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REVIEW

Clear cell sarcoma of the gastrointestinal tract and malignant gastrointestinal neuroectodermal tumour: distinct or related entities? A review

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Summary

Clear cell sarcoma is an uncommon sarcoma which rarely occurs as a primary tumour in the gastrointestinal tract (CCS-GIT). It shares common molecular genetic abnormalities with the more recently described entity, malignant gastrointestinal neuroectodermal tumour (GNET) but is distinguished by its morphological and immunohistochemical findings. The exact nosological relationship between these tumours continues to be debated. In this review, we present two cases of these rare neoplasms from our files and perform a statistical comparison of all published cases to determine if significant differences exist in their clinicopathological features and biological behaviour. Thirteen cases of CCS-GIT and 58 of GNET were included. CCS-GIT occurred more commonly in males (84.6% vs 46.6%, $p = 0.01$) and in an older age group (median 57 vs 33 years, $p < 0.01$). There was no significant difference in their location in the gastrointestinal tract, median tumour size and proportion of cases with an *EWSR1-ATF1* vs *EWSR1-CREB1* fusion. Median survival for CCS-GIT was 13.5 months and for GNET, 9.5 months ($p = 0.78$). There was no significant difference in the Kaplan–Meier survival curves for either time to first metastasis ($p = 0.88$) or overall survival ($p = 0.18$), including after controlling for tumour size using regression models. Our analysis confirms that aside from morphological variations between these tumours, they also exhibit epidemiological and clinical differences. Despite the prevalent perception that GNET is associated with a more aggressive clinical course, our findings indicate that there is no significant difference in their biological behaviour, although both clearly share a bleak prognosis. Further experience is awaited to determine optimal treatment strategies and whether CCS-GIT and GNET would differ in their response to various therapies.

Key words: Clear cell sarcoma; clear cell sarcoma of gastrointestinal tract; clear cell sarcoma-like tumour of gastrointestinal tract; gastrointestinal neuroectodermal tumour; EWSR1; ATF1; CREB1.

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INTRODUCTION

Clear cell sarcoma (CCS) is an uncommon, aggressive sarcoma characterised by distinctive histological features, immunohistochemical expression of S100, SOX10 and melanocytic markers and recurrent balanced translocations involving the *EWSR1* and *ATF1/CREB1* genes.[1–4] It typically arises in association with tendons and aponeuroses in the distal extremities of young adults. However, rare examples primarily affect the gastrointestinal tract (GIT), most frequently the wall of the small bowel.[5–7]

In 2003, Zambrano *et al.* published a small series of neoplasms sharing many features in common with CCS of the GIT (CCS-GIT) but also showing some notable differences, such as a wider spectrum of histological growth patterns, the presence of osteoclast-type giant cells and lack of expression of melanocytic markers. These disparities lead them to propose a new clinicopathological entity which they aptly named 'osteoclast-rich tumour of the GIT with features resembling CCS of soft parts'.[8] Based on more recent work revealing evidence of neuroectodermal differentiation, other investigators have suggested renaming this neoplasm 'malignant gastrointestinal neuroectodermal tumour (GNET)',[9] a term which appears to be rapidly gaining acceptance in the literature.

The nature of the relationship between CCS-GIT and GNET remains a matter of debate. Those in favour of two distinct entities draw attention to their morphological and immunophenotypic differences. Conversely, shared molecular genetic alterations form the basis for arguments that these are related lesions along the same morphological spectrum. Controversies regarding their nosological relationship aside, it remains largely unknown if clinically relevant differences exist between these two groups of neoplasms. In our experience, there is the general impression that GNET is associated with more aggressive biological behaviour. However, to our knowledge, there are no empirical data to support this.

In this review, we present a case of each of these rare tumours from our files to add to the limited published data and perform a comparative analysis of all cases published to date to determine if there are indeed significant differences in their clinicopathological features and, in particular, their prognosis. As a secondary objective, we also compare CCS-GIT

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and somatic CCS to assess if outcome differences might be attributable to their site of origin in the GIT or soft tissues.

REVIEW OF LITERATURE

A comprehensive review was performed for all published cases of CCS-GIT and GNET in the English literature up to August 2017. The search was undertaken by identifying single case reports and case series of CCS-GIT and GNET as well as previous reviews of the subject with the aid of PubMed (National Center for Biotechnology Information, US National Library of Medicine). Search terms used included combinations of 'clear cell sarcoma', 'clear cell sarcoma-like', 'gastrointestinal tract', 'gastrointestinal neuroectodermal tumour' and 'GNET', amongst others. The following data were collected from the reports: age, sex, size and location of tumour, histological features, immunohistochemical profile, molecular genetic findings, time to first metastasis and time to death.

For the secondary objective comparing outcomes for CCS-GIT and CCS of soft tissues, similar details were extracted from any large case series (>15 cases) of the latter containing individual outcome data including time to first metastasis and time to death.

Differences in proportions were analysed using the Pearson's chi-square and Fisher's exact test for parametric and non-parametric data, respectively. Student's t-test was used to assess differences in means. Survival analysis for differences in time to first metastasis and time to death was performed using the Kaplan–Meier method, with the differences between the survival curves assessed using the log-rank test. The Cox proportional hazards model was used to compare survival whilst controlling for the size of tumours (the sample size limited the inclusion of additional potentially confounding variables such as age and sex). The two-tailed significance level was set at 5%. All statistical analyses were performed using SPSS Version 20 (IBM, USA).

CASE STUDIES

Herein, we present the findings of a case each of CCS-GIT and GNET from our personal files, the first unreported and the second included in a previously published case series,[9] but expanded upon here for illustrative purposes.

Case 1

A 64-year-old male with no significant past medical history presented with abdominal pain and bilious vomiting. A computed tomography (CT) scan of his abdomen revealed a small bowel obstruction with possible intussusception due to a 70 mm mass arising in the wall of the ileum. There were no occult primary or metastatic sites of disease revealed on a staging PET scan. An emergency small bowel resection was performed. The excised segment of ileum confirmed the presence of a 72 × 50 × 42 mm ulcerated and polypoid mass invading through the full thickness of the bowel wall into the mesenteric fat. It had a lobulated fleshy cream-coloured cut surface and areas of haemorrhage (Fig. 1).

Histologically, the neoplasm formed a highly cellular, circumscribed, unencapsulated and lobulated mass. It was composed of poorly cohesive epithelioid and spindle cells occurring in diffuse sheets, nests and pseudovascular arrangements (Fig. 1). Whilst multinucleated tumour giant cells also featured, there were no osteoclast-like giant cells. The tumour cells had large and pleomorphic nuclei with vesicular chromatin and prominent nucleoli, surrounded by variable amounts of eosinophilic to clear cytoplasm, lacking any melanin pigment. Mitoses, including atypical forms, were readily identified and there were focal areas of necrosis. There were no metastases in two mesenteric nodes.

Immunohistochemistry showed diffuse, strong staining of the tumour cells for S100 protein (nuclear and cytoplasmic), SOX10, HMB45 and Melan-A, and focal, weak and non-specific staining for CD117 (Fig. 2). There was no immunoreactivity for AE1/AE3, EMA, CD34, DOG-1, alpha-smooth muscle actin, desmin or the neuroendocrine markers, synaptophysin, chromogranin and CD56.

Interphase fluorescence *in situ* hybridisation (FISH) performed on formalin-fixed, paraffin-embedded (FFPE) sections revealed an *EWSR1* alteration at 22q12 (Fig. 2), but no disruption of *ATF1* (12q13) or *CREB1* (2q33). Molecular studies using bidirectional Sanger sequencing did not detect a *BRAF* gene mutation.

Based on the morphological, immunohistochemical and molecular genetic findings, the neoplasm was diagnosed as a CCS-GIT. Surveillance imaging at 6 months post-operatively showed local recurrence at the site of the small bowel resection, with further disease progression involving the small bowel and mesentery at 9 months.

Case 2

A 33-year-old male with no significant prior medical history presented with abdominal and back pain, fever, anorexia and weight loss. An abdominal CT scan showed a 30 mm necrotic pelvic mass involving the small bowel and an enlarged para-aortic lymph node suspicious for a nodal metastasis, both of which were intensely FDG-avid on a PET scan.

A surgical debulking procedure was undertaken. The resected length of ileum contained a 27 × 18 × 15 mm ulcerated and polypoid neoplasm invading through the full thickness of the bowel wall into the adjacent mesentery. It had a pale, fleshy and haemorrhagic cut surface.

Microscopic examination showed the tumour to be cellular, formed by predominantly epithelioid and also spindle cells exhibiting a variety of growth patterns including nests, fascicular, pseudopapillary and pseudoalveolar arrangements (Fig. 3). The cells contained large and pleomorphic nuclei with vesicular chromatin and prominent nucleoli, surrounded by dense eosinophilic cytoplasm. Of note were scattered multinucleated osteoclast-like giant cells. Mitoses were moderately frequent and there were also focal areas of necrosis.

Immunohistochemistry showed strong and widespread staining of the tumour cells for S100 protein (nuclear and cytoplasmic), but without co-expression of HMB45 or Melan-A (Fig. 4). There was also patchy staining for markers associated with neuroectodermal differentiation including SOX10, synaptophysin, CD56 and CD57. Stains for keratin (MNF116), CD34, CD117, h-caldesmon and desmin were negative.

Interphase FISH studies performed on FFPE sections provided presumptive evidence of an *EWSR1-CREB1* fusion, with disruptions of both *EWSR1* (22q12) and *CREB1* (2q33) demonstrated (Fig. 4). The *ATF1* (12q13) gene was intact.

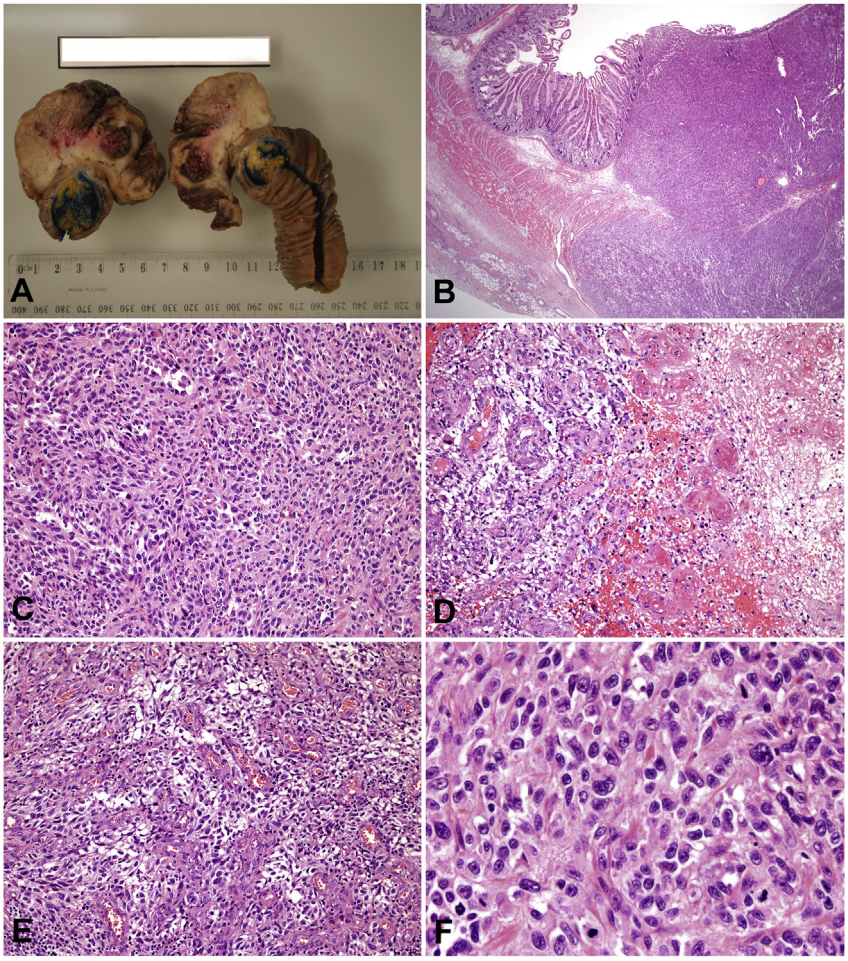


Fig. 1 Clear cell sarcoma of the gastrointestinal tract (CCS-GIT). (A,B) An ulcerated polypoid tumour was seen arising in the ileum, invading through the full thickness of the bowel wall. (C) Epithelioid and spindle cells were organised in diffuse sheets, with areas of (D) necrosis and (E) focal clear cell change. (F) The cells showed moderately pleomorphic nuclei with prominent nucleoli.

Molecular studies using bidirectional Sanger sequencing showed no evidence of a *BRAF* mutation.

Based on the morphological features, immunophenotype and molecular genetic findings, the neoplasm was diagnosed as a GNET. A CT scan of the abdomen 1 month post-surgery revealed multiple liver metastases, with progression to disseminated intra-abdominal disease 2 months later. The patient was palliated and died of his disease 10 months following primary resection.

COMPARATIVE ANALYSIS OF PUBLISHED CASES

Comprehensive review of the English literature identified 12 cases of CCS-GIT[10,11] and 58 of GNET.[9,10,12–21] Adding our index case increased the total number of CCS-GIT to 13 for inclusion in the comparative analysis (the index case of GNET was previously published in another case series[9]).

Statistical analysis revealed significant gender differences between the two groups. CCS-GIT affected males much more commonly than females in comparison to GNET, where the sexes were more equally affected (84.6% males vs 46.6% males, respectively, $p = 0.01$, Table 1). There were also significant differences in age at time of diagnosis with GNET affecting younger patients (median 33 years, range 10–81 years) than CCS-GIT (median 57 years, range 35–85 years, $p < 0.01$).

The small bowel was the most commonly affected site for both CCS-GIT and GNET ($p = 0.25$), although there was a wider distribution of tumour locations observed for GNET, including the oesophagus, stomach and large bowel. Tumour size was comparable between the two groups, the median size for CCS-GIT being 68 mm (range 18–110 mm) and for GNET, 45 mm (range 15–135 mm, $p = 0.26$).

Twelve (92.3%) of the 13 cases of CCS-GIT showed evidence of an *EWSR1* gene re-arrangement at 22q12, which in eight (61.5%) fused with *ATF1* at 12q13. A fusion partner was not identified or not probed for in the remaining cases. Forty-seven (81%) of the 58 cases of GNET showed an *EWSR1* disruption, partnered with the *ATF1* gene in 19 (32.8%) and *CREB1* at 2q33 in 10 (17.2%). The difference in the proportion of cases partnered with either *ATF1* or *CREB1* in CCS-GIT and GNET was not statistically significant ($p = 0.08$).

Median follow-up time for CCS-GIT was 13.5 months (range 1–34 months), during which nine (69.2%) patients developed metastases and six (46.2%) died of their disease. Median follow-up time for GNET was 12 months (range 0–106 months), during which 27 (46.6%) developed

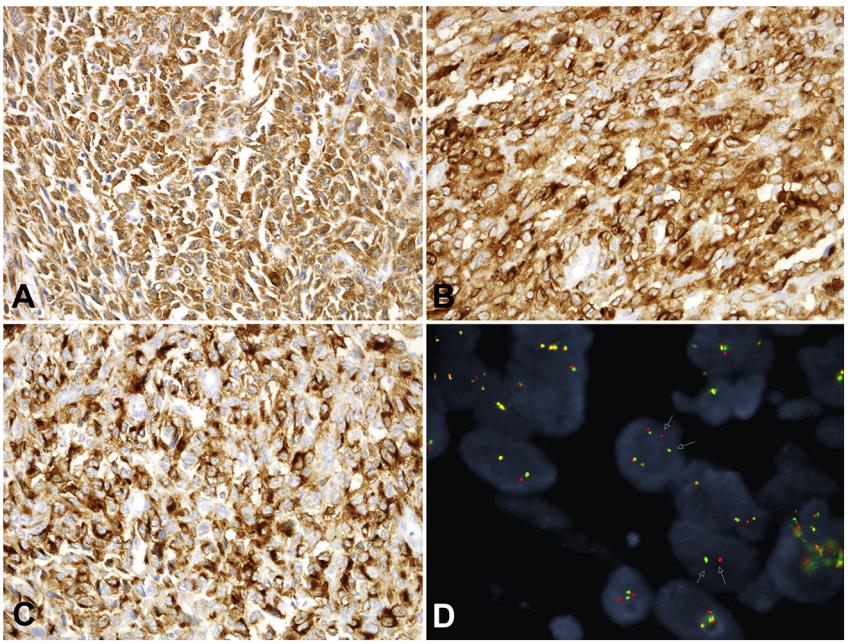


Fig. 2 Clear cell sarcoma of the gastrointestinal tract (CCS-GIT). Immunohistochemistry showed diffuse staining of the tumour cells for (A) S100, (B) Melan-A and (C) HMB45. (D) Interphase FISH analysis demonstrated breakapart of *EWSR1* at 22q12.

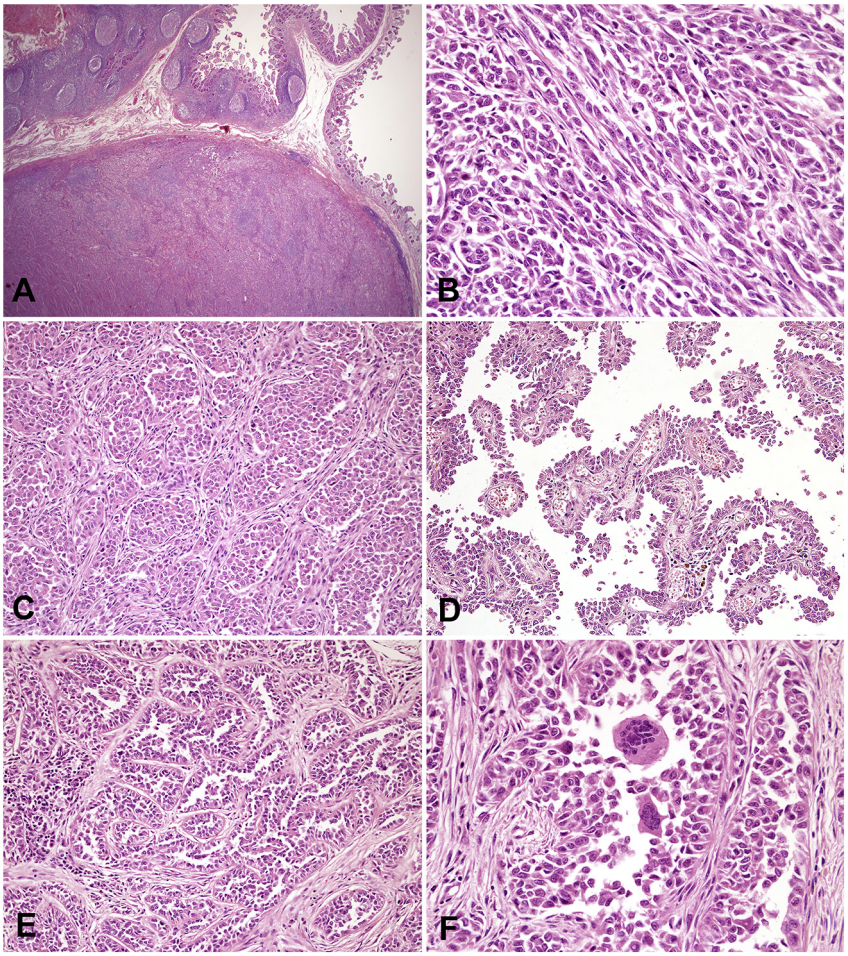


Fig. 3 Malignant gastrointestinal neuroectodermal tumour (GNET). (A) A cellular tumour was seen involving the full thickness of the ileal wall, with varied growth patterns including (B) fascicles, (C) nested, (D) pseudopapillary and (E) pseudoalveolar arrangements. (F) The tumour cells showed moderate nuclear pleomorphism and eosinophilic cytoplasm, admixed with scattered multinucleated osteoclast-like giant cells.

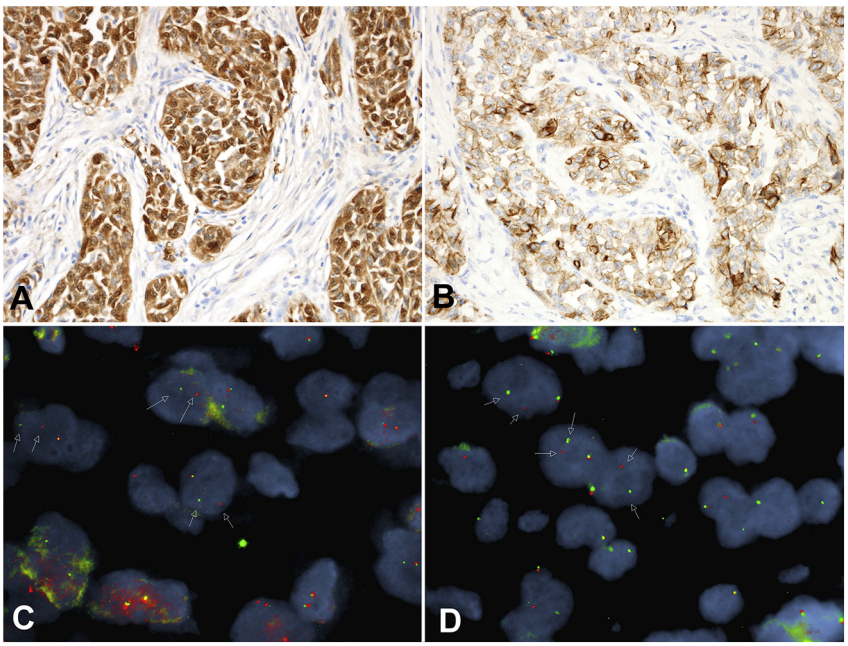


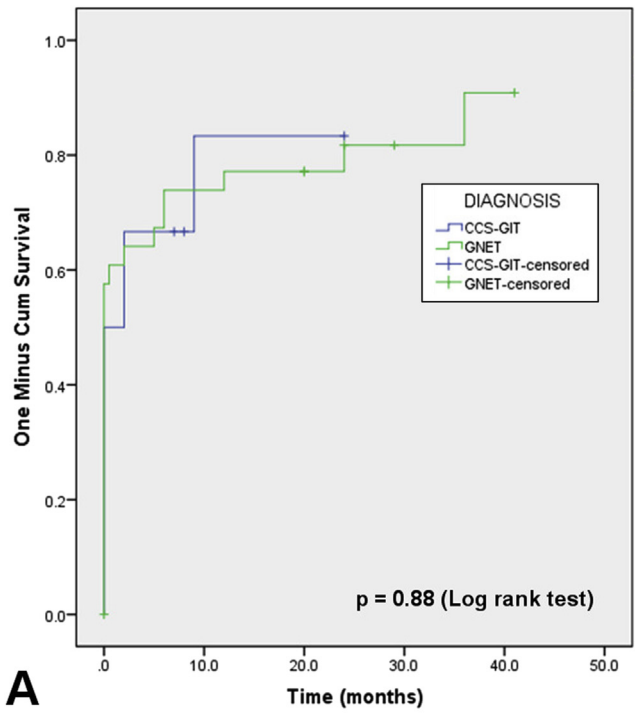
Fig. 4 Malignant gastrointestinal neuroectodermal tumour (GNET). Immunohistochemistry showed diffuse staining of the tumour cells for (A) S100 without co-expression of melanocytic markers (not illustrated). (B) There was patchy staining for neuroectodermal markers such as CD56. (C) Interphase FISH analysis revealed breakapart of *EWSR1* at 22q12 and (D) *CREB1* at 2q33.

metastases and 12 (20.7%) died of their disease. There was no significant difference in median time to first metastasis (1 month for CCS-GIT vs <1 month for GNET, $p = 0.50$) and median survival time (13.5 months for CCS-GIT vs 9.5 months for GNET, $p = 0.78$) between the two groups. Kaplan–Meier survival curves for time to first metastasis ($n = 45$) and time to death ($n = 52$) are shown in Fig. 5. There was no statistically significant difference in the curves for both comparisons ($p = 0.88$ and $p = 0.18$, respectively). Cox proportional hazard models to control for the potential confounding effect of tumour size showed that the diagnosis of CCS-GIT compared to GNET did not independently affect the time to first metastasis [hazard ratio (HR) 1.02, $p = 0.96$] or time to death (HR 1.96, $p = 0.30$).

A secondary objective of this review was to determine if CCS arising primarily in the GIT differs in its biological behaviour compared to its somatic counterpart. Several large published series of CCS of soft tissues were identified from the literature producing a total of 142 cases with sufficient survival data to allow for statistical comparison with CCS-GIT. Median follow-up time for the cohort of CCS of soft tissues was 28 months (range 3–312 months) with metastases in 88 (63.3%) and death due to disease in 77 (55.4%) cases. Median time to first metastasis was significantly shorter for CCS-GIT compared to CCS of soft tissues (1 vs 15 months, $p < 0.01$), as was the median survival time (13.5 vs 28 months, $p < 0.01$) (Table 2). Kaplan–Meier curves for time to first metastasis ($n = 102$) and time to death ($n = 89$) for both groups are shown in Fig. 6. There was a statistically significant difference in the curves for time to first metastasis, with CCS-GIT showing more aggressive behaviour ($p = 0.01$). There was no significant difference in the survival curves for time to death ($p = 0.20$). Cox proportional hazard models to control for the potential confounding effect of tumour size showed that the diagnosis of CCS-GIT was associated with a faster time to first metastasis (HR 2.93, $p = 0.01$) but not time to death (HR 1.85, $p = 0.20$).

Table 1 Statistical comparison of clear cell sarcoma of the gastrointestinal tract (CCS-GIT) and malignant gastrointestinal neuroectodermal tumour (GNET)

	CCS-GIT ($n = 13$)	GNET ($n = 58$)	p value
Sex	Male 84.6% Female 15.5%	Male 46.6% Female 53.4%	0.01
Tumour location	Small bowel 84.6% Large bowel 15.4%	Small bowel 70.7% Large bowel 6.9% Gastric 20.7% Oesophagus 1.7%	0.25
EWSR1 rearrangement present	92.3%	81.0%	
EWSR1 fusion partner	ATF1 61.5% CREB1 0%	ATF1 32.8% CREB1 17.2%	0.08
Median age, years	57.0	33.0	<0.01
Median tumour size, mm	68	45	0.26
Median time to first metastasis, months	1.0	<1.0	0.50
Median survival, months	13.5	9.5	0.78



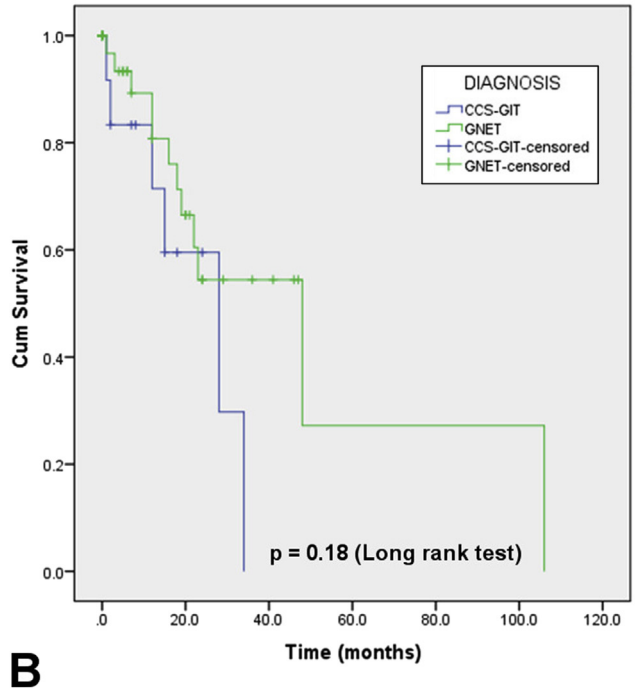


Fig. 5 Kaplan–Meier survival curves showing no significant difference in (A) time to first metastasis and (B) time to death between CCS-GIT and malignant GNET.

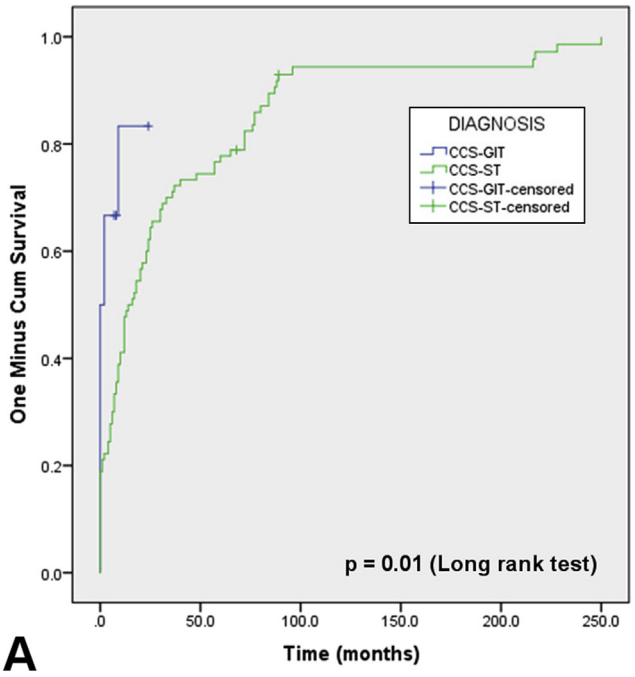
DISCUSSION

Clear cell sarcoma was first described by Enzinger in 1965 as a rare sarcoma, classically arising in association with the tendons and aponeuroses in the lower limbs of young adults.[1] Although renamed by the same author and Chung in 1983 as 'malignant melanoma of soft parts',[2] it is now widely accepted that CCS is a unique clinicopathological entity, separate from malignant melanoma, by virtue of its distinct morphological and molecular genetic features.

In addition to the distal extremities, CCS has been rarely described at other anatomical sites including the ear, penis,

Table 2 Statistical comparison of clear cell sarcoma of soft tissue (CCS-ST) and the gastrointestinal tract (CCS-GIT)

	CCS-GIT (n = 13)	CCS-ST (n = 142)	p value
Median time to first metastasis, months	1.0	15.0	<0.01
Median survival, months	13.5	28.0	<0.01



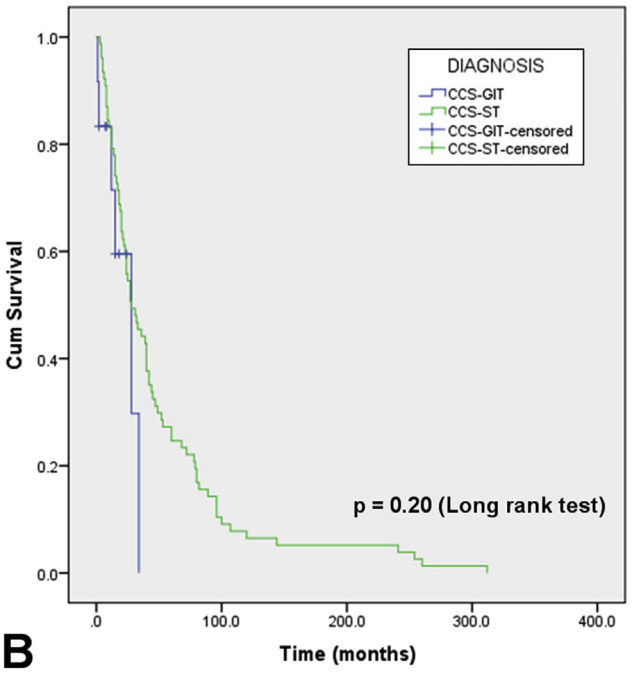


Fig. 6 Kaplan–Meier survival curves showing (A) clear cell sarcoma of the gastrointestinal tract (CCS-GIT) with significantly earlier time to first metastasis compared to clear cell sarcoma of soft tissue (CCS-ST). (B) There was no significant difference in time to death (B).

retroperitoneum, pleura, mediastinum, bone and visceral organs.[10,22–24] Amongst the latter, CCS of the gastrointestinal tract (CCS-GIT) was first reported in 1993 by Ekfors *et al.*, involving the duodenum.[5] Almost a decade later, Zambrano *et al.*[8] published a series of six tumours, all sharing features in common with CCS-GIT but also showing some differences, leading them to propose a new clinicopathological entity which they suitably named 'osteoclast-rich tumour of the GIT with features resembling CCS of soft parts'. Since then, this tumour has been reported under a variety of names, including 'CCS-like tumour of the GIT'.[25] More recently, based on evidence of neuroectodermal differentiation, the term 'malignant gastrointestinal neuroectodermal tumour (GNET)'[9] has been proposed and appears to be gaining widespread acceptance in the literature. Both CCS-GIT and GNET are rare, with only 13 cases of CCS-GIT (including the index case presented in this study)[9] and 58 cases of the GNET[9,10,12,13,15,16,18–21,26,27] reported to date in the literature.

The exact nature of the relationship between CCS-GIT and GNET is still debated with some arguing that they represent distinct entities and others claiming that these are related tumours at different ends of the same morphological spectrum.[28] It may be that both tumours derive from a common precursor cell, likely an autonomic nervous system-related primitive cell of neural crest origin within the gastrointestinal tract, which in the case of GNET retains primitive neuroectodermal/neural features whilst in the case of CCS-GIT, differentiates along a melanogenetic pathway.[9,25,29,30] The aim of this review was to further explore these issues by examining all published cases to identify differences, if any, in the clinicopathological features and in particular, in their biological behaviour.

Our findings indicate that statistically significant differences do exist between the two groups. CCS-GIT occurs more commonly in males (84.6%) unlike GNET, which shows a more equal sex distribution (46.6% males). CCS-GIT also affects an older population, with a median age of 57 years at diagnosis compared to GNET with a median age of 33 years. There is no apparent difference between the two tumours in terms of size (median size for CCS-GIT being 68 mm and for GNET 45 mm) and sites affected along the GIT, with the small bowel being the most commonly affected segment. However, there is a wider distribution of primary sites observed for GNET, which has also been reported in the oesophagus, stomach and colon.[10,19,27] Both tumours are typically centred on the muscularis propria and submucosa with subserosal/serosal and mucosal extension, often producing an annular constricting mass or ulcerated polypoid lesion.[9] Clinical presentations include abdominal pain, bowel obstruction, formation of an abdominal mass as well as systemic features such as fever, anorexia, weight loss, anaemia and generalised weakness.[9,25]

As the two cases presented in this article illustrate, CCS-GIT and GNET can be distinguished based on their morphological features. CCS-GIT maintains histological resemblance to its somatic counterpart, characterised by nests and fascicles of relatively uniform polygonal, epithelioid and spindle cells, separated by delicate fibrous septa.[25,31,32] However, cellular pleomorphism can be encountered as shown in our index case. Diffuse, sheet-like growth and a pseudoalveolar growth pattern have also been described but less commonly. The tumour cells have rounded vesicular nuclei with prominent nucleoli, surrounded by variably clear to eosinophilic cytoplasm. Focal melanin pigment production may be seen in scattered cells but is usually not a prominent finding.[32] Mitotic activity is typically scant and necrosis is sometimes present.

Whilst GNET shares some morphological similarities with CCS-GIT, it shows a wider spectrum of growth patterns including nested, fascicular and solid architecture but also frequent pseudopapillary, pseudoalveolar, microcystic and rosette-like arrangements.[8–10] The tumour cells tend to display a greater degree of nuclear atypia with coarse chromatin, variably prominent nucleoli and intranuclear pseudoinclusions, surrounded by predominantly eosinophilic cytoplasm. Clear cells usually represent a focal finding whilst melanin pigment production is absent.[25] Accompanying the increased atypia are more frequent mitoses and areas of necrosis. Perhaps the most helpful distinguishing feature of GNET is the presence of osteoclast-like multinucleated giant cells, which are usually focal and unevenly distributed, reported in up to 50% of cases.[8,9,25,30] These CD68+ osteoclast-like giant cells differ from the wreath-like tumour giant cells seen in conventional somatic CCS.[26,33]

Immunohistochemical findings further distinguish CCS-GIT and GNET. Whilst both diffusely express S100 protein, markers of melanogenesis including Melan-A, HMB45 and MiTF-1 occur only in CCS-GIT.[18,20,25] Many cases of GNET also show immunophenotypic evidence of neuroectodermal differentiation by way of variable and often focal reactivity for SOX10, synaptophysin, neuron-specific enolase (NSE), neurofilament, CD56 and CD57.[9]

Ultrastructural features confirm the morphological and immunohistochemical findings described. Whilst premelanosomes and melanosomes are often appreciated in CCS-GIT,[17,30] these are typically absent in GNET, which instead demonstrates evidence of neuroectodermal differentiation, manifest as multiple, sometimes bulbous interdigitating cell processes with dense-core secretory granules, clear secretory vesicles, scattered microtubules and synapse-like structures.[9]

There is also molecular support for a possible shared histogenesis. A common set of balanced chromosomal translocations is found in both neoplasms (as well as in somatic CCS). The most common fusions are *EWSR1-ATF1* and *EWSR1-CREB1*, which pair the *EWSR1* (Ewing Sarcoma Breakpoint Region 1) gene at 22q12 with either the *ATF1* (Activating Transcription Factor 1) gene at 12q13 or *CREB1* (Cyclic Adenosine Monophosphate Responsive Binding Protein 1) gene at 2q34.[6,25,29,30] In our review, up to 92.3% of CCS-GIT tested showed evidence of an *EWSR1* gene alteration, which in 61.5% fused with the *ATF1* gene. Similarly, up to 81.0% of GNET showed evidence of an *EWSR1* gene alteration, partnered with the *ATF1* gene in 32.8% and *CREB1* gene in 17.2%. The difference in the proportion of cases partnered with either *ATF1* or *CREB1* in CCS-GIT and GNET was not statistically significant. Importantly, none of these translocations are specific for either CCS or GNET, having been well described in tumours which differ both in nosological classification (hyalinising clear cell carcinoma of salivary glands[34] and pulmonary myxoid sarcoma[35]) and biological behaviour (soft tissue myoepithelioma[36] and angiomatoid fibrous histiocytoma[25,37]).

The differential diagnosis of CCS-GIT and GNET is wide, although primary and metastatic malignant melanoma,

gastrointestinal stromal tumour (GIST), perivascular epithelioid cell tumour (PEComa) and epithelioid malignant peripheral nerve sheath tumour (MPNST) are entities which merit serious consideration. Melanoma is the most difficult to distinguish, particularly from CCS-GIT which retains its capacity for melanogenesis. The diagnosis is best established with molecular genetic studies as *EWSR1* gene rearrangements are, by definition, absent in melanoma,[6,25,38,39] whilst *BRAF* gene mutations have not been described in CCS-GIT or GNET. Testing is still recommended in patients with a prior history of primary melanoma elsewhere as cases of both CCS-GIT and GNET have been reported in this clinical setting.[31] Although GIST is far more common than CCS-GIT and GNET and may share similar morphological features, separation is usually not problematic as the latter do not stain for CD117 or DOG1.[8,20,25] PEComa shares in common with CCS-GIT positive reactions for Melan-A and HMB45 whilst S100 positivity is seen in up to 10% of cases.[40–42] However, myogenic differentiation (which is almost always seen in S100-positive tumours) and staining for TFE3 may help to support a diagnosis of PEComa.[43,44] Finally, although epithelioid MPNST classically shows diffuse S100 expression, negative reactions for Melan-A and HMB45 together with loss of INI1 nuclear expression and absent *EWSR1* rearrangements help facilitate its distinction.[25,45–47]

CCS-GIT and GNET are high-grade sarcomas for which conventional chemotherapy and radiotherapy presently appear to have little to offer. In our review, up to 69.2% of patients with CCS-GIT developed metastases and 46.2% succumbed to their disease, whilst 46.6% of patients with GNET developed metastases and 20.7% died of their disease. Our analysis shows that despite the general impression that GNET is associated with a more aggressive clinical course, there is no statistically significant difference in survival times between the two groups, even after controlling for tumour size. However, notwithstanding the absence of an observable difference between the two groups, both clearly share a poor prognosis with median survival time for CCS-GIT being 13.5 months and for GNET, 9.5 months. Of interest is that, as with other intra-abdominal and retroperitoneal sarcomas compared to their soft tissue counterparts, CCS-GIT shows evidence of a more aggressive clinical course compared to somatic CCS, with a shorter time to first metastasis (1 vs 15 months) and shorter medial survival (13.5 vs 28 months).

The relationship between CCS-GIT and GNET continues to be debated, although the prevailing opinion is that the morphological and immunophenotypic features are sufficiently distinct to warrant their separate classification. Our comparative analysis of all published cases to date confirms that differences between these two groups extend beyond morphological findings to include epidemiological and clinical factors. Despite the common perception that GNET is associated with a more aggressive clinical course, our findings indicate that there is no significant difference in their biological behaviour, although both clearly share a bleak prognosis. Further experience with these rare tumours is awaited to determine the optimal treatment strategy and whether CCS-GIT and GNET would differ in their response to various therapies.

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