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# Mesonephric-like Carcinosarcoma of the Uterine Corpus: Clinicopathological, Molecular and Prognostic Characteristics in Comparison With Uterine Mesonephric-like Adenocarcinoma and Conventional Endometrial Carcinosarcoma

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**Abstract.** *Background/Aim: This study aimed to investigate the clinicopathological, prognostic and molecular characteristics of uterine mesonephric-like carcinosarcoma (MLCS). Patients and Methods: We collected clinical, pathological, and genetic information from 12 MLCS patients, and analyzed their differences from mesonephric-like adenocarcinoma (MLA) and conventional endometrial carcinosarcoma (CECS). Results: The epithelial component was exclusively MLA in all MLCS cases. Metastatic and recurrent tumors consisted predominantly or exclusively of MLA in the majority of MLCS cases. Patients with MLCS and MLA presented with more advanced-stage disease than those with CECS. They also exhibited post-treatment recurrence and lung metastases more frequently than CECS. Disease-free survival rates of MLCS and MLA were shorter than those of CECS. Tumor protein 53 gene mutations were detected in four MLCS cases. Conclusion: The predominance or exclusive presence of MLA in metastatic and recurrent tumors highlights the possibility that MLA may determine the clinical outcomes of patients with MLCS. Further studies are required to provide direct molecular evidence of the monoclonal origin of uterine MLCS.*

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*Key Words:* Uterus, carcinosarcoma, mesonephric-like carcinosarcoma, mesonephric-like adenocarcinoma, tumor protein 53, *TP53*.



Carcinosarcoma (CS) of the endometrium is an aggressive malignant tumor of the female genital tract. Approximately 40% of patients with endometrial CS have extrauterine complications at diagnosis, and more than half of them develop recurrence despite curative treatment (1, 2). CS causes >15% of deaths related to uterine malignancy (3). Histologically, CS comprises of both epithelial (carcinomatous) and mesenchymal (sarcomatous) components. The epithelial element is usually a high-grade carcinoma, including serous, grade 3 endometrioid, clear cell, and undifferentiated carcinoma. The mesenchymal components can be either homologous or heterologous. The former is typically a high-grade non-specific sarcoma (HGNS), and often includes one or more types of sarcomas that are conventionally diagnosed in the uterus, such as leiomyosarcoma, low-grade endometrial stromal sarcoma, and high-grade endometrial stromal sarcoma. In case of heterologous mesenchymal elements, rhabdomyoblasts (rhabdomyosarcoma) or malignant cartilage (chondrosarcoma) are the most commonly observed. Osteosarcomatous or liposarcomatous differentiation rarely occurs. The proportions of the epithelial and mesenchymal components vary widely (4). Accumulating evidence has pointed towards a biological similarity between CS and endometrial carcinoma, and a monoclonal origin of epithelial and mesenchymal components (5). CS is currently considered a high-risk variant of endometrial carcinoma because it shares more similarities in epidemiology, risk factors, and clinical behavior with endometrial carcinoma than uterine sarcoma (5).

Mesonephric-like adenocarcinoma (MLA) of the uterine corpus is a rare but distinct gynecological malignancy that

morphologically resembles mesonephric adenocarcinoma of the uterine cervix or vagina, which originates from mesonephric remnants (6-14). Uterine MLA was introduced as a new histological type in both the endometrium and ovary in the recent 2020 World Health Organization (WHO) classification of female genital tumors (15, 16). Uterine MLA characteristically shows diverse architectural patterns (*e.g.*, tubular, ductal, papillary, solid, retiform, maze-like, sieve-like, sex cord-like, comedonecrosis-like, glomeruloid) and eosinophilic intraluminal secretions. Immunohistochemically, MLA does not react with or only focally expresses hormone receptors; instead, it usually expresses one or more mesonephric markers (7, 8, 11, 12, 17). Although MLA presents with symptoms and signs similar to the more common histological types of endometrial carcinoma, it is more likely to behave aggressively with advanced-stage disease at diagnosis, rapid progression, frequent recurrence, distant metastases and poor prognosis (7, 13, 18, 19).

Uterine mesonephric-like carcinosarcoma (MLCS), also known as malignant mixed mesonephric tumor, is rarer than MLA and has seldom been reported in the literature (20-30). Although mesonephric CS of the uterine cervix has been reported to exhibit a poor prognosis (28), the clinicopathological and prognostic characteristics of MLCS arising from the uterine corpus are yet to be elucidated. Recently, we encountered several cases of uterine MLCS and initiated a review of our archival cases. This study aimed to investigate the clinicopathological characteristics and patient outcomes of uterine MLCS and compare them with those of uterine MLA and 'conventional' endometrial CS (CECS). Comprehensive analyses of uterine MLCS cases have expanded our knowledge of their clinical manifestations, histological and molecular features, and prognostic significance.

## Patients and Methods

*Case selection*. This study was approved by the Institutional Review Board of Samsung Medical Center (protocol code: 2021-11-029; date of approval: November 12, 2021). Two board-certified pathologists specializing in gynecological oncology (S.P. and H-S.K.) reviewed all the available hematoxylin and eosin-stained and immunostained slides. The pathological diagnosis of primary uterine MLCS was established based on the identification of the MLA as an epithelial element and a malignant mesenchymal element. The former was characterized by the following histopathological, immunophenotypical, and molecular characteristics: 1) the presence of a tubular growth pattern with small, closely packed, back-to-back tubules lined by cuboidal cells; 2) a variable amount of eosinophilic intraluminal secretions; 3) diverse architectural patterns; and 4) either immunohistochemical [negative or focal positivity for estrogen receptor and positive immunoreactivity for at least one mesonephric marker, including GATA-binding protein 3, transcription termination factor 1, cluster of differentiation 10 (luminal pattern of expression), and calretinin] or molecular confirmation [pathogenic Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation] (7-11, 19).

*Clinicopathological data collection*. We examined 12, 35, and 26 cases of uterine MLCS, MLA, and CECS, respectively. The following clinicopathological information was obtained from electronic medical records and final pathology reports: age of patients at initial pathological diagnosis, type of surgery, biopsy diagnosis, hysterectomy diagnosis, initial International Federation of Gynecology and Obstetrics (FIGO) stage (31), initial distant metastasis, type of postoperative treatment, post-treatment recurrence, disease-free survival (DFS), current status, and histological types and proportions of epithelial and mesenchymal components in primary, metastatic, and recurrent tumor tissues. We also determined whether the sarcomatous components were homologous (HGNS) or heterologous (rhabdomyosarcoma and chondrosarcoma).

*DNA extraction*. Five-micrometer-thick, formalin-fixed, paraffin-embedded (FFPE) tissue sections were deparaffinized and hydrated using graded alcohols to water. Sections were manually microdissected using a sterile 26-gauge needle dipped in ethanol. The scraped material was then washed in phosphate-buffered saline and digested in proteinase K overnight at 56 ˚C in Buffer ATL (Qiagen, Hilden, Germany). DNA was isolated using a QIAamp DSP DNA FFPE Tissue Kit (Qiagen) (7-9, 11, 12, 29, 32). A Qubit 4 Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA) was used for sample quantification using highly sensitive and accurate fluorescence-based quantitation assays.

*Next-generation sequencing*. Libraries for targeted sequencing were prepared using extracted DNA and Ion AmpliSeq Library Preparation on the IonChef System protocol (Thermo Fisher Scientific). The libraries were quantified using an Ion Library Universal Quantification Kit (Thermo Fisher Scientific). Sequencing was performed on the IonTorrent S5 XL platform (Thermo Fisher Scientific) using the Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific). This is an amplicon-based, targeted assay that enables the detection of relevant single-nucleotide variants and indels from 161 unique genes, and positive control cell line mixtures (Horizon Discovery, Cambridge, UK). Genomic data were analyzed, and the variants were identified using the Torrent Variant Caller plugin (Thermo Fisher Scientific) and Ion Reporter Software v5.6 (Thermo Fisher Scientific). To eliminate error artifacts, sequence data were visually confirmed using Integrative Genomics Viewer (Broad Institute, Cambridge, MA, USA). Only variants in the coding regions, promoter regions, or splice variants were retained. Based on the results of the feasibility study, the variant allele fraction threshold was set to 5%.

*p53 immunostaining*. Formalin-fixed tissues were dehydrated using a graded ethanol series and embedded in paraffin. FFPE tissue blocks were sectioned at 4 μm on a standard rotary microtome, and sections were placed in a water bath on microscopic glass slides. Expression of p53 protein was assessed by immunohistochemistry using a BOND-MAX automated immunostainer (Leica Biosystems, Buffalo Grove, IL, USA) (6, 8, 9, 12, 17, 33-37). After antigen retrieval, the sections were incubated with anti-p53 antibody (dilution 1:200, clone DO-7, catalog number NCL-L-p53-DO7, Leica Biosystems). After chromogenic visualization, the slides were counterstained with hematoxylin and dehydrated using a standard

Table I. *Genomic aberrations giving rise to HMGA2 (on 12q14) truncation or in-frame fusions (denoted with *).*

| Case No | Age (years) | Surgery | Biopsy Dx | Hysterectomy Dx (epithelial component) | Initial stage | Initial distant metastasis | Post-operative treatment | Post-treatment recurrence | DFS (months) | Survival status |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | RH, BSO, PLND, PALND | CS | CS (MLA) | IA | No | Chemotherapy | Yes (lung) | 8.0 | Dead |
| 2 | 57 | RH, BSO, PLND, PALND | ADC | CS (MLA) | IIIC | No | CCRT | Yes (lung) | 12.1 | Dead |
| 3 | 67 | TH, BSO, PLND | CS | CS (MLA) | IB | No | No | Yes (lung, PALN) | 13.4 | Dead |
| 4 | 75 | TH, BSO, PALNS | CS | CS (MLA) | IB | No | No | Yes (lung, liver, abdomen, pelvic wall) | 15.6 | Dead |
| 5 | 66 | TH, BSO | NA | CS (MLA) | IVB | Yes (lung, liver, abdomen) | No | Yes (lung, liver, abdomen, pelvic wall) | 1.1 | Dead |
| 6 | 59 | TH, BSO, PLND | CS | CS (MLA) | IIIC | No | Radiation therapy | Yes (lung) | 12.1 | Alive |
| 7 | 62 | TH, BSO, PLND, PALND | EC | CS (SC) | IA | No | Chemotherapy | Yes (lung, MLN, SCLN) | 34.7 | Alive |
| 8 | 57 | TH, BSO, PLND, PALND | CS | CS (MLA) | II | No | Chemotherapy | Yes (liver, abdomen) | 3.7 | Alive |
| 9 | 67 | TH, BSO, PLND, PALND | CS | CS (MLA) | II | No | Radiation therapy | NA (ongoing radiation therapy) | NA | NA |
| 10 | 64 | TH, BSO | NA | CS (MLA) | IVB | Yes (lung, pleura, abdomen) | Chemotherapy | NA (ongoing chemotherapy) | NA | NA |
| 11 | 47 | TH, BSO, PLND | NA | CS (EC) | IVB | Yes (abdomen) | Chemotherapy | Yes (abdomen) | 0.8 | Alive |
| 12 | 61 | RH, BSO, PLND, PALND | NA | CS (MLA) | II | No | Chemotherapy | Yes (lung, pelvic wall) | 7.9 | Alive |

ADC, Adenocarcinoma; BSO, bilateral salpingo-oophorectomy; CCRT, concurrent chemoradiation therapy; CS, carcinosarcoma; DFS, disease-free survival; Dx, diagnosis; EC, endometrioid carcinoma; MLA, mesonephric-like adenocarcinoma; NA, not applicable; PALND, para-aortic lymph node dissection; PALNS, para-aortic lymph node sampling; PLND, pelvic lymph node dissection; RH, radical hysterectomy; SC, serous carcinoma; TH, total hysterectomy.

procedure and sealed with coverslips. Positive and negative control samples were included in each run to minimize variation between assays. The positive control was high-grade serous ovarian carcinoma sections. The negative control was prepared by using the non-immune serum in place of primary antibodies, which resulted in undetectable staining. Analysis of p53 immunostaining was performed as previously described (35, 38, 39). Its expression pattern was considered aberrant when any one of the following features was observed: diffuse and strong nuclear immunoreactivity in ≥75% of the tumor cells (*i.e.*, overexpression pattern), no nuclear immunoreactivity in any tumor cell (*i.e.*, complete absence pattern), or unequivocal cytoplasmic staining (*i.e.*, cytoplasmic pattern). Immunostained slides exhibiting a variable proportion of tumor cell nuclei expressing p53 protein with mild-to-moderate intensity were considered as the wild-type pattern.

*Statistical analysis*. Pearson chi-squared test, Fisher's exact test, or linear-by-linear association test was performed to examine the differences between discrete variables, including age group (categorized according to the median age of 60 years; ≥60 or <60 years), initial stage (I, II, III, or IV), post-treatment recurrence (yes or no), and lung metastasis (yes or no). Univariate survival analysis with the log-rank test and Kaplan-Meier plots was performed to examine the prognostic significance of DFS. All statistical analyses were performed using IBM SPSS Statistics for Windows, v23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

*Literature review*. The Medline database was thoroughly searched using PubMed retrieval service (https://pubmed.ncbi.nlm.nih.gov/). The keywords used were "uterus," "mesonephric," "mesonephric-like," and "carcinosarcoma." Eleven articles documenting uterine MLCS were identified. We collected survival data from 22 previously reported uterine MLCS cases.

## Results

*Clinical characteristics of uterine MLCS*. The study population included 12 MLCS patients, whose age ranged from 47-67 years (median=61.5 years; mean=61.8 years; Table I). Prior to surgery, eight patients underwent diagnostic procedures, such as endometrial aspiration biopsy or curettage. Six out of eight patients were diagnosed with CS, and the remaining two patients did not have any mesenchymal elements in their endometrial specimens and were diagnosed with "adenocarcinoma" and "endometrioid carcinoma," respectively. All patients underwent total (9/12) or radical (3/12) hysterectomy with bilateral salpingo-oophorectomy (12/12), pelvic lymph node dissection (9/12), and para-aortic lymph node dissection (6/12) or sampling (1/12). The epithelial component was interpreted as MLA in 10/12 hysterectomy specimens. The remaining two patients were diagnosed with serous carcinoma and endometrioid carcinoma, respectively. The initial FIGO stages were distributed as follows: stage IA (2/12), stage IB (2/12), stage II (3/12), stage IIIC (2/12), and stage IVB (3/12). Three patients with stage IVB disease had multiple distant

Table II. *Proportions of histological types observed in primary and metastatic uterine mesonephric-like carcinosarcoma.*

| Case No | Initial stage | Histological type (proportion) | | |
|---|---|---|---|---|
| | | Primary tumor | Initial metastatic tumor | Recurrent metastatic tumor |
| 1 | IA | MLA (80%), HGNS (20%) | NA | MLA (100%) |
| 2 | IIIC | MLA (80%), HGNS (20%) | MLA (100%) | MLA (100%) |
| 3 | IB | MLA (90%), HGNS (10%) | NA | MLA (100%) |
| 4 | IB | MLA (90%), HGNS (10%) | NA | MLA (100%) |
| 5 | IVB | MLA (80%), HGNS (10%), RMS (5%), CHS (5%) | MLA (100%) | MLA (100%) |
| 6 | IIIC | MLA (90%), HGNS (10%) | MLA (100%) | MLA (100%) |
| 7 | IA | MLA (90%), HGNS (10%) | NA | MLA (100%) |
| 8 | II | NA | NA | MLA (90%), HGNS (10%) |
| 9 | IVB | MLA (80%), HGNS (20%) | NA | NA |
| 10 | IVB | MLA (50%), HGNS (45%), RMS (5%) | MLA (40%), HGNS (60%) | NA |
| 11 | II | MLA (50%), HGNS (50%) | NA | NA |
| 12 | II | MLA (90%), HGNS (10%) | NA | NA |

CHS, Chondrosarcoma; HGNS, high-grade non-specific sarcoma; MLA, meso-nephric-like adenocarcinoma; NA, not applicable; RMS, rhabdomyosarcoma.

metastases at the time of the initial diagnosis, including the lungs, pleura, liver, and abdominal peritoneum. Nine patients received postoperative chemotherapy, radiation therapy, or concurrent chemoradiation therapy. Of the three remaining patients, two with stage IB disease did not receive any adjuvant treatment, and one with stage IVB disease died within a short period of time (1.3 months). Except for two patients who are currently receiving postoperative treatment, all patients developed metastatic recurrences in the lung, liver, abdomen, pelvic wall, and lymph nodes (para-aortic, mediastinal, and supraclavicular). During the postoperative follow-up period, bilateral multiple lung metastases were detected in six of the 10 patients. DFS of the 10 patients, whose follow-up information was available, was in the range of 0.8-34.7 months (median=8.0 months; mean=13.4 months). Five patients died from the disease.

*Histological features of uterine MLCS*. Table II summarizes the histological types and their relative proportions in the primary and metastatic MLCS tissues. All except one patient, who did not have archived slides available for review, were diagnosed with MLA as an epithelial component and HGNS as a major mesenchymal component. The proportion of MLA components varied between 50 and 90% among the cases. Heterologous mesenchymal components, including rhabdomyosarcoma (2/12) and chondrosarcoma (1/12), were present in three cases. Representative photomicrographs showing the histological and immunophenotypical features of uterine MLCS are presented in Figure 1 (case 10), Figure 2 (case 9) and Figure 3 (case 5), respectively. The metastatic MLCS tissues almost invariably contained MLA. Most of the initial metastatic lesions involving the ovary, fallopian tube, lymph nodes, liver, abdominal peritoneum, lung, and pleura consisted exclusively of MLA (Figure 4). In case 10, peritoneal metastatic tumors showed both MLA (40%) and HGNS (60%; Figure 4). In seven of the eight cases in which recurrent tumors were surgically resected and examined microscopically, MLA was the only histological component. The omental metastatic tumor identified in case 8 contained 90% MLA and 10% HGNS.

*Clinicopathological differences among MLCS, MLA and CECS*. As shown in Table III, the initial FIGO stage showed a significant difference between MLA and CECS ($p$=0.008); 77.1% (27/35) of MLA patients had stage III-IV disease, while only 38.5% (10/26) of CECS were staged as III-IV. Post-treatment recurrences were more frequent in MLCS and MLA than in CECS ($p$=0.006 and 0.014, respectively), as all patients (12/12) with MLCS and 80% (28/35) with MLA experienced recurrent disease as compared to 50% (13/26) of patients with CECS who developed post-treatment recurrences. Lung metastasis was also more frequent in the MLCS and MLA groups than in the CECS group ($p$=0.012 and 0.010, respectively); 75.0% (9/12) of patients with MLCS, 60% (21/35) with MLA, and 26.9% (7/26) with CECS had lung metastases. There were no significant differences in the clinicopathological characteristics between MLCS and MLA. Although patients with MLA tended to exhibit more advanced stages of the disease, the difference in the distribution of the initial FIGO stage was not significant ($p$=0.067).

*Survival differences among MLCS, MLA, and CECS groups*. Kaplan-Meier plots for DFS in uterine MLCS, MLA, and endometrial CECS are shown in Figure 5. All patients with

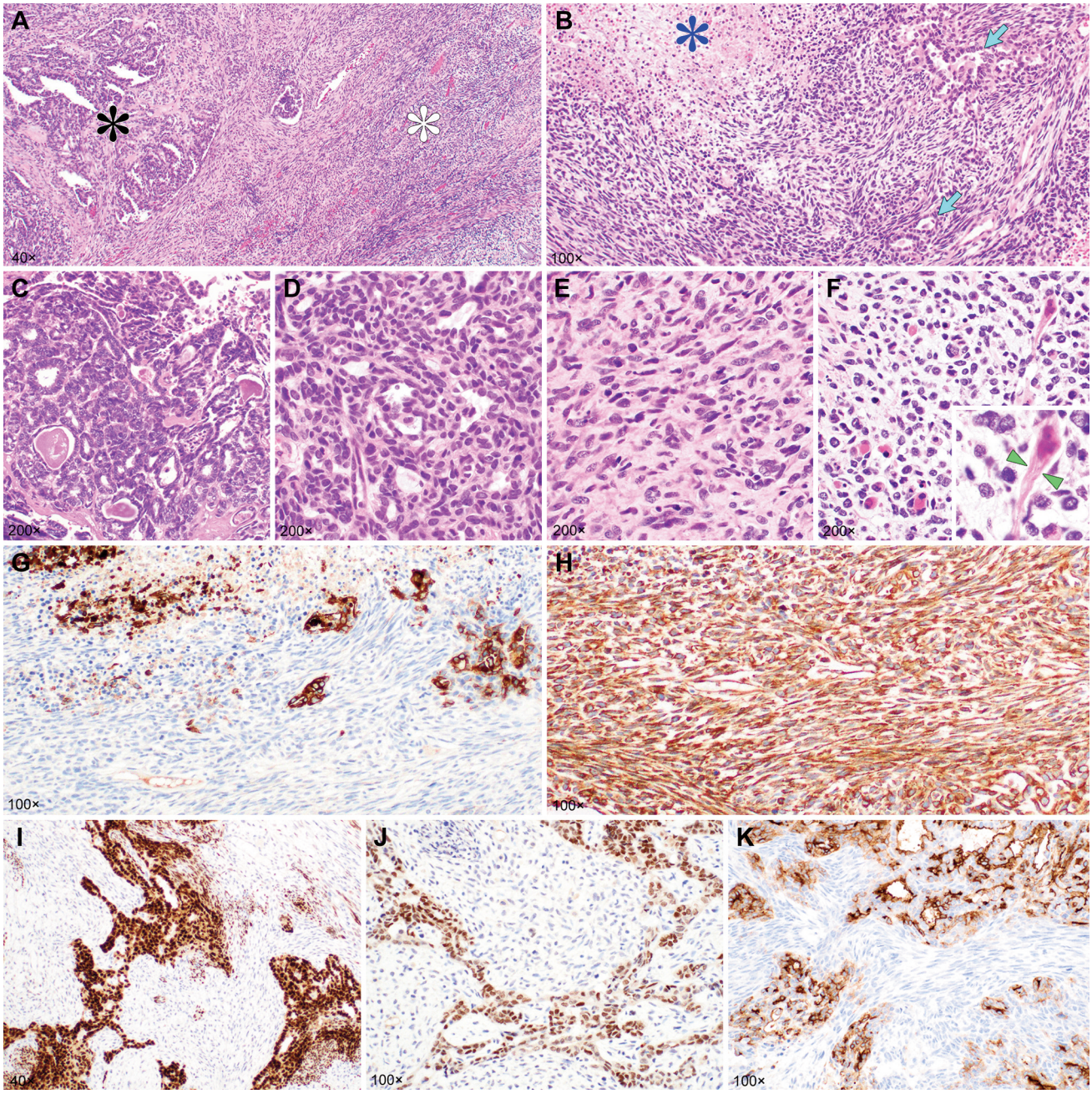


Figure 1. *Histological features of uterine mesonephric-like carcinosarcoma: case 10. (A) The presence of both epithelial (black asterisk) and mesenchymal (white asterisk) components is compatible with carcinosarcoma (CS). (B) In some areas, the epithelial component (skyblue arrows) is intermingled with the mesenchymal component. Foci of tumor cell necrosis (blue asterisk) are occasionally identified. (C and D) The mesonephric-like adenocarcinoma (MLA) component is the only epithelial component. (E) The mesenchymal component consists predominantly of high-grade non-specific sarcoma (HGNS). (F) Approximately 5% of the mesenchymal component was rhabdomyosarcoma (RMS) showing rhabdomyoblasts possessing eosinophilic cytoplasm with cross-striations (green arrowheads; inset). (G-K) Immunostaining reveals uniform and intense immunoreactivities for (G) cytokeratin 7 in MLA and (H) vimentin in HGNS, respectively. MLA also expresses (I) paired box 8, (J) transcription termination factor 1, and (K) cluster of differentiation 10 (luminal pattern). Original magnification is indicated in the right lower corner of each image.*

MLCS and MLA experienced recurrence within the first three years following treatment. As shown in Table IV, MLCS and MLA showed significantly shorter DFS than CECS ($p$=0.006 and 0.004, respectively). The median DFS of patients (16.9 months) was significantly longer than MLCS (10.1 months) and MLA (7.7 months) groups. The

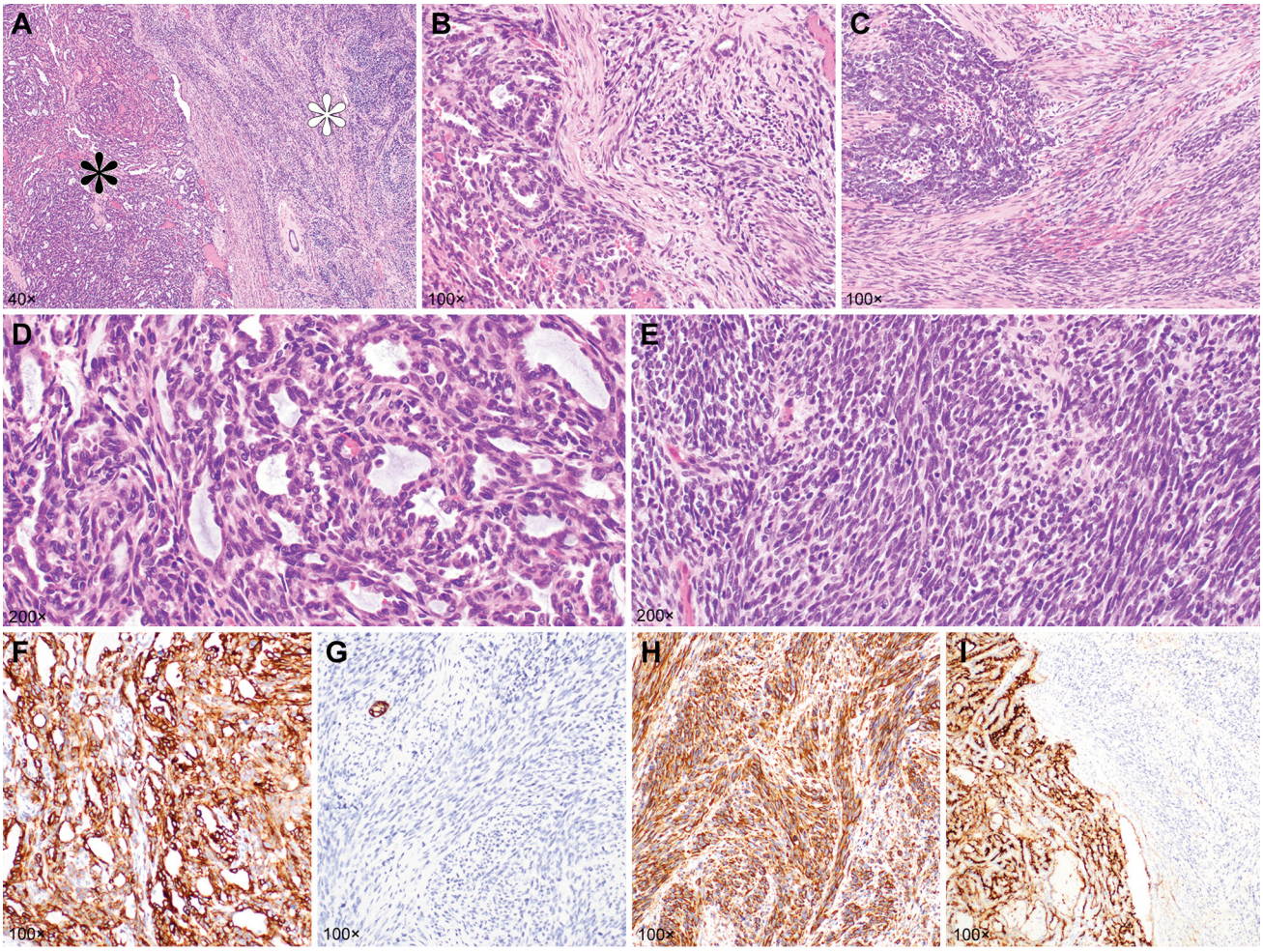


Figure 2. *Histological features of uterine mesonephric-like carcinosarcoma (MLCS): case 9. (A) Black and white asterisks indicate the epithelial and mesenchymal components of MLCS, respectively. (B and C) In these foci, areas of mesonephric-like adenocarcinoma (MLA; left half) are relatively well demarcated from those of high-grade non-specific sarcoma (HGNS; right half). (D) MLA exhibits a characteristic small tubular pattern. Compactly aggregated tubules are lined by cuboidal epithelium, of which the nuclei are relatively small and hyperchromatic. (E) HGNS displays elongated tumor cells with ovoid or tapered, hyperchromatic nuclei and variable amounts of cytoplasm. (F-I) Immunohistochemically, (F) cytokeratin 7 is strongly expressed in MLA, (G) but not in HGNS. However, (H) HGNS reacts uniformly with vimentin with strong staining intensity. (I) MLA shows strong cluster of differentiation 10 immunoreactivity in their luminal surfaces. Original magnification is indicated in the right lower corner of each image.*

DFS of patients with MLA was shorter than that of patients with MLCS, but the difference was not significant ($p$=0.875).

*Next-generation sequencing and p53 immunostaining*. Tissue samples for targeted sequencing were available for eight of the 12 MLCS cases. As shown in Figure 6A, five of the eight tumors (62.5%) harbored activating missense *KRAS* mutations, including c.35G>T (p.G12V; 2/5), c.34G>T (p.G12C; 1/5), c.35G>A (p.G12D; 1/5), and c.37G>T (p.G13C; 1/5). Pathogenic tumor protein 53 (*TP53*) mutations were found in four tumors (50%). Particularly, two missense mutations (c.742C>T, p.R248W; c.313G>C, p.G105R), one nonsense mutation (c.1027G>T, p.E343*), and one frameshift insertion (c.210_211insG, p.P71fs*78) were detected in *TP53*. Immunostaining for p53 (Figure 6B-G) revealed that two concordant cases demonstrated p53 overexpression (in a case harboring a missense mutation) and complete absence of p53 immunoreactivity (in a case harboring a frameshift insertion). In one MLCS case with a frameshift insertion (c.210_211insG), p53 protein expression was completely negative in both the epithelial and mesenchymal components. In contrast, in other MLCS samples harboring missense *TP53* mutations (c.742C>T), the mesenchymal component only displayed p53 overexpression (diffuse and strong nuclear immunoreactivity), while the epithelial component had a wild-type p53 immunostaining pattern (patchy positivity with

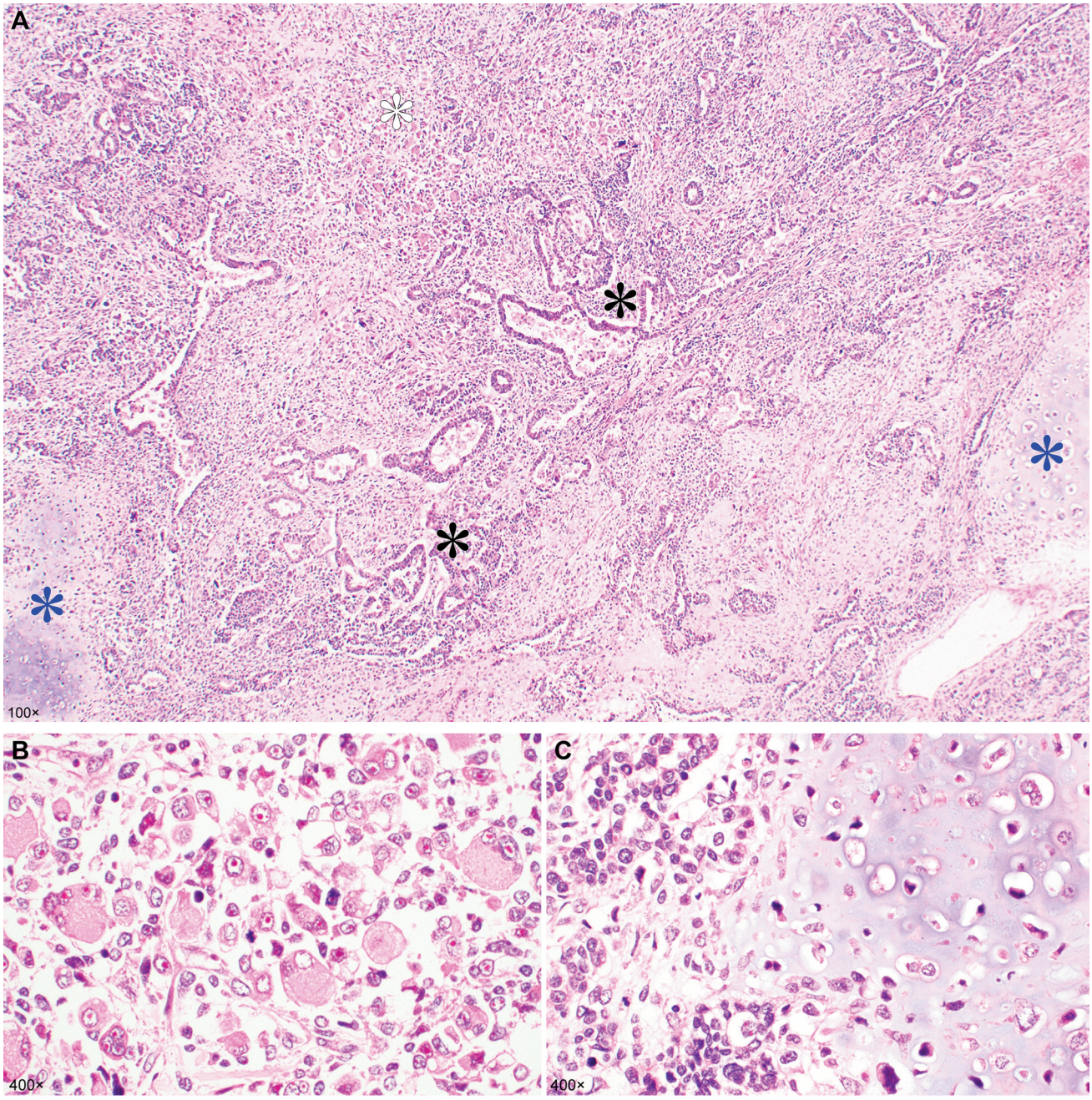


Figure 3. *Histological features of uterine mesonephric-like carcinosarcoma (MLCS): uncommon mesenchymal components in case 5. (A) Rhabdomyosarcoma (RMS) and chondrosarcoma (CHS), heterologous mesenchymal components, are observed in two and one cases, respectively. In case 5, a low-power magnification reveals an admixture of microscopic areas showing mesonephric-like adenocarcinoma (black asterisks), RMS (white asterisk), and CHS (blue asterisks). (B) A high-power magnification of RMS reveals discohesive, large tumor cells showing marked nuclear pleomorphism and eosinophilic cytoplasm. Conspicuous, cherry-red nucleoli are easily identifiable. (C) CHS demonstrates enlarged, pleomorphic chondrocytes with occasional plump multinucleated lacunae. Original magnification is indicated in the right lower corner of each image.*

weak-to-moderate staining intensity). The remaining two tumors harboring pathogenic *TP53* mutations (c.313G>C and c.1027G>T) exhibited a wild-type p53 expression pattern, which was discordant with *the TP53* mutational status. There was only one case in which concurrent *KRAS* and *TP53* mutations were detected. This case also harbored truncating nonsense G protein subunit alpha q (*GNAQ*) mutation (c.303C>A, p.Y101*) and missense phosphatase and tensin

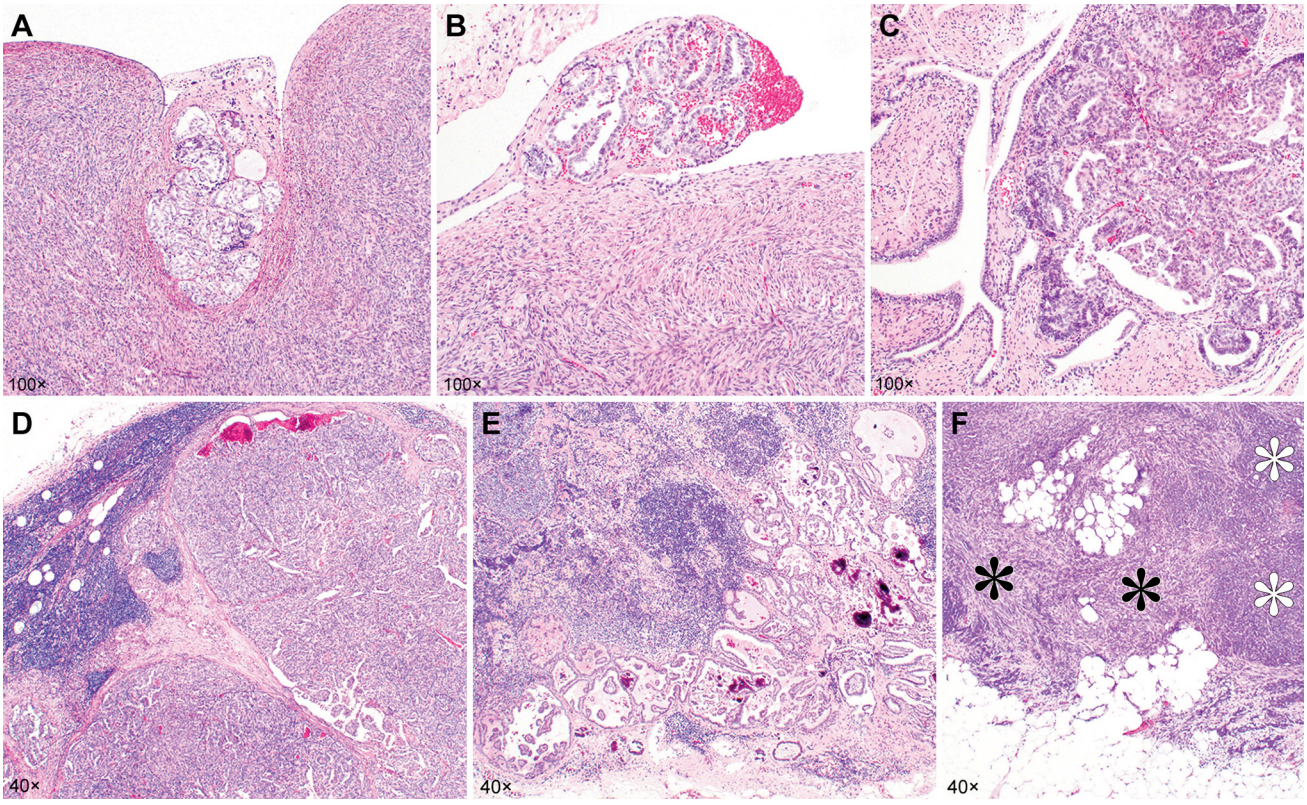


Figure 4. *Histological features of metastatic mesonephric-like carcinosarcoma (MLCS). The metastatic MLCS tissues almost invariably consist of mesonephric-like adenocarcinoma (MLA). (A and B) The ovarian surface shows microscopic foci of metastatic MLA. (C) The tubal mucosa is involved by the metastatic MLA. (D and E) The nodal metastatic lesions consist exclusively of MLA. (F) The omental metastatic tumor of case 8 contains both MLA (white asterisks) and high-grade non-specific sarcoma (black asterisks). Original magnification is indicated in the right lower corner of each image.*

homolog (*PTEN*) mutation (c.804C>A, p.D268E). In another case harboring multiple pathogenic mutations, *KRAS* mutations were accompanied by mutations in ataxia-telangiectasia mutated (*ATM*; c.1262C>A, p.S421*), v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*; c.1801A>G, p.K601E) and *GNAQ* (c.303C>A, p.Y101*) genes. Three patients with *TP53* mutations did not harbor *KRAS* mutations.

## Discussion

The histological type of the epithelial component was originally misdiagnosed as serous carcinoma and endometrioid carcinoma in two cases (16.7%) because of the diagnostic difficulty of MLA, as described in several previous studies (7, 8, 11, 12, 29). As MLA has a more aggressive behavior than more frequent histological types of endometrial carcinoma, identifying or suspecting MLA is important in the diagnosis of uterine malignancies. Uterine MLA displays a wide range of morphological diversities and can contain spindle cells arranged in solid, fascicular and storiform growth patterns. If a considerable portion of MLA tissue demonstrates a spindle cell component, it is difficult to distinguish MLCS from MLA with prominent spindle cells. MLCS should be diagnosed when spindle cells exhibit high-grade cytological atypia, including obvious nuclear enlargement, pleomorphism and brisk mitotic activity (14, 27). Although relatively rare, coexistence with heterologous elements strongly supports the diagnosis of MLCS. If the areas showing spindle/solid growth patterns exhibit nuclear features similar to those of the adjacent tumor cells with other architectural patterns of MLA, the diagnosis of MLA with spindle cell component is favored (12). Uterine MLA typically lacks severe nuclear pleomorphism except in rare cases.

In this study, more than two-third of the patients with MLCS initially presented with stage III-IV disease. Moreover, all patients experienced disease metastasis within the first three months despite adjuvant treatment, and half of the patients died during the follow-up period. Our observations of aggressive clinical behavior are in line with previous reports on MLCS (16-17, 26-33). Our literature search revealed a poor prognosis in 22 previously reported uterine MLCS cases (Table V) (20-30). Among the 14

Table III. *Differences in clinical features among mesonephric-like carcinosarcoma (MLCS), conventional endometrial carcinosarcoma (CECS), and mesonephric-like adenocarcinoma (MLA).*

| Parameter | | Number of cases (%) | | | *p*-Value | | |
|---|---|---|---|---|---|---|---|
| | | MLCS | CECS | MLA | MLCS *vs.* CECS | MLA *vs.* CECS | MLCS *vs.* MLA |
| Age (years) | ≥60 | 8 (66.7) | 11 (42.3) | 18 (51.4) | 0.295[a] | 0.481[b] | 0.505[a] |
| | <60 | 4 (33.3) | 15 (57.7) | 17 (48.6) | | | |
| Initial stage | I | 4 (33.3) | 10 (38.5) | 7 (20.0) | 0.720[c] | 0.008[c,*] | 0.067[c] |
| | II | 3 (25.0) | 6 (23.1) | 1 (2.9) | | | |
| | III | 2 (16.7) | 7 (26.9) | 15 (42.9) | | | |
| | IV | 3 (25.0) | 3 (11.5) | 12 (34.3) | | | |
| Post-treatment recurrence | Yes | 10 (100.0) | 13 (50.0) | 28 (80.0) | 0.006[a,*] | 0.014[b,*] | 0.320[a] |
| | No | 0 (0.0) | 13 (50.0) | 7 (20.0) | | | |
| Lung metastasis | Yes | 9 (75.0) | 7 (26.9) | 21 (60.0) | 0.012[a,*] | 0.010[b,*] | 0.492[a] |
| | No | 3 (25.0) | 19 (73.1) | 14 (40.0) | | | |

Calculated by [a]Fisher exact test, [b]Pearson chi-square test, or [c]linear-by-linear association test. *Statistically significant.

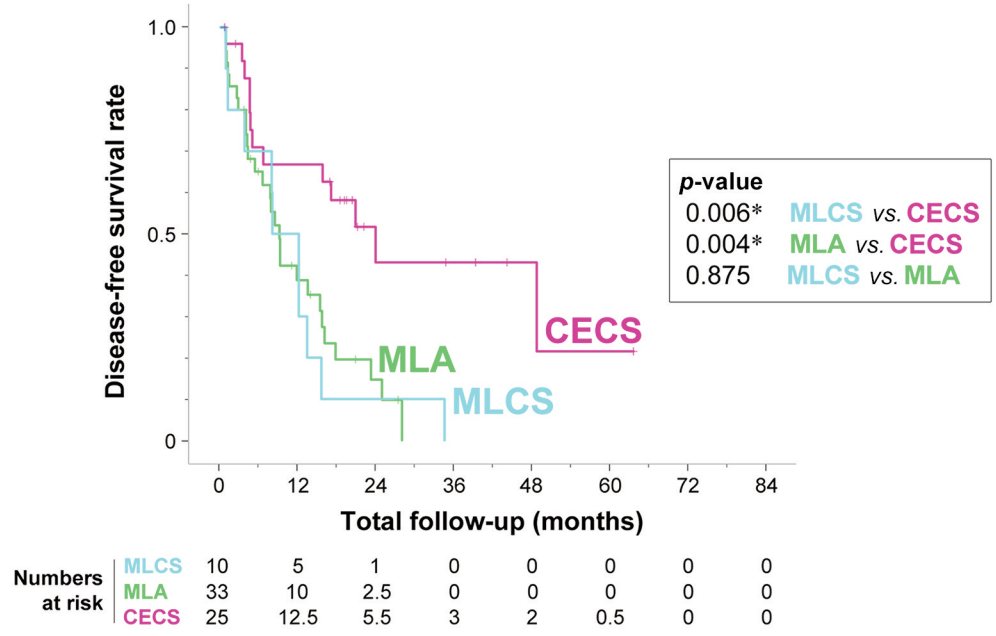


Figure 5. *Kaplan-Meier plot for disease-free survival of patients with uterine mesonephric-like adenocarcinoma (MLA), mesonephric-like carcinosarcoma (MLCS), and conventional endometrial carcinosarcoma (CECS). MLCS and MLA have significantly lower disease-free survival rates than CECS.*

patients whose prognostic data were available, four (28.6%) died of the disease. The median and mean overall survival period was 11.5 and 22.4 months, respectively.

In the initial and recurrent metastatic tumors of MLCS, the epithelial component almost invariably consisted of MLA, except for one case harboring 40% of MLA and 60% of HGNS in peritoneal metastases. This finding raises the suspicion that the MLA component may contribute to the migratory properties of MLCS. Furthermore, MLCS and MLA showed significantly higher frequencies of distant metastases and shorter DFS than CECS, whereas MLCS and MLA showed relatively similar clinicopathological features and survival outcomes. Collectively, the MLA component may determine the biological aggressiveness of uterine MLCS and ultimately lead to a poor prognosis, comparable to that of MLA. Previous studies have also documented that the epithelial component, and not the mesenchymal one, determines the biological behavior of CECS; this is based on

Table IV. *Differences in disease-free survival (DFS) among mesonephric-like carcinosarcoma (MLCS), conventional endometrial carcinosarcoma (CECS), and mesonephric-like adenocarcinoma (MLA).*

| Parameter | | Number of cases (%) | | | *p*-Value | | |
|---|---|---|---|---|---|---|---|
| | | MLCS | CECS | MLA | MLCS *vs.* CECS | MLA *vs.* CECS | MLCS *vs.* MLA |
| DFS | Median (months) | 10.1 | 16.9 | 7.7 | 0.006[a,*] | 0.004[a,*] | 0.875[a] |
| | Mean (months) | 10.9 | 15.4 | 9.8 | | | |
| | 5-year survival rate (%) | 0.0 | 21.5 | 0.0 | | | |

[a]Calculated by log-rank test. *Statistically significant.

Table V. *Patient outcomes of previously reported uterine mesonephric-like carcinosarcoma cases.*

| No | Year published | Authors | Number of cases | Outcome | Survival status | Overall survival |
|---|---|---|---|---|---|---|
| 1 | 1988 | Bloch *et al.* (20) | 1 | NED | Alive | 23 months |
| 2 | 1995 | Yamamoto *et al.* (21) | 1 | DOD | Dead | 8 months |
| 3 | 1995 | Clement *et al.* (22) | 4 | AWD | Alive | 11 months |
| | | | | NED | Alive | 2.3 years |
| | | | | NED | Alive | 3 years |
| | | | | DOD | Dead | 6.2 years |
| 4 | 2004 | Bague *et al.* (23) | 5 | NED | Alive | 45 months |
| | | | | NA | NA | NA |
| | | | | DOD | Dead | 7 months |
| | | | | NED | Alive | 13 months |
| | | | | AWD | Alive | 36 months |
| 5 | 2013 | Meguro *et al.* (24) | 1 | NED | Alive | 10 months |
| 6 | 2014 | Roma (25) | 2 | NA | NA | NA |
| | | | | NA | NA | NA |
| 7 | 2014 | Tseng *et al.* (26) | 1 | NED | Alive | 4 months |
| 8 | 2018 | Pors *et al.* (27) | 3 | NA | NA | NA |
| | | | | NA | NA | NA |
| | | | | NA | NA | NA |
| 9 | 2019 | Ribeiro *et al.* (28) | 1 | DOD | Dead | 7 months |
| 10 | 2021 | da Silva *et al.* (29) | 2 | NA | NA | NA |
| | | | | NA | NA | NA |
| 11 | 2021 | Marani *et al.* (30) | 1 | NED | Alive | 1 year |

AWD, Alive with disease; DOD, dead of disease; NA, not applicable; NED, no evidence of disease.

the findings that the epithelial component causes vascular invasion, recurrence and metastasis, leading to poor prognosis (40, 41).

Targeted sequencing was performed using uterine MLCS tissues. *KRAS* mutations, which are found in most MLAs (7, 11, 12, 18, 29, 42-44), were found in more than half of the examined cases. *TP53* mutations, which are extremely rare in MLAs (45), were detected in 50% of the cases. The unexpectedly high frequency of *TP53* mutations in uterine MLCS was different from that of previously reported MLA cases. In our recent study (45), we thoroughly reviewed previous literature regarding malignant mesonephric lesions and documented that three cervicovaginal mesonephric adenocarcinomas (3/67, 4.5%) and one utero-ovarian MLA (1/112, 0.9%) harbored *TP53* mutations. We found that four (2.2%) of the 179 malignant mesonephric lesions of the female genital tract harbored *TP53* mutations, suggesting that *TP53* mutations are a very uncommon phenomenon in mesonephric lesions. To the best of our knowledge, this is the first study to report that uterine MLCS harbors *TP53* mutations more frequently than MLA. This result is consistent with previous data demonstrating that most CECS cases harbor *TP53* mutations (46). Based on the notion that p53 plays an important role in regulating epithelial-mesenchymal transition (47), our findings raise the possibility that p53-mediated epithelial-mesenchymal transition plays a role in the development of MLCS. It is now accepted that the mesenchymal component is derived from the epithelial component as a result of epithelial-

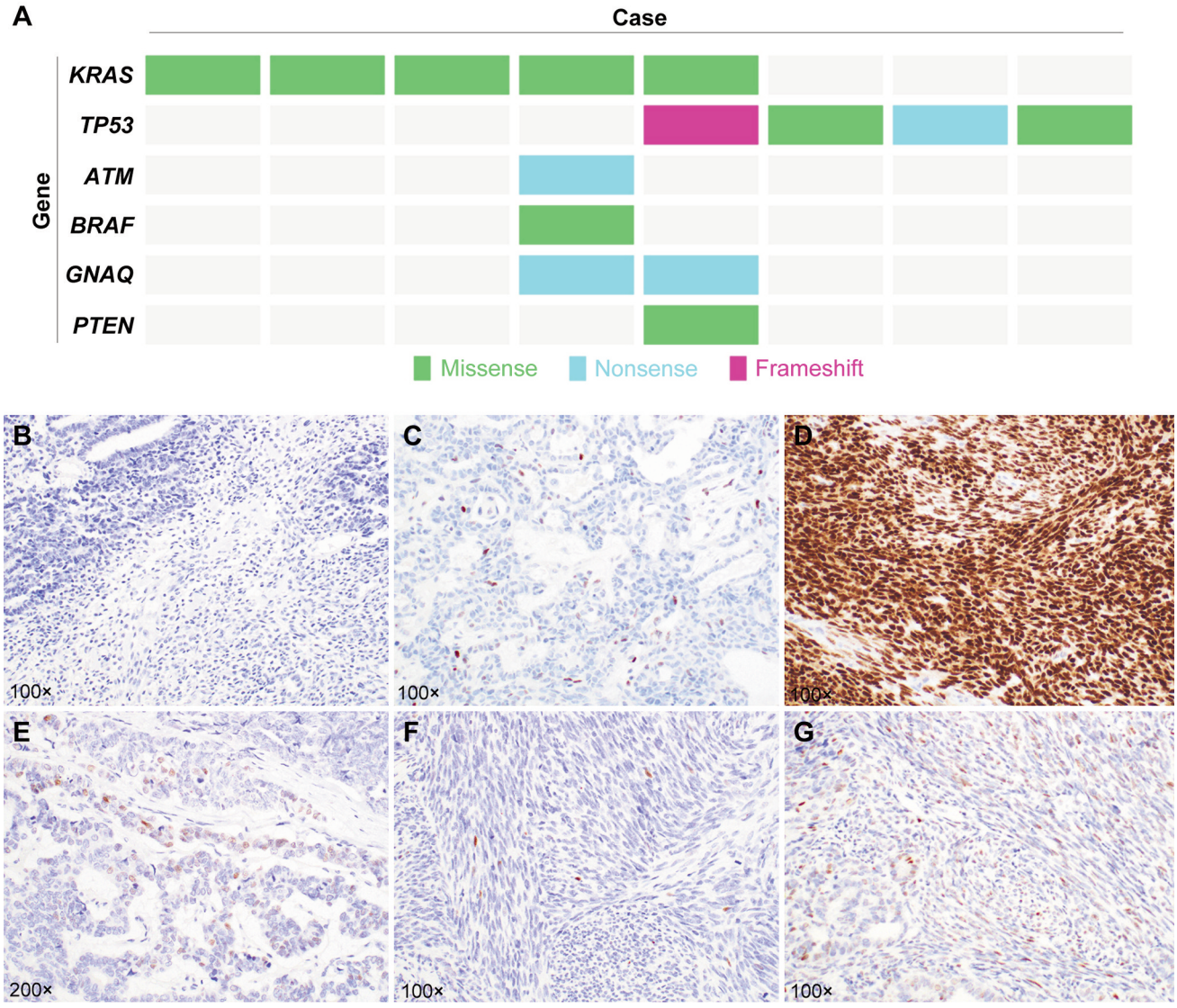


Figure 6. *Results of next-generation sequencing and p53 immunostaining in eight cases of uterine mesonephric-like carcinosarcoma (MLCS). (A) Pathogenic mutations are detected in the following genes: Kirsten rat sarcoma viral oncogene homolog (KRAS), tumor protein 53 (TP53), ataxia-telangiectasia mutated (ATM), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), G protein subunit alpha q (GNAQ), and phosphatase and tensin homolog (PTEN). Four cases of MLCS harbor TP53 mutations. (B-G) Immunohistochemically, (B) in one case with a frameshift insertion, p53 protein expression is completely absent in both the epithelial and mesenchymal components. (C and D) In contrast, in other case harboring missense TP53 mutations, (C) the epithelial component had a wild-type p53 immunostaining pattern, (D) while the mesenchymal component only displays p53 overexpression. (E and F) One of the remaining two tumors harboring pathogenic TP53 mutations exhibits a wild-type p53 expression pattern in both the (E) epithelial and (F) mesenchymal components. (G) The other TP53-mutant MLCS shows a discordant wild-type p53 expression pattern.*

mesenchymal transition or trans-differentiation (16), based on the finding that the two components of CECS share the same *TP53* mutation. However, the mutational profiles were not analyzed by separating epithelial and mesenchymal components. We could not determine whether the epithelial, mesenchymal, or both components harbored *TP53* mutations. We performed p53 immunostaining and observed aberrant p53 expression in either the mesenchymal component only in one case or both components in the other case. The two tumors even showed discrepant results for *TP53* mutational status and p53 protein expression. Furthermore, since there was only one case of uterine MLCS in which *KRAS* and *TP53* were found simultaneously, it is difficult to draw conclusions regarding the pathogenesis of MLCS.

This study had some limitations. First, the number of patients was relatively small. However, since malignant mesenchymal lesions account for only approximately 1% of all gynecological tumors, our results from the 12 and 26 cases of uterine MLCS and MLA diagnosed in the two institutions seem meaningful enough to explain their clinicopathological and prognostic significance. Second, the number of CECS compared to that of MLCS was also small because we extracted a subset of CECS patients whose postoperative follow-up period was similar to that of MLCS patients. In fact, we acknowledge that the incidence of uterine MLCS relative to CECS encountered in daily practice will be much lower than that in this study. Third, we did not analyze the comprehensive immunophenotype of each of the epithelial and mesenchymal components of uterine MLCS. Similarly, comprehensive genomic profiling of each component has not been performed. Additional immunostaining and molecular testing are required to confirm the monoclonality of both components and clarify the pathogenesis of MLCS. Finally, even though we demonstrated that DFS was significantly different among groups, we were unable to examine whether there was any difference in overall survival because the survival information was insufficient due to a short follow-up time. Further investigations on patient outcomes are warranted in a larger cohort of uterine MLCS patients with a longer observation period.

## Conclusion

In conclusion, uterine MLCS is a morphologically biphasic malignancy with aggressive biological behavior. In all our MLCS cases, the epithelial component consisted exclusively of MLA. Metastatic and recurrent tumors also predominantly or exclusively consisted of MLA in the majority of MLCS cases. We found that both MLCS and MLA presented with more advanced-stage disease than CECS and exhibited post-treatment recurrences and lung metastases more frequently. Survival analyses revealed that MLCS and MLA had significantly lower DFS rates than CECS. Our data suggest that aggressive behavior might be associated with the epithelial component, *i.e.*, MLA. Regarding the worse prognosis of MLCS compared to CECS, the presence of the MLA component should be recognized in the diagnosis of CS, and MLCS should be distinguished from CECS. To improve the prognosis, patients with uterine MLCS may require more aggressive treatment than those with CECS. Further studies are warranted to provide direct molecular evidence of the monoclonal origin of uterine MLCS.

## Conflicts of Interest

The Authors have no conflicts of interest to declare.

## Authors' Contributions

All Authors made substantial contributions to the conceptualization and design of the study; the acquisition, analysis, interpretation, and validation of the data; drafting of the article; critical revision of the article for important intellectual content; and final approval of the version to be published.

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