% (76). Unfortunately, little is known about their genetic background or their tendency to undergo malignant transformation. Nevertheless, their ability to implant ectopically is a reason for concern and there is insufficient data available to show whether the new environment or particular driver mutations may increase their ability to undergo malignant transformation. In general and as discussed in detail above, there is compelling evidence that, albeit as a very rare event, *MED12*-mutated fibroids seem to be able to undergo malignant transformation. Likewise, it is tempting to speculate that other much less frequent genetic subtypes of fibroids are also able to do so. This assumption is supported by recent findings obtained by our group. We presented the case of a 50-year-old woman who initially underwent laparoscopic subtotal hysterectomy because of symptomatic fibroids. While in none of the samples examined was histopathological evidence for malignancy noted, she presented again more than 2 years later with peritoneal nodules of a leiomyosarcoma. Akin to a fingerprint, these lesions revealed identical characteristic patterns of healed chromothripsis when compared with one of the initial tumors by genomic comparative hybridization (33). This case would have had escaped attention in any of the studies dealing only with the prevalence of primary LMS detected at the time of initial surgery. In general, there is currently no evidence whether or not ectopically placed fragments of parasitic UL have a higher risk of undergoing malignant transformation than the primary tumor.

Similarly, the so-called benign metastasizing leiomyomas (ICD-O 8898/1) require some attention. By definition, these are rare benign smooth muscle neoplasms originating in the uterus that have the potential to metastasize to distant sites, most commonly the lungs. Accordingly, they are often noted at distant sites several years after hysterectomy or myomectomy. Of note, the presence of UL-specific *MED12* mutations has been described in apparent lung metastases in a patient suffering from benign metastasizing leiomyoma

with fatal outcome (46), while other cases showed mutations different from those typically found in UL (77, 78).

However, a considerably long follow-up period seems to be required for all cases instead of restricting follow-up evaluation to those patients not showing the classical histology of leiomyoma.

Studies Involving Morcellated Specimens

Morcellation usually results in a high number of tissue fragments and accordingly some problems arise when histopathological evaluation of the samples is performed (79). For example, if specimens are morcellated that contain more than one fibroid it is, as a rule, impossible to unambiguously allocate a single fragment to a particular tumor. Accordingly, it is also nearly impossible to ensure that every tumor has been examined histopathologically, which may result in tumors that have not been sampled at all. The presence of such non-sampled tumors can be expected to increase with an increasing number of morcellated fibroids, as well as with their decreasing size.

In their study on iatrogenic spreading of uterine mesenchymal neoplasms due to power morcellation, Seidman *et al*. have recommended histological evaluation by generously sampling these cases with multiple lesions, "aiming to cut one section each per 1 cm of the dominant lesion(s), as well as several sections representing any secondary lesions", feeling that this may best recapitulate the degree of sampling performed on an equivalent en bloc resection. Moreover, it is recommended to sample "any areas of yellow coloration (as opposed to tan), any softened or 'degenerated' areas, tissue adjacent to necrosis, and any areas of hemorrhage" (71). Obviously, this procedure addresses the problem of undersampling and takes into account possible histological and heterogeneity along the lesions, but in general problems arising from the destruction of the spatial organization of the specimens are not avoided. Of note, Mittal and co-workers found leiomyoma-like areas in leiomyosarcomas in 18/26 tumors examined. In five of these cases, histology of the leiomyoma-like area corresponded to a usual-type leiomyoma and not to any of the variants (42). Nevertheless, to the best of our knowledge, commonly accepted rules for sampling considering the number and size of the single fibroids are lacking and it seems tempting to speculate that in rare cases, undersampling may preclude histological detection of malignant nodules. Therefore, the results of studies involving morcellated specimens are, as a rule, not well-suited to addressing risk estimates for unexpected malignancy.

Conclusion

It is well documented that morcellation of specimens obtained by laparoscopic hysterectomy or myomectomy is
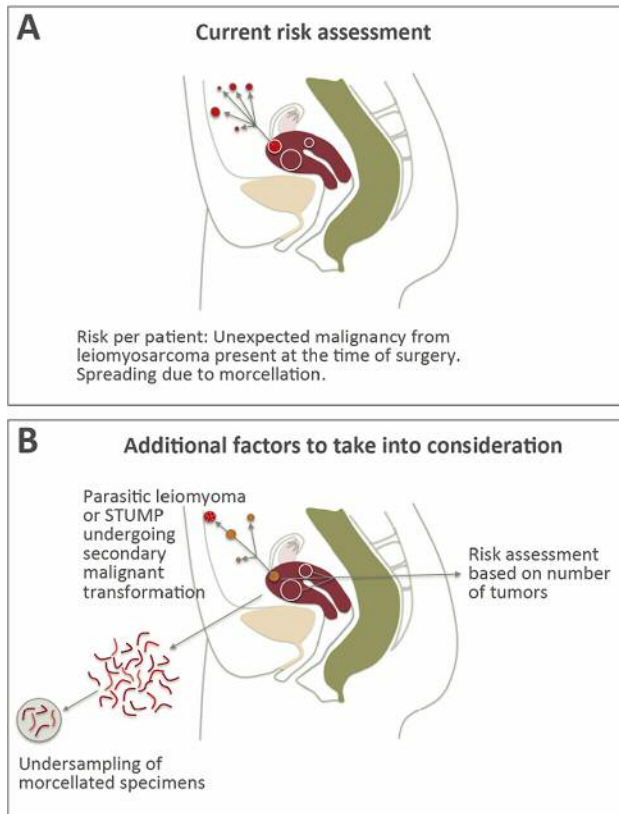
Figure 1. *Classical assessment of risks associated with power morcellation of uterine fibroids compared to factors recommended for additional consideration. A: Evaluation of a patient's risk having an unexpected leiomyosarcoma at the time of surgery based on retrospective analyses of histopathology. B: Recommended factors to be taken into consideration for an advanced risk assessment. STUMP: Smooth muscle tumors of uncertain malignant potential.*

associated with the risk of spreading an unexpected malignancy or of benign tissue [for review and clinical recommendations see (80)], but risk estimates vary over a broad range. However, a sufficient calculation of risks associated with the procedure is of outstanding importance when considering its pros and cons. We feel that previous risk estimates failed to address factors that can act as risk modifiers, as summarized in Figure 1. First of all, a major risk factor is the number of lesions that are morcellated which, according to the biology of the lesions, is assumed to act as a direct risk multiplier. Moreover, there is some evidence that in some cases, spreading of benign lesions such as the so-called parasitic leiomyomas may precede their malignant transformation at ectopic sites. Accordingly, for future studies, a clinical follow-up of all patients undergoing morcellation should be performed in order to avoid underestimating the risks associated with parasitic behavior

of initially benign tumors of uterine smooth muscle. For assessment of the risk of spreading an unexpected malignancy, the results of available studies based on morcellated specimens should be interpreted with caution because of possible undersampling.

Finally, the Authors are well aware of the fact that they did not cite all relevant articles in this field. Accordingly, if such an article is missing from this review, it does not mean anything about its impact on the field.

Conflicts of Interest

J.B.: Invited speaker for Gedeon Richter.

Authors' Contributions

C. Holzmann: Conception, wrote the article, and approved the final version. W. Kuepker: Discussed and revised the article, approved the final version. B. Rommel: Discussed and revised the article, approved the final version. B. M. Helmke: Discussed and revised the article, approved the final version. J. Bullerdiek: Conception, wrote the article, approved the final version.

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