Sarcomatoid urothelial carcinoma: advances and challenges

Antonio Lopez-Beltran[a], *Alessia Cimadamore*[b], *Ana Blanca*[a], *Rodolfo Montironi*[c] *and Liang Cheng*[d,e]

Purpose of review
This review provides a comprehensive and updated overview of current concepts, technical advances, and future directions regarding sarcomatoid urothelial carcinoma, an aggressive subtype of urothelial carcinoma that affects the urinary bladder and upper tract.

Recent findings
This review examines recent advances in pathology, molecular profiles, and molecular therapeutic targets in sarcomatoid urothelial carcinoma with emphasis on their clinical impact in practice. Recent data on chemotherapy and surgical approaches to these aggressive tumors are also discussed. Of relevance is the identification of sarcomatoid urothelial carcinoma as a basal molecular subtype, characterized by frequent expression of PD-1/PD-L1 and a potential response to immune checkpoint inhibitors. The status of other potential targets of novel therapies, such as Nectin-4, TROP2, *FGFR3*, and *HER2*, is also addressed.

Summary
The implications of new developments in clinical practice range from the corrected differential diagnosis of sarcomatoid urothelial carcinoma from its mimics to the potential value of neoadjuvant chemotherapy followed by radical cystectomy, and the use of immune checkpoint inhibitors in metastatic sarcomatoid urothelial cancer, which improve clinical management and offer survival benefits for these patients. The use of novel therapies targeting molecular pathways represents a significant advance, enabling more precise and individualized treatment strategies.

Keywords
chemotherapy, cystectomy, Nectin-4, PD-L1, sarcomatoid, targeted therapy

INTRODUCTION

Sarcomatoid urothelial carcinoma (SUC) is a rare aggressive subtype of urothelial carcinoma characterized by morphological or immunohistochemical evidence of both epithelial and mesenchymal (sarcoma-like) features [1–12,13,14▪,15,16▪,17–26,27▪,28–30]. Heterologous elements may be present, and it should be documented in the pathology report [1–12,13,14▪,15,16▪,17–26,27▪,28–30]. Key features of SUC include patients with a mean age of 66 years (range, 50–77 years), representing 1% of all urothelial tumors, and showing 'biphasic' histology with both epithelial cells and mesenchymal cells, which can mimic a sarcoma [1,2,11,26,27▪,28]. The tumor is highly aggressive, with rapid progression and a significantly worse prognosis compared to conventional urothelial carcinoma. Pathological stage is the best predictor of survival in sarcomatoid carcinoma [1,2, 4,25,26,27▪,28]. Most frequently, patients present with hematuria, dysuria, nocturia, acute urinary retention, and lower abdominal pain [1,2,4,25,26,27▪,28]. TERT C228T promoter mutations have been linked to its aggressive behavior [31]. Radical surgery, such as radical cystectomy for bladder tumors, is often the standard treatment [8,15,22,30,31,32▪▪,33–35]. Neoadjuvant chemotherapy before surgery or adjuvant chemotherapy after surgery is used to enhance outcomes [32▪▪,35,36]. Due

[a]Department of Morphological Sciences, Cordoba University, Medical School, Cordoba, [b]Institute of Pathological Anatomy, Department of Medicine (DMED), Udine University, Udine, [c]Department of Clinical and Molecular Sciences, Polytechnic, University of the Marche Region, Ancona, [d]Department of Pathology and Laboratory Medicine and [e]Department of Surgery/Urology, Warren Alpert Medical School of Brown University, Brown University Health, and The Legorreta Cancer Center at Brown University, Providence, Rhode Islands, USA

Correspondence to Professor Dr Antonio Lopez-Beltran, Department of Morphological Sciences, Cordoba University Medical School, Avda. Menéndez-Pidal, E-14004 Córdoba, Spain. E-mail: em1lobea@uco.es; em1lobea@gmail.com

Curr Opin Urol 2026, 36:147–154
DOI:10.1097/MOU.0000000000001367

KEY POINTS

- Sarcomatoid urothelial carcinoma is a rare tumor, accounting for less than 1% of all urothelial tumors, and is highly aggressive, with rapid progression and shorter survival compared to conventional urothelial carcinoma. TERT promoter mutations have been linked to its aggressive behavior. It can occur in the urinary tract, most commonly the bladder, but also the renal pelvis, ureter, and urethra.
- It exhibits a mixed 'biphasic' histology, characterized by the coexistence of epithelial (urothelial) cells and mesenchymal (spindle-shaped) cells, which can mimic a sarcoma. The current WHO classification of urinary tract tumors recommends using the term sarcomatoid of urothelial carcinoma for these biphasic malignant neoplasms.
- Sarcomatoid carcinoma develops from the progression of basal urothelial carcinoma. It is divided into epithelial and mesenchymal (the most aggressive) molecular types. Dysregulation of cell cycle and EMT networks drives tumor progression.
- Sarcomatoid carcinoma has an infiltrated immune phenotype with upregulation of PD-L1, with immune checkpoint inhibitors as an important treatment option when metastatic. Combinations of immune checkpoint inhibitors with novel targeted therapies, such as enfortumab vedotin, represent an active field of research.

to high PD-L1 expression in SUC, immunotherapy is a promising treatment option, but some approaches combine chemotherapy with adjuvant radiation therapy or radiotherapy alone to enhance outcomes [32▪▪,35–49]. Other proposals include immunotherapy and molecular targeted therapies [50▪,51,52▪▪,53–56]. Known risk factors associated with SUC include exposure to prior radiation or long-term treatment with cyclophosphamide [1]. Reportedly, sarcomatoid carcinoma seems to be the common final pathway of all forms of epithelial bladder tumors [3]. The current WHO classification of urinary tract tumors recommends using the term sarcomatoid of urothelial carcinoma for these biphasic malignant neoplasms [26]. Other terms, such as carcinosarcoma, metaplastic carcinoma, spindle cell carcinoma, and malignant mixed tumor, have been used interchangeably but can lead to confusion and are therefore discouraged [27▪].

PATHOLOGY

Sarcomatoid carcinoma can be present at any site of urothelial epithelium along the urinary tract, including the pelvis, ureters, bladder, bladder diverticula, and prostatic urethra [1–12,13,14▪,15,16▪,17–26,27▪,28–30]. Despite this, it is exceedingly rare in locations outside the bladder. The tumors are usually described as polypoid masses, pedunculated, or broadly based, projecting into the lumen of the bladder [1,26]. Most tumors extend into or beyond the muscularis propria of the bladder. Sarcomatous component occupies more than 50% of the tumor area in most cases. Pure SUC represents approximately 20% of cases [1,4,22,26]. The epithelial and mesenchymal components demonstrate phenotypic variability. In most reported cases, the epithelial component is composed of moderately to poorly differentiated, high-grade, invasive urothelial carcinoma, characterized by brisk (atypical) mitoses and necrosis. While the tumor cells are most frequently spindled shape, occasionally they tend to be more rounded and epithelioid. Non-invasive papillary urothelial carcinoma and flat carcinoma *in situ* have been identified in multiple cases; occasionally, carcinoma *in situ* is the only epithelial component [1,3,5,7,9,10]. Squamous cell carcinoma, adenocarcinoma, and large and small cell neuroendocrine carcinoma are other types of epithelial differentiation in SUC [20].

Various heterologous components, such as osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma, or a combination of sarcoma histologies, may be observed [1,4]. Some tumors have prominent giant cells or inflammatory cells, and frequently exhibit pleomorphic and hyperchromatic nuclei, prominent nucleoli, high mitotic activity, and atypical mitotic figures. The presence of various components should be mentioned in the final pathological report [26]. However, the presence or absence, as well as the specific types of heterologous components, do not have a clinical impact on prognosis [1,7,11,14▪]. Sarcomatoid carcinomas are always high-grade carcinomas and frequently present at high pathological stages [8,11,26].

Differential diagnosis

The combination of epithelial and mesenchymal components in SUC may pose differential diagnostic considerations. When prominent, sarcomatoid carcinoma with myxoid and sclerosing stroma may be mistaken for pseudosarcomatous myofibroblastic tumor, postoperative spindle cell nodule, or urothelial carcinoma with prominent pseudosarcomatous stroma [1,3,4]. In this regard, immunohistochemical staining is used to identify markers of both epithelial and mesenchymal differentiation, enabling an accurate diagnosis and differentiation from their mimics (Fig. 1). Sarcomatoid carcinomas are typically basal or double negative regarding molecular taxonomy [55].

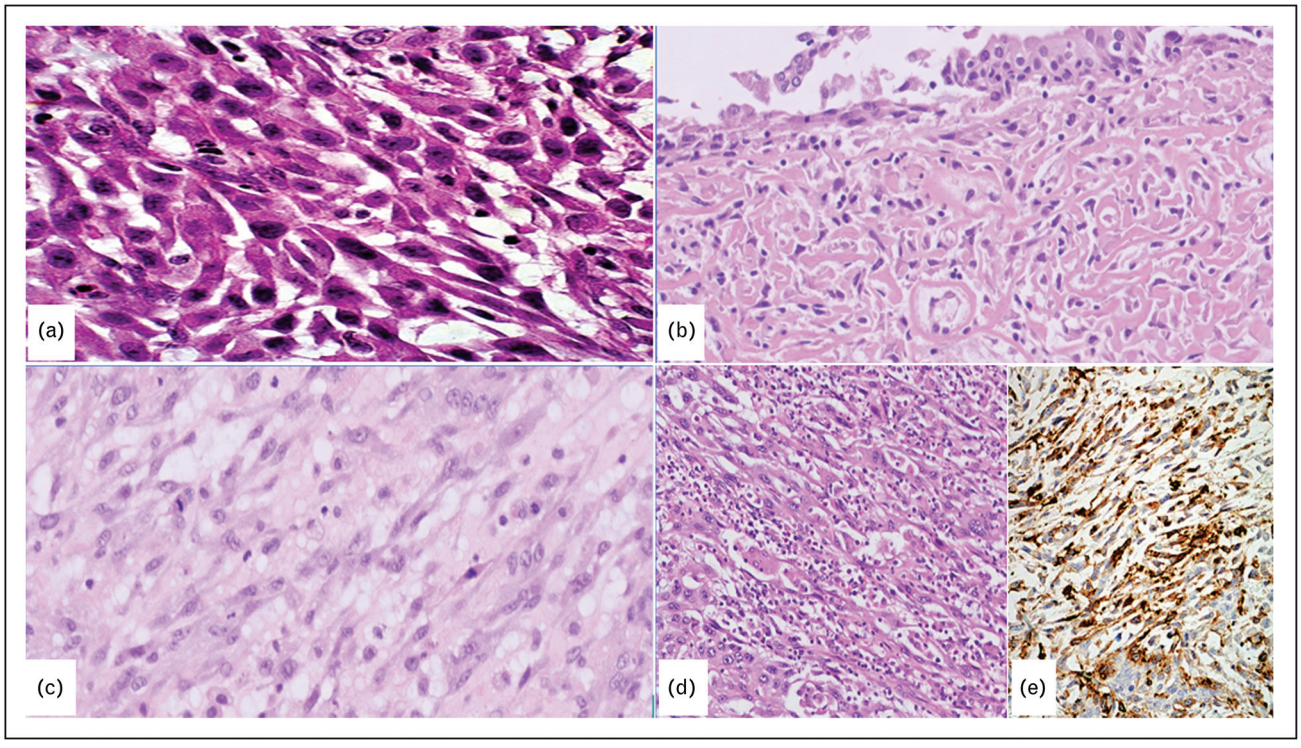

FIGURE 1. Microscopic features of sarcomatous urothelial carcinoma of the bladder showing spindle cell proliferation (a) with sclerosing (b) or myxoid (c) stroma. Immune cell infiltration (d) is a feature of several sarcomatoid urothelial carcinomas and is related to PD-L1 (e) expression (antibody SP263).

Sarcomatoid carcinoma is characterized by strong staining with CK (AE1/AE3, CAM5.2, CK7), p63, GATA3, and/or EMA with co-expression of vimentin and smooth-muscle actin in most cases. In contrast to smooth muscle neoplasms, actin and desmin are typically negative. Other negative staining includes ALK1, calponin, Caldesmon, and myogenin. CK5/6 and 34βE12 cytokeratin may be present in approximately 25% of cases. PAX8 may be present in some cases, particularly those from the upper urinary tract. However, sarcomatoid carcinomas with heterologous differentiation may be encountered rarely, and in such cases, expression of other mesenchymal markers, such as actin, desmin, or S100, may be observed (Table 1). When pure or predominant, sarcomatoid carcinoma with myxoid and sclerosing stroma may be mistaken for an inflammatory myofibroblastic tumor, a postoperative spindle cell nodule, or urothelial carcinoma with pseudosarcomatous stroma. The presence of slit-like vessels and the absence of atypical mitotic figures, deep necrosis, and significant cytologic atypia favor the diagnosis of a benign lesion.

Sarcomatoid urothelial carcinoma of the upper tract

While the majority of sarcomatoid carcinomas occur in the urinary bladder, upper urinary tract sarcomatoid carcinoma is extremely rare. The clinical presentation of upper urinary tract SUC is like that of conventional carcinomas in this location. Heterologous osteosarcoma was identified in two cases. Pathologic stage was pT4 in all patients with lymph-node metastasis in 65% of patients; 87% died within 2 years [4,12].

When dealing with sarcomatoid carcinoma of the upper tract, sarcomatoid renal cell carcinoma must always be included in the differential diagnosis. The frequent PAX8 positivity in renal cell sarcomatoid tumors may be helpful, as this is typically negative or weak and focally positive in urothelial sarcomatoid carcinomas. GATA3 and uroplakin II positivity are also of great value to define the urothelial lineage [55]. TERT C228T promoter mutation has been described in 35% of sarcomatoid carcinoma of the upper tract and is associated with poor prognosis [31].

MOLECULAR PATHOLOGY OF SARCOMATOID CARCINOMA

Recent molecular studies have provided insight into the histogenesis of SUC. Sung *et al.*[10] analyzed LOH and X-chromosome inactivation analysis in 30 SUCs from 10 female patients and 20 male patients. Their results showed a concordant pattern of nonrandom

Table 1. Main differential diagnosis of sarcomatoid urothelial carcinoma in clinical practice

	Inflammatory myofibroblastic tumor[b]	Postoperative spindle cell nodule	Sarcomatoid carcinoma[a]	Leiomyosarcoma
ALK1	Pos	Neg	–	–
Pan-cytokeratin	pos/neg	neg/pos	Pos	neg/pos
EMA	pos/neg	Neg	Pos	neg
h-Caldesmon	–	–	–	pos
Muscle-specific actin	Pos	Pos	pos/neg	pos
Desmin	pos/neg	pos/neg	neg/pos	pos
MyoD1	–	–	–	neg
Myogenin	–	–	–	neg
Myoglobin	Neg	–	–	–
Smooth muscle actin	Pos	pos/neg	neg/pos	pos
S100 protein	Neg	–	–	neg
Vimentin	Pos	Pos	pos/neg	pos
CD34	–	–	–	neg/pos
GATA3	–	–	Pos	–
P63			pos (50%)	
CK5/6			pos (27%)	
Histological features	High mitotic index, no atypical mitosis, detrusor muscle invasion,	Recent instrumentation	Various epithelial components, heterologous elements, significant atypia, high mitotic, atypical mitosis, variable necrosis	Infiltrative borders, uniform appearance, significant atypia, coagulative necrosis, high mitotic, atypical mitosis, most common adult bladder sarcoma

ALK, anaplastic lymphoma kinase; EMA, epithelial membrane antigen; Neg, negative; Neg/Pos, variable staining; Pos, positive.
[a]Sarcomatoid carcinoma typically expresses AE1/AE3, CAM5.2, CK7, p63, GATA3 and/or EMA, sometimes with focal or patchy staining. Vimentin and smooth-muscle actin are also frequently expressed. Negative staining includes ALK1, Desmin, Calponin, Caldesmon, and myogenin. TERT C228T promoter mutation is typically seen in sarcomatoid carcinoma (1/3 of cases) and is absent in inflammatory myofibroblastic tumor.
[b]Cytoplasmic smooth muscle actin and ALK1 positivity are typically used to support the diagnosis of inflammatory myofibroblastic tumor in cases with histologically supportive features.

X-chromosome inactivation in the informative female patients, supporting the idea that both the carcinomatous and sarcomatous components of SUC are of monoclonal origin. A separate analysis of the TP53 mutation status in 17 sarcomatoid carcinomas, using single-strand conformation polymorphisms (SSCP), DNA sequencing, and immunohistochemistry, revealed identical mutation patterns and nuclear p53 immunohistochemical staining characteristics in a subset of cases [9]. These findings provided further evidence of a common clonal origin for both the phenotypically distinct components of this biphasic tumor. Cheng *et al.*[3] postulated that sarcomatoid carcinoma is the common final pathway of all forms of epithelial bladder tumors.

Epithelial-to-mesenchymal transition

An epithelial-to-mesenchymal transition (EMT) may be responsible for the sarcomatoid transformation in carcinomas. Frequent expression of EMT-related biomarkers in sarcomatoid carcinoma of the bladder, in particular vimentin, FocC2, SNAIL, and ZEB1, has been reported [25,52▪▪]. More recently, Guo *et al.* [2,52▪▪] have suggested that dysregulation of EMT drives the progression to clinically aggressive sarcomatoid carcinoma of the bladder. About half of the cases exhibited a heavily infiltrated immune phenotype consistent with the observed response to immune checkpoint inhibitors in these patients [2,52▪▪]. Garioni *et al.*[42] confirmed the basal molecular subtype classification for sarcomatoid carcinoma

of the bladder and identified downregulation of EMT-related biomarkers, including E-Cadherin, ZEB1, and TWIST1. A concurrent loss of E-cadherin and elevated N-cadherin expressions is also evident in most cases. Molecular alterations of the chromatin remodeling and cell cycle control genes ARID1A and CDKN2A, have been reported [2,52▪▪].

Molecular profiling

SUC exhibits biphasic features, characterized by definitive urothelial differentiation. In other SUC, the mesenchymal component shows features of heterologous differentiation, such as chondrosarcoma, osteosarcoma, rhabdomyosarcoma, or angiosarcoma [1,3,2,52▪▪]. Sarcomatoid carcinomas exhibit uniformly low mRNA expression levels of the luminal genes and develop from basal precursor urothelial carcinomas. Synchronous sarcomatoid carcinoma and conventional urothelial carcinoma arising from the same bladder cancer foci share truncal somatic mutations and exhibit enriched basal gene expression, supporting the hypothesis that they originate from the same common ancestor with a basal-like phenotype [2,52▪▪]. Moreover, sarcomatoid carcinomas can be subdivided into those that retain expression of basal markers, such as basal keratins, CD44, and P-cadherin (CDH3), and those lacking the expression of both basal and luminal markers (double negative) [2,52▪▪]. This subset of purely mesenchymal sarcomatoid carcinomas shares overlapping features with the claudin-low and TCGA cluster IV subtypes that have been previously identified. The double-negative, purely mesenchymal subtype of sarcomatoid carcinoma seems to be the most aggressive subtype of the disease [2,52▪▪]. The observed changes converge on the loss of the epithelial phenotype, suggesting that dysregulation of EMT is a driver of this progression [2]. EMT is involved in cancer invasion and metastasis. In this process, epithelial cells lose their adhesive properties and develop migratory and infiltrative characteristics, which are typically associated with mesenchymal cells. Quantitative assessment of EMT revealed that basal and double-negative sarcomatoid carcinomas exhibited intermediate and low EMT scores, reflecting their partial or incomplete EMT activation status [2]. Among the top-activated pathways associated with sarcomatoid progression were TGFB1 and RhoA, coupled with the downregulation of target genes of p53 and p63, all of which can be viewed as synergistic mechanisms that create the so-called permissive EMT state. Sarcomatoid carcinomas also exhibited widespread downregulation of multiple miRNA species involved in EMT regulation, including miR-100, miR-203, miR-205, and all members of the miR-200 family. Sarcomatoid carcinomas have high mutational loads, like those found in conventional urothelial carcinoma or melanoma. The top three mutated genes in sarcomatoid carcinomas are TP53 (72%), PIK3CA (39%), and RB1 (39%) [2,52▪▪].

Sarcomatoid urothelial cancers also display heterogeneity in expression profiles characteristic of different immune cell types. Approximately half of sarcomatoid carcinomas express very high levels of B-cell, T-cell, CD8, TH1 macrophage, and dendritic cell biomarkers. Immune infiltration has been linked to EMT, with the double-negative and mesenchymal types exhibiting higher immune scores than the more 'epithelial' basal sarcomatoid carcinomas. The activation of immune-cell infiltration, accompanied by an increase in CD8+ cytotoxic lymphocytes, was particularly evident in the double-negative, purely mesenchymal subtype of the disease [2,52▪▪].

OVERVIEW OF PROGNOSIS AND THERAPY

For nonmuscle invasive sarcomatoid carcinoma, NCCN guidelines recommend radical cystectomy as a preferred option in patients who are BCG-naive. For invasive, nonmetastatic sarcomatoid carcinoma, management also includes radical cystectomy, which improves overall survival [58]. While previous retrospective analyses have shown only a nonsignificant survival benefit when patients with sarcomatoid carcinoma receive neoadjuvant chemotherapy, a more recent meta-analysis indicated significant benefit for NAC vs. those who did not receive neoadjuvant chemotherapy, and a recent single-institution data set noted similar rates of partial and complete response with neoadjuvant chemotherapy when compared with conventional urothelial carcinoma (20 vs. 24% pCR rate for sarcomatoid and urothelial carcinoma, respectively) [35,36,48,49,59]. Thus, neoadjuvant cisplatin-based chemotherapy in eligible patients followed by cystectomy is becoming the preferred approach among patients with nonmetastatic SUC.

PD1/PD-L1 and systemic immunotherapy

PD-L1 is frequently overexpressed in sarcomatoid carcinoma, which supports treating these patients with systemic immunotherapy. Sarcomatoid carcinomas are typically basal or double-negative regarding molecular taxonomy but often show immune cell infiltrates and high tumor mutation load and lack of mismatch repair proteins alterations [2,52▪▪,57]. PD-L1 expression is significantly higher in sarcomatoid carcinoma than in conventional urothelial carcinoma. It is overexpressed in 50% of SUC cases at both the mRNA and IHC levels (using mouse

monoclonal anti-PD-L1 clones 22C3 and SP263) [32▪▪,40,45,52▪▪,53–64] (Table 2). Consistent with this, immune checkpoint inhibitor treatment had a 35–40% response rate, and thus it could be considered for sarcomatoid carcinoma in advanced or unresectable disease. Of interest is a recent study that suggests classifying urothelial carcinoma as either immune-high or immune-low based on PD-L1, CD3, and CD8 expression [32▪▪,40,45,52▪▪,53–64]. The use of artificial intelligence measurement models may improve PD-L1 detection and reporting soon [37]. Additionally, IA, with or without the use of multiomics, enabled the identification of gene signatures predictive of response to immune checkpoint inhibitors, chemotherapy, or novel targeted therapies in clinical practice [38,39].

Molecular targets with clinical implications

The antibody-drug conjugate Enfortumab-vedotin (EV) plus the anti–PD-1 agent pembrolizumab is currently the first-line treatment for metastatic urothelial carcinoma; thus, expression of the target for EV (nectin-4) is of interest, but there is low expression of

Table 2. Targeted therapy in study for the treatment of sarcomatoid urothelial carcinoma and related biomarkers

SUC: molecular target, related drug, and biomarkers	Remarks
High mutational load. Maintained mismatch repair proteins. Top three mutated genes are *TP53* (72%), *PIK3CA* (39%) and *RB1* (39%). Altered EMT genes and overexpression of protein markers. Basal or double negative (for basal and luminal) molecular classification. High CD8+ cells. Overexpression of PD-L1	Potential for response to chemotherapy including neoadjuvant chemotherapy High level of response to immune check point-inhibitors
target: Nectin-4. Drug: Enfortumab vedotin (an antibody targeting Nectin-4 linked to a microtubule inhibitor conjugate) Biomarker: Nectin-4 by IHC or molecular analysis not required for therapy	Enfortumab vedotin plus pembrolizumab. Ongoing clinical trial: NCT05756569
	UNITE study [14]: Enfortumab vedotin ORR 38%
Target: Trop-2. Drug: Sacituzumab govitecan (antibody–drug conjugate that targets Trop-2, and is coupled with SN-38, an active metabolite of irinotecan) Biomarker: Trop-2 by IHC or molecular analysis not required for therapy	About 11% of SUC express TROP2. Not in use to treat SUC
Target: *HER2* (ERBB2). Drugs: trastuzumab, trastuzumab deruxtecan, Disitamab vedotin, lapatinib Biomarker: *HER2* analysis by IHC or gene amplification status (FISH analysis) required for therapy	About 11% of SUC express Her2 by immunohistochemistry. Part of ongoing clinical trials for solid tumors. Antibody drug conjugate Disitamab vedotin in *HER2*+ Phase II in urothelial carcinoma patients with progression of disease after >1 prior treatment. ORR 50.5%, median PFS 5.9 months, median OS 14.2 months (NCT06003231) Responders to sorafenib in mUC demonstrated higher mutations in the HER family of genes, DDR genes, and RAS/RAF pathway. DESTINY (trastuzumab deruxtecan): Ongoing clinical trial pan tumor for agnostic treatment of solid tumors Her2 3+ or 2+. Early result urothelial carcinoma ORR 39% for all patients, 56.3% for IHC 3+, 35% for IHC 2+

Many other new drugs using the same molecular targets presented in this table are part of different protocols for ongoing clinical trials. SUC, sarcomatoid urothelial carcinoma.

nectin-4 by sarcomatoid carcinoma [50▪,51]. Nectin-4 gene amplification has been suggested as a method to detect better responders to EV [65]. In a small retrospective reported series, the ORR to EV with sarcomatoid carcinoma was 38% [14▪]. A clinical trial evaluating the role of EV plus pembrolizumab in sarcomatoid carcinoma is ongoing (ClinicalTrials.gov identifier: NCT05756569). Sarcomatoid carcinomas do not carry activating *FGFR3* mutations, which are enriched in luminal cancers. Using patient-derived organoids, compounds targeting microtubules, heat shock proteins, proteasomes, and the mTOR pathway, as well as glucocorticoid receptor agonists and compounds that targeted the p53 and AKT pathways, were identified as potential novel targets for sarcomatoid carcinoma [42]. Approximately 11% of sarcomatoid carcinomas expressed TROP2, Nectin-4, and *HER2*, as recently reported, indicating a potential for novel therapy assessment in clinical trials [50▪]. Anecdotal case reported significant benefits of tislelizumab combined with anlotinib in metastatic upper tract SUC [55]. Given the aggressive nature of sarcomatoid carcinoma and most evidence reporting a benefit with systemic chemotherapy and immune checkpoint inhibitors, it is often reasonable to treat sarcomatoid carcinoma patients with these agents.

CONCLUSION

Sarcomatoid carcinoma has a poor prognosis with worse overall and cancer-specific survival as compared to conventional urothelial carcinoma and presents at an advanced stage. Recent data support using neoadjuvant chemotherapy together with radical surgery to treat patients with sarcomatoid carcinoma. Additionally, the frequent PD-L1 expression in sarcomatoid carcinoma highlights the potential of using immune checkpoint inhibitors to improve the survival of patients with metastatic sarcomatoid carcinoma. Molecular profiles identified sarcomatoid carcinoma as a basal molecular subtype with an immune-infiltrated phenotype and high tumor mutation load in keeping with a good response to checkpoint inhibitors. Furthermore, molecular profiles have identified targets for novel drugs that hold promise for personalized treatment, resulting in improved survival rates. SUC is a rare disease and remains a challenge to make large-scale clinical trials difficult, highlighting the need for collaborative multicenter studies for advancing our understanding and defining the role of immunotherapy, chemotherapy, and targeted therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Lopez-Beltran A, Pacelli A, Rothenberg HJ, *et al.* Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. J Urol 1998; 159:1497–1503.
2. Guo CC, Charles C, Majewski, *et al.* Dysregulation of EMT drives the progression to clinically aggressive sarcomatoid bladder cancer. Cell Rep 2019; 27:178.e41–1793.e4.
3. Cheng L, Zhang S, Alexander R, *et al.* Sarcomatoid carcinoma of the urinary bladder: the final common pathway of urothelial carcinoma dedifferentiation. Am J Surg Pathol 2011; 35:e34–46.
4. Wang X, MacLennan GT, Zhang S, *et al.* Sarcomatoid carcinoma of the upper urinary tract: clinical outcome and molecular characterization. Hum Pathol 2009; 40:211–217.
5. Wright JL, Black PC, Brown GA, *et al.* Differences in survival among patients with sarcomatoid carcinoma, carcinosarcoma and urothelial carcinoma of the bladder. J Urol 2007; 178:2302–2307.
6. Wang J, Wang FW, Lagrange CA, *et al.* Clinical features of sarcomatoid carcinoma (carcinosarcoma) of the urinary bladder: analysis of 221 cases. Sarcoma 2010; 2010:454792.
7. Almassi N, Vertosick EA, Sjoberg DD, *et al.* Pathological and oncological outcomes in patients with sarcomatoid differentiation undergoing cystectomy. BJU Int 2022; 129:463–469.
8. Rink M, Robinson BD, Green DA, *et al.* Impact of histological variants on clinical outcomes of patients with upper urinary tract urothelial carcinoma. J Urol 2012; 188:398–404.
9. Armstrong AB, Wang M, Eble JN, *et al.* TP53 mutational analysis supports monoclonal origin of biphasic sarcomatoid urothelial carcinoma (carcinosarcoma) of the urinary bladder. Mod Pathol 2009; 22:113–118.
10. Sung MT, Wang M, MacLennan GT, *et al.* Histogenesis of sarcomatoid urothelial carcinoma of the urinary bladder: evidence for a common clonal origin with divergent differentiation. J Pathol 2007; 211:420–430.
11. Lobo N, Shariat SF, Guo CC, *et al.* What is the significance of variant histology in urothelial carcinoma? Eur Urol Focus 2020; 6:653–663.
12. Lopez-Beltran A, Escudero AL, Cavazzana AO, *et al.* Sarcomatoid transitional cell carcinoma of the renal pelvis. A report of five cases with clinical, pathological, immunohistochemical and DNA ploidy analysis. Pathol Res Pract 1996; 192:1218–1224.
13. ▪ Seven İ, Aktürk Esen S, Sekmek S, *et al.* Clinicopathological features and treatment outcomes of urothelial carcinoma variant histologies and nonurothelial bladder cancers. Int Urol Nephrol 2025; 57:1451–1463.
Brief review of current therapies in sarcomatoid carcinoma and other variant histologies and nonurothelial bladder cancers.
14. ▪ Jindal T, Jiang CY, Alhalabi O , *et al.*et al Outcomes with Enfortumab Vedotin in Patients with Histologic Subtypes of Advanced Urothelial Carcinoma: Analysis of the UNITE Study. Eur Urol 2025; S0302-2838:00490-7.
Brief report on the effect of in enfortumab vedotin in sarcomatoid carcinoma.
15. Moschini M, D'Andrea D, Korn S, *et al.* Characteristics and clinical significance of histological variants of bladder cancer. Nat Rev Urol 2017; 14:651–668.
16. ▪ Xiao J, Chen H, Ge J, Liu T. Clinical efficacy analysis of partial cystectomy and radical cystectomy in the treatment of muscle-invasive sarcomatoid carcinoma of the urinary bladder. Front Oncol 2024; 14:1324487.
The paper reviews aspects of surgical approach to sarcomatoid carcinoma.
17. Tang LS, Zhou YW, Wang JL, *et al.* Epidemiology, site-specific characteristics and survival of carcinosarcoma: a retrospective study based on SEER database. BMJ Open 2023; 13:e077974.
18. Kadouri Y, Ouskri S, Sayegh HE, *et al.* Sarcomatoid carcinoma of the urinary bladder: analysis of five cases and literature review. Pan Afr Med J 2020; 36:369.
19. Basibuyuk I, Topaktaş R, Elbir F. Bladder carcinosarcoma: a case report with review of the literature. Arch Ital Urol Androl 2017; 89:240–242.
20. Urrea YR, Epstein JI. Sarcomatoid carcinoma associated with small cell carcinoma of the urinary bladder: a series of 28 cases. Hum Pathol 2017; 67:169–175.
21. Malla M, Wang JF, Trepeta R, *et al.* Sarcomatoid carcinoma of the urinary bladder. Clin Genitourin Cancer 2016; 14:366–372.

22. Diamantopoulos LN, Dimitrios K, Michail Al, Jonathan L. Sarcomatoid urothelial carcinoma: a population-based study of clinicopathologic characteristics and survival outcomes,. Clin Genitourin Cancer 2022; 20:139–147.
23. Fatima N, Canter DJ, Carthon BC, *et al.* Sarcomatoid urothelial carcinoma of the bladder: a contemporary clinicopathologic analysis of 37 cases. Can J Urol 2015; 22:7783–7787.
24. Venyo AK, Titi S. Sarcomatoid variant of urothelial carcinoma (carcinosarcoma, spindle cell carcinoma): a review of the literature. ISRN Urol 2014; 2014: 794563.
25. Sanfrancesco J, Jesse K, McKenney H, *et al.* Sarcomatoid urothelial carcinoma of the bladder: analysis of 28 cases with emphasis on clinicopathologic features and markers of epithelial-to-mesenchymal transition:. Arch Pathol Lab Med 2016; 140:543–551.
26. WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours 5th series).
27. ■ Brown ML, Tretiakova M. Sarcomatoid variant. PathologyOutlines.com website. Available at: https://www.pathologyoutlines.com/topic/bladdersarcomatoidvariant.html. (Accessed 29 September 2025).

Pathologic approach to diagnosis of sarcomatoid urothelial carcinoma.

28. Lopez-Beltran A, Henriques V, Montironi R, *et al.* Variants and new entities of bladder cancer. Histopathology 2019; 74:77–96.
29. Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 2009; 27: 3–7.
30. Gu L, Ai Q, Cheng Q, *et al.* Sarcomatoid variant urothelial carcinoma of the bladder: a systematic review and meta-analysis of the clinicopathological features and survival outcomes. Cancer Cell Int 2020; 20:550.
31. Wang K, Liu T, Liu L, *et al.* TERT promoter mutations in renal cell carcinomas and upper tract urothelial carcinomas. Oncotarget 2014; 5:1829–1836.
32. ■■ Evangelia V, Burles AJ, Ezra B, *et al.* Current advances in the management of nonurothelial subtypes of bladder cancer. Am Soc Clin Oncol Educ Book 2024; 44:e438640.

A brief review of the current status of therapy in sarcomatoid carcinoma and other variants of bladder cancer.

33. Minato A, Furubayashi N, Nagata Y, *et al.* Prognostic Impact of histologic subtype and divergent differentiation in patients with metastatic urothelial carcinoma treated with enfortumab vedotin: a multicenter retrospective study. Curr Oncol 2024; 31:862–871.
34. Necchi A, Raggi D, Gallina A, *et al.* Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. Eur Urol 2020; 77: 439–446.
35. Damiano R, D'Armiento M, Cantiello F, *et al.* Gemcitabine and cisplatin following surgical treatment of urinary bladder carcinosarcoma. Tumori 2004; 90:458–460.
36. Johnson Iii BA, Teply BA, Kagemann C, *et al.* Neoadjuvant cisplatin, gemcitabine, and docetaxel in sarcomatoid bladder cancer: clinical activity and whole transcriptome analysis. Bladder Cancer 2024; 10:133–143.
37. Rüschoff J, Kumar G, Badve S, *et al.* Scoring PD-L1 expression in urothelial carcinoma: an International Multi-Institutional Study on Comparison of Manual and Artificial Intelligence Measurement Model (AIM-PD-L1) Pathology Assessments. Virchows Arch 2024; 484:597–608.
38. Xu Y, Sun X, Liu G, *et al.* Integration of multi-omics and clinical treatment data reveals bladder cancer therapeutic vulnerability gene combinations and prognostic risks. Front Immunol 2024; 14:1301157.
39. Xu H, Liu Z, Weng, *et al.* Artificial intelligence-driven consensus gene signatures for improving bladder cancer clinical outcomes identified by multi-center integration analysis. Mol Oncol 2022; 16:4023–4042.
40. Li H, Zhang Q, Shuman L, *et al.* Evaluation of PD-L1 and other immune markers in bladder urothelial carcinoma stratified by histologic variants and molecular subtypes. Sci Rep 2020; 10:1439.
41. Kobayashi M, Narita S, Matsui Y, *et al.* Japan Urological Oncology Group. Impact of histological variants on outcomes in patients with urothelial carcinoma treated with pembrolizumab: a propensity score matching analysis. BJU Int 2022; 130:226–234.
42. Garioni M, Tschan VJ, Blukacz L, *et al.* Patient-derived organoids identify tailored therapeutic options and determinants of plasticity in sarcomatoid urothelial bladder cancer. NPJ Precis Oncol 2023; 7:112.
43. Godlewski D, Czech S, Szpara J, *et al.* Narrative review of current advances and future changes regarding bladder cancer treatment. Urology 2025; 5:11.
44. Olisaemeka O, Abdo H, Nima A, *et al.* Overview of histologic variants of urothelial carcinoma: current trends and narrative review on treatment outcomes. Transl Androl Urol 2022; 11:877–901.
45. Hooshmand F, Mokhtari M, Aminnia S, *et al.* PD-1 and PD-L1 expression in molecular subtypes of muscle-invasive bladder cancer: immunohistochemical characterization and correlation with clinicopathological features. Diagn Pathol 2025; 20:97.
46. Wu S, Wang X, Zuo Y, *et al.* Clinical evolution of bladder carcinosarcoma: a case report and literature review. Medicine (Baltimore) 2024; 103:e39225.
47. Badheeb AM, Alkhanbashi O, Al Hammadi SS, *et al.* Urinary bladder carcinosarcoma (sarcomatoid carcinoma) with long survival after transurethral resection: a case report. Cureus 2024; 16:e59992.
48. Sekar RR, Diamantopoulos LN, Bakaloudi DR, *et al.* Sarcomatoid urothelial carcinoma is associated with limited response to neoadjuvant chemotherapy and poor oncologic outcomes after radical cystectomy. Clin Genitourin Cancer 2023; 21:507.e1–507.e14.
49. Froehner M, Gaertner HJ, Manseck A, Wirth MP. Durable complete remission of metastatic sarcomatoid carcinoma of the bladder with cisplatin and gemcitabine in an 80-year-old man. Urology 2001; 58:799.
50. ■ Brunelli M, Gobbo S, Malpeli G, *et al.* TROP-2, NECTIN-4 and predictive biomarkers in sarcomatoid and rhabdoid bladder urothelial carcinoma. Pathologica 2024; 116:55–61.

Expression of molecular targets in sarcomatoid carcinoma.

51. Hoffman-Censits JH, Lombardo KA, Parimi V, *et al.* Expression of nectin-4 in bladder urothelial carcinoma, in morphologic variants, and nonurothelial histotypes. Appl Immunohistochem Mol Morphol 2021; 29:619–625.
52. ■■ Guo CC, Lee S, Lee JG, *et al.* Molecular profile of bladder cancer progression to clinically aggressive subtypes. Nat Rev Urol 2024; 21:391–405.

Excellent review on the molecular aspects of tumor progression associated to sarcomatoid carcinoma.

53. Wang J, Gillaspie C, Kunadharaju R, *et al.* Sarcomatoid urothelial carcinoma: a single cancer center experience. World J Oncol 2011; 2:175–180.
54. Anraku T, Hashidate H, Nakahara A, *et al.* Sarcomatoid urothelial carcinoma of the renal pelvis treated with immunotherapy. BMC Urol 2023; 23:38.
55. Chang A, Brimo F, Montgomery EA, Epstein JI. Use of PAX8 and GATA3 in diagnosing sarcomatoid renal cell carcinoma and sarcomatoid urothelial carcinoma. Hum Pathol 2013; 44:1563–1568.
56. Liu L, Zhu J, Tian Y. Carcinosarcoma is an aggressive subtype of bladder cancer: a population-based study. Cancer Med 2022; 11:2216–2223.
57. Kunc M, Gabrych A, Rękawiecki B, *et al.* Immunohistochemical evaluation of mismatch repair proteins and p53 expression in extrauterine carcinosarcoma/sarcomatoid carcinoma. Contemp Oncol (Pozn) 2020; 24:1–4.
58. NCCN Guidelines Version 1.2025. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417. (Accessed 2 October 2025)
59. Kouhen F, Dahbi Z, Afif M, *et al.* Bladder carcinosarcoma treated by cystectomy and adjuvant chemotherapy with good outcomes: a case report. J Med Case Rep 2023; 17:320.
60. Zhu S, Yu C, Wang C, *et al.* Case report: Significant benefits of tislelizumab combined with anlotinib in first-line treatment of metastatic renal pelvic urothelial carcinoma with sarcomatoid carcinoma differentiation. Front Oncol 2022; 12:969106.
61. Wallach JB, Wang B, Sanfilippo N. High-grade hyperinvasive sarcomatoid urothelial bladder carcinoma demonstrating complete response to bladder-preserving chemoradiation. Curr Oncol 2009; 16:55–57.
62. Miller NJ, Khaki AR, Diamantopoulos LN, *et al.* Histological subtypes and response to PD-1/PD-L1 blockade in advanced urothelial cancer: a retrospective study. J Urol 2020; 204:63–70.
63. Miyama Y, Kanao K, Uranishi K, *et al.* Complete response to pembrolizumab in a patient with recurrent and metastatic urothelial bladder carcinoma reflecting coexisting sarcomatoid subtype and glandular differentiation: a case report. Int Cancer Conf J 2022; 12:24–30.
64. Polyakova AS, Sokolov EA, Pushkar DYu. Effectiveness of pembrolizumab in therapy of sarcomatoid variant of metastatic urothelial carcinoma. Clinical case 2025; 20:104–111.
65. Klümper N, Tran NK, Zschäbitz S, *et al.* NECTIN4 amplification is frequent in solid tumors and predicts enfortumab vedotin response in metastatic urothelial cancer. J Clin Oncol 2024; 42:2446–2455.