Review Uterine leiomyosarcomas: a review of the diagnostic and therapeutic pitfalls

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Key content:
• Uterine leiomyosarcomas are the most common uterine sarcoma and they are notoriously aggressive in nature.
• Preoperative diagnosis is difficult and they are usually detected as an incidental finding at surgery.
• Tumour stage is the most important prognostic factor.
• Misdiagnosis or delay in diagnosis can occur following the use of conservative techniques for managing uterine fibroids.
• The primary treatment is surgical, while the role of adjuvant therapy is still to be clearly defined.

Learning objectives:
• To appreciate the diagnostic challenges faced with uterine leiomyosarcomas, especially in view of the similarities with uterine fibroids.
• To learn about the current views on surgical treatment and adjuvant therapy.
• To have an understanding of the novel therapies currently under investigation.

Ethical issues:
• Can we offer women conservative non-surgical treatment for fibroids if we cannot confidently exclude leiomyosarcomas?

Keywords chemotherapy / FIGO criteria / radiotherapy / uterine fibroids / uterine leiomyosarcomas
Introduction

Uterine sarcomas account for between 3–7% of all malignant diseases of the uterine corpus. They can be classified broadly into leiomyosarcomas, which arise from the smooth muscle of the myometrium, and endometrial stromal tumours, which originate from the endometrial stroma.\(^6\) Mixed mesodermal tumours or carcinosarcomas have both epithelial and mesenchymal components and are now thought to be metaplastic carcinomas, rather than a subgroup of sarcomas. Leiomyosarcomas are the most common, accounting for about 25–36% of uterine sarcomas,\(^4\) and they are notorious for their aggressive nature and poor prognosis. This may be the result of their location in the vascular myometrium of the uterus, which allows for early invasion and widespread metastases, particularly to the lungs. The relative rarity of uterine leiomyosarcomas, as well as their pathological diversity, hinders studies aimed at improving understanding of the disease and makes it difficult to define the optimum management.

Uterine fibroids are not generally thought to develop into malignant leiomyomas but leiomyosarcomas frequently coexist within a fibroid uterus\(^7\) and approximately 0.5% of women who have hysterectomies for uterine fibroids are found to have leiomyosarcomas.\(^7\)

Worryingly, the incidental finding of a leiomyosarcoma at surgery remains the most common form of presentation as preoperative diagnosis remains inadequate. With the increasing use of conservative techniques for treating uterine fibroids, the likelihood of a delay in diagnosis or misdiagnosis of these tumours remains a particularly disturbing problem. This review aims to explore the current dilemmas surrounding management of women with uterine leiomyosarcomas, including clinical presentation, diagnosis, prognosis, treatment options and exploration of novel therapies that might play a role in improving survival in the future.

Clinical presentation

The median age at presentation is usually between 47 and 56 years of age, although the range varies widely, between 22 and 89 years of age.\(^6\)

Risk factors for uterine sarcomas are similar to those for endometrial carcinoma and are summarised in Box 1. A history of pelvic radiation has also been identified as an aetiological factor, as well as exposure to tamoxifen.\(^11\)

Unfortunately, there are no symptoms specific to leiomyosarcomas. Abnormal vaginal bleeding and pelvic or abdominal pain are the most frequent presenting symptoms but the similarity to the presentation of benign leiomyomas further compounds the difficulty in diagnosis.\(^1,6\)

Although the finding of a rapidly enlarging fibroid may cause concern that it has undergone sarcomatous change, this has not been validated.

Diagnosis

Most leiomyosarcomas are detected only at the time of histopathological evaluation of a hysterectomy or myomectomy specimen.\(^2\) The incidence of leiomyosarcomas being found in women operated on for presumed uterine fibroids is about 0.5%.\(^6\)

This clinical overlap emphasises the critical need for reliable preoperative diagnosis, as tumour stage is the only proven prognostic factor to affect a woman’s survival. The earlier a leiomyosarcoma is detected, the greater the likelihood of prolonged survival.

As conservative non-surgical techniques of treating uterine fibroids are becoming more popular, the non-detection of leiomyosarcomas is a major concern. This can result not only in a delay in diagnosis but also in instituting the appropriate surgical staging and treatment. Uterine artery embolisation has been introduced for treating symptomatic fibroids but, regrettably, there have been several case reports of undetected leiomyosarcomas being inadvertently embolised, resulting in late presentation of this disease.\(^7,10\) Similar experiences have also been reported with the use of gonadotrophin-releasing hormone (GnRH) agonists.\(^3\) It is, therefore, clear that there is a definite and mandatory need for preoperative assessment of these women to attempt to reduce the number of subsequent incidental findings of leiomyosarcomas.

Histology

Unfortunately, preoperative diagnosis so far has many deficiencies. Histological diagnosis by endometrial sampling is unreliable as it cannot reach the surface of the endometrial cavity which gives a low sensitivity of approximately 30%.\(^6\) Similarly, intraoperative frozen sections performed for suspicious fibroids are often inaccurate.\(^7\) Recently, Kawamura et al.\(^1\) suggested the use of a transcervical needle biopsy of a myoma-like lesion combined with magnetic resonance imaging (MRI) as a reliable diagnostic test for the differential diagnosis between uterine sarcoma and fibroids.

<table>
<thead>
<tr>
<th>Risk factors for uterine sarcoma</th>
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<tr>
<td>Nulliparity</td>
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<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Obesity</td>
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<tr>
<td>History of pelvic radiation</td>
</tr>
<tr>
<td>Exposure to tamoxifen</td>
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Box 1
As for the histological differentiation between leiomyomas and leiomyosarcomas, the mitotic count (number of mitoses per 10 high-power microscopic fields) has traditionally been used and has been considered to be a prognostic factor. However, more recent criteria give greater importance to the presence of coagulative tumour cell necrosis and cytological atypia. Hence, the absence of coagulative necrosis and atypia suggest a fibroid, even if the mitotic count is as high as 20.

Immunohistochemistry can also be useful in differentiating between benign and malignant disease. Mayerhofer et al. have suggested that expression for Ki67 could be an important immunohistochemical variable that could predict the potential for malignant disease and also that significantly raised levels of Ki67 antigen correlate well with increased tumour growth.

Imaging

At present, the lack of ability of imaging techniques to detect these tumours, especially in differentiating malignant from benign disease, is disappointing. Doppler flow studies have been used in some studies to assess intratumoural blood flow in an attempt to improve preoperative diagnosis of sarcomas but reports, so far, have been conflicting.

Although MRI and computed tomography (CT) may be able to describe a pelvic mass, there is definite difficulty in distinguishing between leiomyosarcomas and degenerating uterine fibroids. Other conditions that mimic the appearance of sarcomas when using CT or MRI are: adenomyosis, IV leiomyomatosis, lymphoma and endometrial carcinoma. However, using dynamic contrast-enhanced MRI with a gadolinium-based contrast agent increases the likelihood of differentiating between leiomyosarcomas and degenerated fibroids. Goto et al. show that specificity, positive predictive value, negative predictive value and diagnostic accuracy of conventional MRI alone are 93%, 53%, 100% and 93%, respectively but, for dynamic MRI, this is 93%, 83%, 100% and 95%. Combined use of dynamic MRI and serum measurement of lactate dehydrogenase (LDH) isozymes increased all these values to 100%. Similarly, fluorodeoxyglucose–positron emission tomography (FDG-PET) has also been shown to be of some use in the differentiation of uterine leiomyosarcomas.

With rapid advances being made in terms of improved image resolution, reduced artefact, use of contrast and the added benefit of being non-invasive and reproducible, imaging techniques, especially MRI, hold the most promise for preoperative diagnosis. This is essential in detecting these tumours at an early stage or where conservative treatment is contemplated.

Prognosis

The modified 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria used typically for endometrial adenocarcinoma are also used to assign stages for uterine leiomyosarcomas. Tumour stage and grade are the main prognostic factors that have been shown to influence disease-specific mortality, while other factors (as shown in Box 2) have also been investigated, although they are not clearly proven to have an impact on survival.

In a review of 208 women with leiomyosarcomas, Giuntoli et al. devised a risk assessment index using the variables of age, tumour size, stage and grade. Women were assigned points for each of these three variables: age >51 years, tumour size >5 cm and stage II, III or IV. In addition, 2 points were assigned for grade 2, 3 or 4. The women were then classified as low risk (0–1 points), intermediate risk (2–3 points) and high risk (4–5 points). This index proved to be highly predictive of disease-specific survival.

More recently, Wu et al. recorded similar findings by demonstrating that age >50 years, stage III or IV disease and tumour size >11 cm significantly influenced overall survival, even though only tumour stage, size and the use of adjuvant chemotherapy were independent significant prognostic factors.

Overall, tumour stage has been confirmed as the strongest prognostic variable. The reported 5-year overall survival ranged from 62–65% in studies that included predominantly stage I disease, in contrast with studies with a higher proportion of advanced disease where the 5-year overall survival rate was as low as 29%.

Surgical management

There have been relatively few randomised controlled trials (RCTs) specifically investigating different treatment options for leiomyosarcomas. This is mainly because of the uncommon nature of these tumours. Also, since leiomyosarcomas belong to the overall group of uterine sarcomas, a heterogeneous group of tumours with...
pathological diversity, few clinical trials identify leiomyosarcoma separately from the other types of sarcomas. For instance, in a systematic review of chemotherapy for advanced uterine sarcomas, no RCTs reported results for separate histological subtypes and only eight prospective phase II trials reported the effects of first and second line chemotherapy for uterine leiomyosarcomas.9

It is universally accepted that surgery is the primary treatment for uterine leiomyosarcomas. A total abdominal hysterectomy and bilateral salpingo-oophorectomy and appropriate surgical staging, including peritoneal washings and sampling of suspicious nodules, should be carried out. This should be done by a gynaecological oncologist in the setting of a cancer centre. Sagae et al.4 found that having no residual disease at surgery was an important prognostic factor and it has been recommended that aggressive surgical cytoreduction at the time of initial diagnosis offers the best possibility of prolonged survival.10

Three areas of contention with regard to surgery are, however, oophorectomy in the premenopausal woman, incidental finding of a leiomyosarcoma in a myomectomy specimen and pelvic lymphadenectomy.

Oophorectomy in the young woman
The issue of oophorectomy in the young, premenopausal woman is still under debate because of the low reported incidence of ovarian metastases in uterine leiomyosarcomas.2 It has been established that some leiomyosarcomas of the uterus express estrogen receptors, with concern for the effect of hormonal stimulation of the tumour accounting for the inclination towards bilateral oophorectomy.3 Despite this, several studies show no difference in overall survival and recurrence rates were unaffected in women with early stage disease whose ovaries were preserved.3,5,6 A large case-control study by Giuntoli et al.7 also found that ovarian preservation did not affect prognosis in selected cases. It may be reasonable to consider ovarian conservation in young women with early stage disease.

Leiomyosarcomas found in myomectomy specimens
Another therapeutic dilemma in treating younger women is the discovery of a leiomyosarcoma during histological examination of a myomectomy specimen. Total hysterectomy has been established as the safest surgical procedure for these cases. However, Gaducci et al.8 reported a subset of eight such women who were managed conservatively with myomectomy alone and who were disease free after a median follow-up of 13.5 months, two of whom went on to have subsequent pregnancies. A conservative approach following myomectomy should only be taken for specific and accurately selected women who strongly desire pregnancy and who are well counselled about the risks involved.

Pelvic lymphadenectomy
The role of lymphadenectomy is unclear because of the limited number of studies in this area and reports in the available literature are conflicting. The incidence of lymph node metastasis from uterine leiomyosarcomas is very low and is unlikely in the absence of extrauterine disease. As a result, routine lymph node dissection is not usually done for women with the disease confined to the uterus and with normal lymph nodes on observation and palpation.3,10,11 In a retrospective review by Giuntoli et al.12 of 208 women with uterine leiomyosarcomas, 36 had lymph node dissection, of whom 4 (11%) had positive nodes. Lymph node status may, however, have a role as a staging procedure as well as in determining the need for adjuvant pelvic radiotherapy, although the therapeutic benefit (as with endometrial carcinoma) is still to be proven.

Adjuvant therapy
Because of the limited local control of uterine leiomyosarcomas, adjuvant pelvic radiotherapy and chemotherapy have, to some extent, been investigated over the last 30 years. Unfortunately, as many of these studies were underpowered, there have been conflicting reports and, again, they have not evaluated the different histological subtypes of uterine sarcomas separately.

Pelvic radiotherapy
Adjuvant pelvic radiotherapy has been shown by some to improve disease-free survival rates. Echt et al.13 reported a 38% disease-free survival rate in women receiving adjuvant radiotherapy compared with 18% in women receiving surgery alone. However, despite the possible benefit in reducing local recurrence rates, there has not been a proven significant impact on overall survival. In addition, as leiomyosarcomas tend to recur outside the pelvis, this further limits any potential advantages of regionally directed radiotherapy.

Chemotherapy
Similarly, the role of adjuvant chemotherapy has not been clearly defined. There have been no RCTs, to date, that have unambiguously demonstrated improved survival when using adjuvant chemotherapy in completely resected high-grade leiomyosarcomas.

A non-blinded RCT by Muss et al.14 compared doxorubicin alone with doxorubicin plus cyclophosphamide for first-line treatment for advanced or recurrent uterine sarcomas, which included 38 women with leiomyosarcomas. The response rate of 19% was identical for both arms.
but the rate for leiomyosarcomas was not reported separately. The only other RCT to include women with leiomyosarcomas compared doxorubicin with doxorubicin plus dacarbazine and noted a significantly higher overall response rate with the combination regime but, again, subgroup analysis was not done and separate response rates for leiomyosarcomas were not reported.  

Although not all women will have adjuvant therapy, the most active agents for advanced uterine leiomyosarcomas appear to be anthracycline-based or ifosfamide. This has been examined by several studies, although there is the expense of increased toxicity.  

A Gynecologic Oncology Group study evaluated adjuvant chemotherapy in 136 eligible women with uterine sarcomas, 48 of whom had leiomyosarcoma. Women were randomised to either doxorubicin or an observation arm and adjuvant radiotherapy before chemotherapy was allowed. In the women with leiomyosarcomas, 61% of those who received no chemotherapy suffered recurrences, while 44% of those who received doxorubicin had recurrent disease. There was a trend toward improved survival and reduced recurrence rates in the arm treated with doxorubicin, although subgroup analysis did not reach statistical significance. Another study by Pautier et al. compared adjuvant chemotherapy with cisplatin, ifosfamide and doxorubicin followed by radiotherapy versus radiotherapy alone or no adjuvant therapy, and found that the 3-year overall survival (100% versus 76%) and recurrence-free survival (76% versus 43%) were better for the chemotherapy and radiation arm. A multi-centre phase III study in France is investigating this further. As shown in Table 1, there have been several prospective phase II studies by the Gynecologic Oncology Group investigating different chemotherapy regimens for uterine leiomyosarcomas.

Recently, however, a retrospective study by Wu et al. demonstrated the benefit of adjuvant chemotherapy for uterine leiomyosarcomas, despite having a small sample size of 51 women. In the women who did not have adjuvant therapy, 35.5% developed recurrence while only 1 (11.1%) had a relapse after adjuvant chemotherapy.

It may be worthwhile to conclude that, until further evidence is obtained from randomised trials, adjuvant radiotherapy should not be used as a result of its limited impact on overall survival but anthracycline-based chemotherapy certainly appears to have some benefit and should be offered to eligible women.

### Recurrent disease

Secondary resection of a single metastasis may be indicated in a subgroup of women but only if the pelvic disease has been controlled.  

For women with persistent disease, systemic therapy should be considered. Gemcitabine has been shown to have a role in women with persistent or recurrent uterine leiomyosarcomas and, when combined with docetaxel, the overall response rate has been shown to be 53% (95% CI 35–70%),  

### Novel therapies

As some sarcomas have been shown to express angiogenic factors, such as vascular endothelial growth factor, there is some promise in the use of anti-angiogenic agents, especially as they have reasonable toxicity profiles. Thalidomide, an angiogenesis inhibitor, is currently being investigated in a Gynecologic Oncology Group study as a treatment for uterine leiomyosarcomas. Tyrosine kinase inhibitors may also prove to be of benefit as some stromal tumours express oncogenes that encode for tyrosine kinase receptors.  

Temozolomide is an oral alkylating agent with demonstrated efficacy in melanoma and glioblastoma. It may have therapeutic benefit in women with metastatic unresectable leiomyosarcomas and appears to be well tolerated.  

### Conclusion

Most leiomyosarcomas are diagnosed incidentally at an advanced stage and they are invariably

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of women</th>
<th>Treatment</th>
<th>Complete response (%)</th>
<th>Partial response (%)</th>
<th>Stable disease (%)</th>
<th>Increasing disease (%)</th>
<th>Unable to assess (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutton et al. (2000)</td>
<td>31</td>
<td>Liposomal doxorubicin</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>10 (32)</td>
<td>15 (49)</td>
<td>1 (3)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Edmonson et al. (2003)</td>
<td>35</td>
<td>Doxorubicin, mitomycin, cisplatin</td>
<td>3 (9)</td>
<td>5 (14)</td>
<td>14 (40)</td>
<td>13 (37)</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Miller et al. (2000)</td>
<td>36</td>
<td>Topotecan</td>
<td>1 (3)</td>
<td>3 (8)</td>
<td>12 (33)</td>
<td>20 (56)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Sutton et al. (1999)</td>
<td>33</td>
<td>Paclitaxel</td>
<td>3 (9)</td>
<td>0</td>
<td>8 (24)</td>
<td>22 (67)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Cumis et al. (1999)</td>
<td>38</td>
<td>Hydroxyurea, dimethyl triazenoimidazole, etoposide</td>
<td>2 (5)</td>
<td>5 (13)</td>
<td>20 (53)</td>
<td>11 (38)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Sutton et al. (1996)</td>
<td>33</td>
<td>Ifosfamide, mesna, doxorubicin</td>
<td>1 (3)</td>
<td>9 (27)</td>
<td>17 (52)</td>
<td>6 (18)</td>
<td>Not reported</td>
<td></td>
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<tr>
<td>Trojman et al. (1996)</td>
<td>28</td>
<td>Etoposide</td>
<td>0</td>
<td>0</td>
<td>13 (48)</td>
<td>16 (54)</td>
<td>9.2</td>
<td></td>
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<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Lock et al. (2004)</td>
<td>44</td>
<td>Gemcitabine</td>
<td>1 (2)</td>
<td>8 (18)</td>
<td>7 (16)</td>
<td>26 (64)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Gallup et al. (2003)</td>
<td>48</td>
<td>Paclitaxel</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>11 (23)</td>
<td>33 (69)</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Hersley et al. (2002)</td>
<td>34</td>
<td>Gemcitabine, docetaxel</td>
<td>3 (9)</td>
<td>15 (44)</td>
<td>7 (21)</td>
<td>9 (26)</td>
<td>17.5</td>
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aggressive. Prognosis depends heavily on tumour stage; survival has not significantly improved over the last 30 years. Adjuvant radiotherapy has not proved very helpful, while adjuvant anthracycline-based chemotherapy may have a role in management, although this is yet to be clearly defined by rigorous randomised trials.

Early diagnosis with complete surgical clearance gives the most promising chance of improved survival and this will depend heavily on development of imaging techniques and biochemical or molecular markers that will increase preoperative detection of early stage disease.

Long-term follow-up studies involving women with uterine fibroids are needed to identify any radiological or biochemical features associated with early stage leiomyosarcomas and to help in avoiding diagnostic pitfalls. Multi-centre randomised trials are also urgently required to evaluate treatment strategies geared toward improving survival rates.

References


