

REVIEW

Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas?

W G McCluggage

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Uterine carcinosarcomas (malignant mixed Mullerian tumours) are highly aggressive and have traditionally been regarded as a subtype of uterine sarcoma. However, in recent years convincing evidence has suggested that most, but not all, are monoclonal in origin rather than true collision tumours. Data confirm that the carcinomatous element is the “driving force” and that the sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation. Thus, uterine carcinosarcomas are best regarded as metaplastic carcinomas, although the designation carcinosarcoma is likely to remain. Adjuvant treatment for uterine carcinosarcoma should probably be similar to that directed against aggressive high grade endometrial carcinomas rather than being sarcoma based. Importantly, a small proportion of uterine carcinosarcomas are true collision tumours and should be recognised as such because, in some instances, the prognosis may be better than for a similar stage carcinosarcoma.

(2) The combination theory suggests that both components are derived from a single stem cell that undergoes divergent differentiation early in the evolution of the tumour.

(3) The conversion theory suggests that the sarcomatous element derives from the carcinoma during the evolution of the tumour.

(4) The composition theory suggests that the spindle cell component is a pseudosarcomatous stromal reaction to the presence of the carcinoma.

The last of these theories can be easily excluded because, in these neoplasms, the sarcomatous component exhibits undoubted malignant histological features. In recent years, there has been a plethora of evidence that most, but not all, carcinosarcomas are monoclonal, being initially derived from a single stem cell, and that the carcinomatous component is the “driving force”. This evidence suggests that the combination or conversion theories, which are not mutually exclusive, are the prime nodes of histogenesis of these neoplasms. The evidence, which includes clinical, histopathological, immunohistochemical, ultrastructural, tissue culture, and molecular data, is summarised in this leader. The evidence suggests that, analogous to the situation in other organs, such as breast and urinary bladder, uterine carcinosarcomas are in reality metaplastic carcinomas.

CLINICAL DATA

As stated previously, uterine carcinosarcomas are highly aggressive neoplasms usually arising in elderly postmenopausal women. They often present at an advanced stage, commonly FIGO III or IV, and consequently have an extremely poor prognosis. However, recent studies have shown that uterine carcinosarcomas and endometrial carcinomas share a similar risk factor profile,^{6,7} with both neoplasms being associated with obesity, exogenous oestrogen use, and nulliparity. In contrast, oral contraceptive use protects against the development of both. In addition, recent reports have raised the possibility of an association between long term tamoxifen treatment, with its resultant oestrogenic effects, and the development of uterine carcinosarcoma,^{8–13} although without proper case controlled studies it

Malignant uterine neoplasms containing both carcinomatous and sarcomatous elements are designated in the World Health Organisation (WHO) classification of uterine neoplasms as carcinosarcomas.¹ An alternative designation is malignant mixed Mullerian tumour. Carcinosarcomas may also arise in the ovary,² fallopian tube, cervix,³ or peritoneum,⁴ although with a much lower frequency than in the uterus. These neoplasms, in which the sarcomatous component may be either homologous (composed of tissues normally found in the uterus) or heterologous (containing tissues not normally found in the uterus, most commonly malignant cartilage or skeletal muscle) usually occur in elderly postmenopausal women and are extremely aggressive, with a very poor overall prognosis.⁵ Traditionally, carcinosarcomas have been regarded as a subtype of uterine sarcoma and adjuvant oncological treatments have often been similar to those used for high grade uterine sarcomas, such as leiomyosarcoma. There are four main theories regarding the histogenesis of uterine carcinosarcomas, namely:

(1) The collision theory suggests that the carcinoma and sarcoma are two independent neoplasms.

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Abbreviations: CK, cytokeratin; GOG, Gynecologic Oncology Group; LOH, loss of heterozygosity; MMP-7, matrix metalloprotease 7; MVD, microvessel density; VEGF, vascular endothelial growth factor; WHO, World Health Organisation

is difficult to prove such an association. The association between long term tamoxifen treatment and the development of endometrial proliferative lesions, including atypical hyperplasia and adenocarcinoma, is well established. Studies investigating sites of metastatic disease in uterine carcinosarcoma have found that the pattern of metastasis is more akin to aggressive variants of endometrial cancer than to aggressive sarcomas, such as leiomyosarcoma. Carcinosarcomas primarily spread via lymphatics, similar to endometrial carcinomas, whereas pure sarcomas commonly metastasise haematogenously.¹⁴⁻¹⁷ In addition, most patients with carcinosarcoma die from local recurrence in the pelvis and abdomen rather than from metastatic disease.¹⁸ A Gynecologic Oncology Group (GOG) study of stage I and II uterine "sarcomas" found that pelvic and para-aortic lymph node metastases were rare in leiomyosarcoma, in contrast to lung secondaries, which were common. Moreover, lymph node metastases were frequent in carcinosarcomas and lung secondaries less common.¹⁶ Although these clinical data provide strong evidence that uterine carcinosarcomas are more akin to aggressive endometrial cancers than high grade sarcomas, other studies have found that the overall prognosis of uterine carcinosarcoma is significantly worse than for FIGO grade 3 endometrioid adenocarcinoma and aggressive subtype endometrial carcinomas, such as serous and clear cell carcinomas.¹⁹ Although this is partly because carcinosarcomas are often higher stage at presentation, the prognosis is worse even after other important prognostic variables such as stage, depth of myometrial invasion, and lymphovascular invasion are taken into account.¹⁹ Interestingly, in this study the frequency of distant metastasis in carcinosarcoma was only slightly higher than for grade 3 endometrioid carcinoma and serous and papillary carcinomas and was not significant. This worse prognosis has led to the conclusion that carcinosarcoma should continue to be recognised as a distinct entity. I agree with this conclusion, but this does not detract from the overwhelming evidence that the histogenesis and behaviour of uterine carcinosarcoma is more akin to high grade carcinoma than to sarcoma. It is likely that a sarcomatous component within an endometrial cancer is a histological marker of increased aggressiveness.

HISTOPATHOLOGICAL DATA

As stated previously, uterine carcinosarcomas can be subdivided into homologous and heterologous subtypes, depending on the characteristics of the stroma. Several older studies suggested that neoplasms with a heterologous stroma behaved more aggressively, with a subsequently worse outcome than homologous neoplasms.^{15 16} These studies also suggested that the presence of stromal cartilaginous differentiation was relatively favourable, whereas the presence of skeletal muscle was unfavourable. However, more recent and in general larger studies have concluded that the histological features of the stromal component including grade, mitotic index, and the presence or absence (and types) of heterologous elements bore no relation to the likelihood of metastases or overall prognosis.^{5 20-27} In contrast, with the epithelial elements, high grade carcinoma and serous and clear cell components were associated with a higher frequency of metastases, deep myometrial invasion, lymphatic or vascular space invasion, and cervical involvement, all parameters indicative of an aggressive behaviour.^{5 28} This again provides indirect evidence that the carcinomatous component is the driving force in uterine carcinosarcomas, although other studies have not confirmed independent prognostic factors other than tumour stage. Additional evidence of the link between endometrial carcinoma and carcinosarcoma is the finding of endometrial hyperplasia or endometrial intraepithelial carcinoma in the endometrium adjacent to carcinosarcoma.²⁵

Histopathological examination of tumour emboli within lymphovascular channels and of metastatic disease also provides strong evidence for the dominant role of the carcinomatous component. Such studies have found that these elements almost invariably represent carcinoma (with or without sarcomatous differentiation), and that pure sarcoma in lymphovascular channels and in metastatic disease is uncommon.^{5 14 29} Sreenan and Hart, in studying the histological features of 62 metastases of uterine carcinosarcomas, found carcinoma only in 43, both carcinoma and sarcoma in 15, and sarcoma alone in four.¹⁴ Furthermore, the single example of a purely sarcomatous lymph node metastasis occurred in a probable uterine collision tumour. These authors also speculated that the potential for sarcomatous differentiation in metastatic lesions is enhanced in anatomical sites that allow polypoid growth, such as the peritoneal cavity and vagina. This is in keeping with the observation that primary carcinosarcomas in the genital tract and non-genital tract areas, such as the oesophagus, are typically polypoid neoplasms that tend to grow intraluminally in organs with hollow spaces.

IMMUNOHISTOCHEMICAL DATA

Immunohistochemical studies using antibodies against intermediate filaments, such as cytokeratins (CK) and vimentin, have shown that both the sarcomatous and carcinomatous components often coexpress CK and vimentin.^{26 29-33} The immunohistochemical expression, albeit usually focal, of CK by the sarcomatous elements has been interpreted as evidence of an epithelial origin of the mesenchymal components. However, I would regard this as weak evidence because focal CK positivity may be found in a variety of sarcomas, including leiomyosarcoma and endometrial stromal sarcoma, both of which may comprise the sarcomatous component of uterine carcinosarcoma. Moreover, endometrial adenocarcinomas often exhibit coexpression of CK and vimentin.

Several studies have found concordance of p53 staining between the carcinomatous and sarcomatous components in uterine carcinosarcoma.^{34 35} In other words, p53 protein expression was either positive in both components or negative in both. This has been interpreted as evidence of a common origin for the epithelial and mesenchymal components because, if these were true collision tumours, such concordance in all cases would be extremely unlikely. Although the published studies have not investigated this issue, it is probable that p53 positivity is present in those neoplasms where the carcinomatous component is of the serous type, whereas when this is endometrioid in type (especially grade 1 or 2) p53 is likely to be negative. Similarly, a small study found positivity for either the oestrogen or progesterone receptor in four of 11 uterine carcinosarcomas. In all four cases, positivity was present in the epithelial component, whereas in two cases there was staining of the mesenchymal element.³⁶ The authors concluded that staining of the epithelial component correlated with the degree of epithelial differentiation.

"Cell culture and heterotransplantation studies using cell lines established from patients with uterine carcinosarcoma also support the monoclonal theory of histogenesis"

Other immunohistochemical studies also support the theory that the carcinomatous component is dominant in uterine carcinosarcoma. One such study investigating angiogenesis in these neoplasms, using an anti-vascular endothelial growth factor (VEGF) antibody and using CD34 to measure microvessel density (MVD), found that VEGF expression and MVD were significantly higher in the epithelial than in the mesenchymal elements.³⁷ In addition, tumours with lymphovascular invasion showed a higher VEGF expression than

those without. The authors concluded that angiogenesis is more active in the epithelial than in the mesenchymal elements and that the carcinomatous component plays a key role in the angiogenesis of this neoplasm. Another study came to similar conclusions and also showed, using DNA nick end labelling, that the apoptotic index was significantly higher in the sarcomatous than the carcinomatous component, suggesting that the carcinomatous element is more aggressive with an increased survival advantage.³⁸ A further study found that the mitotic index and the proliferation index, as demonstrated by MIB1 immunostaining, was higher in the carcinomatous than in the sarcomatous component, also suggesting that the carcinomatous element is dominant.³⁹ In addition, there was a significant difference in the immunohistochemical expression of matrix metalloproteinase 7 (MMP-7) between the carcinomatous and sarcomatous components, expression being much stronger in the epithelial elements.⁴⁰ Because overexpression of MMP-7 has been postulated to contribute to the invasive nature or growth capacity of tumours, this again provides evidence for the dominant role of the epithelial component in uterine carcinosarcoma.

ULTRASTRUCTURAL DATA

Previous ultrastructural studies of uterine carcinosarcoma have revealed focal epithelial differentiation, in the form of desmosomes and/or bundles of cytokeratin tonofilaments, in the sarcomatous component, with a blending of the epithelial and stromal elements and transitional forms between the two.^{31 32} Again this has been interpreted as suggesting a monoclonal origin for uterine carcinosarcoma.

MOLECULAR DATA

Molecular studies, microdissecting the epithelial and stromal components and investigating the pattern of X chromosome inactivation, in uterine carcinosarcomas have indicated that most are monoclonal.^{41 42} One study found identical patterns of X chromosome inactivation in the epithelial and stromal components in 21 carcinosarcomas, whereas in three cases the patterns of X chromosome inactivation were different, indicating that these three almost certainly were true collision tumours.⁴¹ Once again this indicates that most, but not all, carcinosarcomas are derived from a single cell of origin. However, when both components show identical patterns of X chromosome inactivation, there remains a 50% possibility that these represent collision tumours. In such instances, further molecular analysis is necessary to determine the relation between the two components. These studies were performed by Wada *et al* who (in addition to identical patterns of chromosome inactivation) found identical mutations of p53 and K-ras in the two components.⁴¹ Another study found identical p53 point mutations in both components, again supporting a monoclonal origin.⁴³ Loss of heterozygosity (LOH) using polymorphic microsatellite markers has also been investigated in the two elements of uterine carcinosarcoma after microdissection.⁴⁴ LOH was seen in five of six uterine carcinosarcomas and identical alleles were lost in the epithelial and mesenchymal components. No genetic differences were seen between the two cell types for any of the informative markers. These results support a monoclonal origin of uterine carcinosarcomas and also provide evidence for the hypothesis of metaplastic transformation (conversion theory), rather than the hypothesis of early divergence of neoplastic clones (combination theory). A similar study also found that the carcinomatous and sarcomatous components shared numerous genetic alterations, suggesting that these neoplasms are monoclonal and that divergence most likely occurs relatively late in evolution, again supporting the conversion theory of histogenesis.⁴⁵

TISSUE CULTURE DATA

Cell culture and heterotransplantation studies using cell lines established from patients with uterine carcinosarcoma also support the monoclonal theory of histogenesis.⁴⁶⁻⁵² Morphological, immunohistochemical, ultrastructural, and molecular studies on these cell lines have shown similar features in both the epithelial and mesenchymal elements. In addition, when transplanted into nude mice, these cell lines reproduced and maintained the characteristics of the original tumour.^{46 48}

NOT ALL UTERINE CARCINOSARCOMAS ARE MONOCLONAL

From the evidence presented here it is apparent that most uterine carcinosarcomas are monoclonal with the carcinomatous component being the driving force. However, it is also apparent that a small proportion of these neoplasms are true collision tumours, consisting of independent unrelated carcinomas and sarcomas. For example, in the study of Sreenan and Hart, two of 29 uterine carcinosarcomas were considered to be collision tumours.¹⁴ In both these tumours, the carcinomatous and sarcomatous components were histologically separate, with no intermingling. Interestingly, in this study the only lymph node metastasis that consisted of pure sarcoma was from one of these collision tumours.

“It may be of prognostic importance to identify those uterine carcinosarcomas that are likely to represent true collision tumours”

Molecular evidence that a small proportion of uterine carcinosarcomas represent collision tumours was provided by Wada *et al* in their study investigating patterns of X chromosome inactivation.⁴¹ They found that three of 25 carcinosarcomas exhibited different patterns of X chromosome inactivation in the epithelial and mesenchymal components, indicating true collision tumours. Other publications of small numbers of cases have convincingly demonstrated true uterine collision tumours, usually consisting of endometrioid adenocarcinoma and stromal sarcoma.^{33 34} It may be of prognostic importance to identify those uterine carcinosarcomas that are likely to represent true collision tumours. Separate gross and histological neoplasms with little or no histological intermingling of the two components is the usual clue that one may be dealing with a collision tumour. Uterine carcinosarcomas are, of course, highly aggressive neoplasms with a dismal prognosis, especially with deep myometrial invasion or advanced stage. With a true collision tumour, the ultimate prognosis will depend on the most aggressive component and the outcome may be better than for a similar stage carcinosarcoma. For example, if the epithelial and mesenchymal components of a collision tumour consisted of a stage IA or IB, grade 1 or 2 endometrioid adenocarcinoma, and a low grade endometrial stromal sarcoma, respectively, the ultimate prognosis, even with extrauterine spread of the sarcoma, might be quite good with late recurrence or metastasis likely.

TREATMENT IMPLICATIONS

It is beyond the scope of this pathological review to discuss in detail the optimal management, in the form of adjuvant treatment, of uterine carcinosarcoma. However, in the past oncologists have tended to consider uterine carcinosarcomas as analogous to high grade uterine sarcomas, such as leiomyosarcoma or undifferentiated uterine sarcoma. As a result, adjuvant chemotherapeutic regimens, or chemotherapy directed against known residual disease following surgical debulking, have been directed along these lines. Because there is now ample evidence that most uterine carcinosarcomas are monoclonal and that the carcinomatous element is the driving

Take home messages

- There is now convincing evidence that most, but not all, uterine carcinosarcomas (malignant mixed Mullerian tumours) are monoclonal in origin rather than true collision tumours
- Clinical, histopathological, immunohistochemical, ultrastructural, tissue culture, and molecular data confirm that the carcinomatous element is the “driving force” and that the sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation
- Thus, uterine carcinosarcomas should be regarded as metaplastic carcinomas and adjuvant treatment should probably be similar to that directed against aggressive high grade endometrial carcinomas, rather than being sarcoma based
- Nonetheless, a small proportion of uterine carcinosarcomas are true collision tumours and this is important because the prognosis can sometimes be better than for a similar stage carcinosarcoma

force, it is probable that adjuvant chemotherapy should be more akin to that given for a high stage, high grade endometrial adenocarcinoma or an aggressive histological subtype of endometrial adenocarcinoma, such as serous or clear cell adenocarcinoma. Personal communication with local oncologists suggests that there is now a realisation of this and that the adjuvant chemotherapies now used are akin to those used for advanced endometrial carcinoma. It has been shown in a small series that doxorubicin treatment (active against sarcomas) has little or no effect on the carcinomatous component of uterine carcinosarcoma and that the addition of cisplatin based substances directed against the carcinoma gave a better response rate.⁵⁵ Previous GOG phase III trials have shown a better response to single agent treatment using cisplatin rather than doxorubicin.^{56,57} It is also possible that combining these two chemotherapeutic agents would result in a better response than the use of single agent chemotherapy.⁵⁵ Clearly, oncologists must devise and participate in properly controlled studies of large numbers of patients to ascertain which chemotherapeutic agents are of most benefit.

NOMENCLATURE CONSIDERATIONS

In the WHO classification of uterine neoplasms, the term carcinosarcoma is used for those neoplasms composed of malignant epithelial and mesenchymal components.¹ This is synonymous with malignant mixed Mullerian tumour. However, clearly most, but not all, of these neoplasms are monoclonal in origin, the carcinomatous component being the driving force. As stated previously, it is important to recognise and separate those neoplasms that represent true collision tumours. These should be reported as consisting of two distinct and separate tumours. For most uterine carcinosarcomas perhaps a better term would be metaplastic carcinoma or carcinoma with sarcomatous metaplasia. This is analogous to the nomenclature used in other organs, such as the breast, where these neoplasms may occur. However, I recognise that the term carcinosarcoma is in widespread use and likely to remain. This does not detract from the fact that clinicians, pathologists, and oncologists must be aware that most of these neoplasms are carcinomas and that the sarcomatous elements are a histological manifestation of increased aggressiveness.

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