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Uterine sarcomas—Recent progress and future challenges

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ABSTRACT

Uterine sarcomas are a group of rare tumours that provide considerable challenges in their treatment. Radiological diagnosis prior to hysterectomy is difficult, with the diagnosis frequently made post-operatively. Current staging systems have been unsatisfactory, although a new FIGO staging system specifically for uterine sarcomas has now been introduced, and may allow better grouping of patients according to expected prognosis. While the mainstay of treatment of early disease is a total abdominal hysterectomy, it is less clear whether routine oophorectomy or lymphadenectomy is necessary. Adjuvant pelvic radiotherapy may improve local tumour control in high risk patients, but is not associated with an overall survival benefit. Similarly there is no good evidence for the routine use of adjuvant chemotherapy. For advanced leiomyosarcoma, newer chemotherapy agents including gemcitabine and docetaxel, and trabectedin, offer some promise, while hormonal therapies appear to be more useful in endometrial stromal sarcoma. Novel targeted agents are now being introduced for sarcomas, and uterine sarcomas, and show some indications of activity. Non-pharmacological treatments, including surgical metastatectomy, radiofrequency ablation, and CyberKnife® radiotherapy, are important additions to systemic therapy for advanced metastatic disease.

1. Introduction

In 2006, uterine cancer was only the thirteenth commonest cancer in the UK, and only the fourth commonest cancer in women in the UK, with an incidence of 18.1 per 100,000, accounting for 7045 cases [1]. Uterine sarcomas are especially rare, comprising only 8.4% of uterine cancers [2]. Nevertheless, there has in recent years been significant progress in the more accurate classification, staging and management of patients with uterine sarcoma. Despite the rarity of this tumour, in the last two years several review articles have been published on the current management of uterine sarcomas [3–12]. Thus, the emphasis of this article is not to repeat previous reviews, but rather to highlight recent progress, emerging evidence, and future challenges of relevance and interest to both oncologists and radiologists (Table 1).

2. Pathology

The current World Health Organisation classification of tumours of the female genital tract classifies uterine mesenchymal tumours into smooth muscle and endometrial stromal tumours [13]. Smooth muscle tumours are benign or malignant neoplasms composed of cells showing smooth muscle differentiation arising within the myometrium. They are divided into benign leiomyoma, smooth muscle tumour of uncertain malignant potential (STUMP), and leiomyosarcoma (LMS). Endometrial stromal tumours arise from the endometrial stroma, and are divided into the benign endometrial stromal nodule, endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma (UES).

Leiomyomas (fibroids) are common benign neoplasms composed of smooth muscle cells with fibrous stroma, frequently manifesting as multiple myometrial masses. STUMP refers to a smooth muscle tumour that cannot be reliably diagnosed as either benign or malignant on current diagnostic criteria. LMS is the commonest uterine sarcoma, a malignant smooth muscle tumour composed of spindle cells, characterised by often prominent necrosis, and a mitotic index frequently exceeding 15 per 10 high power fields, and moderate to severe cytological atypia [13,14]. Diagnosis is made on a combination of some or all of these features [14].

Endometrial mesenchymal tumours are considerably rarer than smooth muscle uterine tumours. Endometrial stromal nodule is a benign endometrial stromal tumour manifesting as a well-defined lesion composed of tumour cells resembling proliferative phase stromal cells. ESS is a densely cellular tumour composed of sheets of ovoid cells again resembling endometrial stroma. There is frequently little cytological atypia or pleomorphism, and mitoses are scant. In contrast, UES is a high grade tumour that lacks specific differentiation and any features of normal endometrial stroma. It is a highly aggressive neoplasm, exhibiting haemorrhage and necrosis,

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Table 1
Abbreviations.

Abbreviation	Definition
ADC	Apparent diffusion coefficient
AJCC	American Joint Commission on Cancer
CBR	Clinical benefit rate
CR	Complete response
CS	Carcinosarcoma
CSF-1	Colony stimulating factor-1
CSS	Cause specific survival
DSS	Disease specific survival
EMEA	European Medicines Agency
ER	Oestrogen receptor
ESS	Endometrial stromal sarcoma
FIGO	Federation of Gynaecology and Obstetrics
HR	Hazard ration
IGF1	Insulin-like growth factor-1
LMS	Leiomyosarcoma
MRI	Magnetic resonance imaging
OS	Overall survival
FDG PET	Fluorodexoxyglucose positron emission tomography
PDGF	Platelet derived growth factor
PFR	Progression free rate
PR	Partial response
PrR	Progesterone receptor
RFA	Radiofrequency ablation
RR	Response rate
SD	Stable disease
STUMP	Smooth muscle tumour of uncertain malignant potential
VEGF	Vascular endothelial growth factor
UES	Undifferentiated endometrial sarcoma

Table 2
Hormone receptor expression in uterine sarcomas.

Study	*N*	ER positivity	PrR positivity
Leiomyosarcoma			
Sutton et al., 1986 [95]	43	56%	56%
Rao et al., 1999 [161]	14	70%	–
Zhai et al., 1999 [162]	14	100%	100%
Mittal et al., 2001 [163]	12	–	17%
Bodner et al., 2003 [23]	21	57%	43%
Leitao et al., 2004 [21]	31	40%	38%
O'Cearbhaill et al., 2009 [129]	31	71%	50%
Ioffe et al., 2009 [24]	13	100%	–
Endometrial stromal sarcoma			
Sabini et al., 1992 [164]	5	–	100%
Reich et al., 2000 [165]	21	71%	95%
Chu et al., 2003 [74]	10	80%	90%
Ballerine et al., 2004 [166]	9	–	100%
Zhu et al., 2004 [167]	21	48%	52%
Kurihara et al., 2008 [27]	18	94%	94%
Ioffe et al., 2009 [24]	17	76%	–

ER – oestrogen receptor, PrR – progesterone receptor.

often myometrial invasion, and marked nuclear pleomorphism and high mitotic activity [13,14].

In the last decade there have been a number of changes in the pathological description of uterine sarcomas. Carcinosarcoma (CS; malignant mixed Müllerian tumour) had traditionally been considered as a sarcoma. It is a biphasic tumour, consisting of both carcinomatous epithelial and malignant mesenchymal components. It had been assumed that these two components were separate, resulting in a 'collision' tumour. However, it is now clear that the epithelial and mesenchymal components derive from a single stem cell [15,16], with the epithelial element of the tumour dominant in determining the biological behaviour. Carcinosarcoma has therefore now been re-classified as a de-differentiated/metaplastic endometrial carcinoma [17], and therefore will not be discussed further.

Classification of ESS has also been revised in recent years. Endometrial stromal malignancies were previously divided into low and high grade ESS on the basis of number of mitoses seen on microscopy (less than or greater than 10 mitoses per 10 high power fields) [18]. However, it became apparent that these tumours were better divided into two different clinicopathological entities, ESS and UES [14,19,20]. ESS is a 'low grade' tumour, behaving in an indolent fashion irrespective of mitotic index. In contrast, UES is a 'high grade' rapidly growing tumour, characterised by aggressive behaviour and poor outcomes [14].

Immunohistochemical studies have demonstrated expression of oestrogen receptors (ER) and progesterone receptors (PrR) in both LMS and ESS (Table 2). The studies have universally been small and have shown wide variation in receptor expression, but broadly they indicate that both tumours express both receptors with relatively high frequency. This hormone expression is of relevance as it provides a possible therapeutic strategy for treatment, which will be discussed later (Section 8). It has been reported that hormone receptor positivity in uterine sarcoma may have prognostic implications, with some studies relating hormonal expression to improved survival [21,22], although other studies have not found such a relationship [23]. Nevertheless, in a recent study of 54 patients with uterine sarcoma (ESS, LMS, UES and CS) of whom 34 were ER positive, those with ER-positive tumours had an improved median overall survival of 36 months compared with 16 months in patients with ER-negative tumours ($p = 0.004$) [24]. On multivariate analysis, ER positivity retained significance as an independent predictor of survival, after controlling for stage, age, histology, and the use of pelvic radiotherapy. The poorer survival in receptor negative tumours may reflect less hormone receptor expression in less well-differentiated tumours, which would be expected to have a more aggressive clinical course. Certainly hormone receptor expression is more frequent in benign leiomyomata than LMS [21].

Study of the tumour biology of ESS has provided further insight into this disease. Endometrial stromal sarcomas have been found to be characterised by the chromosomal translocation t(7:17)(p15;q21) which results in the juxtaposition of two zinc finger genes JAZF1 and JJAZ1, at the sites of 7p15 and 17q21 breakpoints, resulting in the JAZF1/JJAZ1 fusion gene [25]. In this study, the translocation was found in 7/7 cases of ESS, 3/3 cases of endometrial stromal nodule, but only in 3/7 cases of UES. These results have been repeated in subsequent larger studies, with translocations detected in 8/16 cases of ESS and 4/4 ESN [26], and 6/12 cases of ESS but only 1/9 cases of UES [27]. The presence of the translocation in ESN raises the possibility that ESS may arise from a progression from a benign stromal proliferation. Furthermore, the lack of the translocation in more than half the cases of UES suggests that the origin of this disease may not be universally due to further malignant progression from ESS, but via a distinct pathogenetic mechanism at least in some cases. While only approximated 50% of ESS cases exhibit the JAZF1/JJAZ1 translocation, two further fusion genes associated with ESS have now been identified, JAZF1/PHF1 and EPC1/PHF1 [28]. The exact role and function of these fusion genes in the development of ESS is not clearly understood, although the JAZF1, PHF1 and EPC1 genes are all members of the polycomb group (PcG) of genes, known to be involved in regional chromatin remodelling and compaction, and suppression of gene transcription associated with these regions. Further investigation into the potential mechanism for these genes in ESS may reveal potential therapeutic targets for the treatment of this disease.

In contrast, leiomyosarcoma is not characterised by a specific chromosomal translocation, but rather is associated with a complex karyotype with numerous chromosomal gains and losses [29].

3. Clinical presentation and diagnosis

The clinical presentation of uterine sarcomas is non-specific. The peak incidence is between 50 and 65 years of age. The classical history is often of a rapidly growing uterine mass, and