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RESEARCH ARTICLE

Yan et al: Endometrial MLA: Features and outcomes

Endometrial mesonephric-like adenocarcinoma: Clinicopathologic features, treatment, and outcomes

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ABSTRACT

Endometrial mesonephric-like adenocarcinoma (MLA) is a rare subtype of uterine corpus endometrial carcinoma (UCEC) first described in 2016. The clinicopathological features, treatment options, and prognosis of endometrial MLA remain poorly understood. In this study, we retrospectively analyzed the clinicopathological characteristics, molecular features, treatment regimens, and outcomes of 11 patients diagnosed with endometrial MLA. The most prevalent symptom observed was postmenopausal bleeding. Notably, 78% (7 out of 9) of patients were diagnosed at advanced FIGO stages (II-IV), with four cases presenting with distant metastasis upon initial examination. Multivisceral metastases were identified in three cases, with lung metastases being the most common, occurring in 45% of patients. The median progression-free survival (PFS) was 16 months (95% confidence intervals: 6-26). All tumors tested negative for progesterone receptors (PR), while 91% of patients (10 out of 11) were negative for estrogen receptors (ER). Most patients exhibited positive immunohistochemical staining for "mesonephric-like" markers, including GATA-binding protein 3 (GATA-3), thyroid transcription factor-1 (TTF-1), and CD10. Furthermore, 91% of patients showed a wild-type p53 immunostaining pattern. Among the 11 patients, five underwent *KRAS* mutation testing, revealing *KRAS* mutations in all tested individuals (p.G12D in 2/5, p.G12A in 1/5, p.G12V in 1/5, and p.G13D in 1/5). These findings indicate that 78% of endometrial MLA patients were diagnosed at an advanced stage and suggest that this subtype may exhibit more aggressive behavior compared to endometrial endometrioid carcinoma. The consistent presence of *KRAS* mutations in patients who underwent testing highlights the potential role of *KRAS* in the initiation and progression of endometrial MLA, positioning it as a promising therapeutic target.

Keywords: Uterine cancer, mesonephric-like adenocarcinoma, clinicopathological features, prognosis, retrospective analysis, KRAS mutation.

INTRODUCTION

Uterine cancer is one of the most common gynecological malignancies globally with its incidence increasing annually(1,2). According to the cancer statistics in 2023, uterine corpus cancer is the 4th leading cancer in women malignancies with nearly 66,200 cases newly diagnosed and 13,030 deaths in the United States(1). In China, uterine cancer is the 8th most commonly diagnosed malignancy among women(3). Approximately 90% of uterine cancers are endometrial carcinomas (ECs)(4). In recent years, the incidence of ECs has been annually increasing with early onset age. Various factors have been identified as risk factors for ECs, including obesity, nulliparity, high insulin levels, and tamoxifen use(5). The most common subtypes of ECs are endometrioid and serous carcinomas, accounting for 80-85% and 5-10% of newly diagnosed cases, respectively(6). A recent study identified novel/rare histopathological subtypes. McFarland M *et al* (7)in 2016 described 7 cases of uterine cancers and 5 cases of ovarian cancers which were diagnosed as mesonephric-like adenocarcinoma (MLA). Subsequently, an increasing number of endometrial MLA cases have been reported. These patients tend to correlate with poor prognosis. However, since the pathogenesis of MLA has not been fully elucidated, there is a need to allocate resources to the clinical, pathological, and molecular features of MLA in order to guide therapy and improve prognosis.

In 2020, the World Health Organization (WHO) classified MLA as a novel pathological classification of female genital tumors(8). So far, MLA remains an exceedingly rare and diagnostically challenging subtype of ECs. Previous studies have shown that endometrial MLA accounts for approximately 1% of ECs(9). Despite its low incidence, MLA has gained global attention as a distinct entity within the spectrum of endometrial malignancies. It typically affects postmenopausal women. Endometrial MLA often manifests as abnormal uterine bleeding, pelvic pain, or an incidental finding on imaging studies(10). Endometrial MLA is malignant with an aggressive growth pattern, and poor prognosis(7). Pors *et al.* diagnosed patients with an advanced-stage endometrial MLA with a worse prognosis, including shorter

progression-free survival (PFS) and overall survival (OS)(10,11). Platinum-and taxane-based chemotherapy is the standard first-line chemotherapeutic for ECs(12). However, the prognosis of advanced and recurrence ECs has been improved with the advent of targeted therapy and immunotherapy(13,14). At present, surgery remains the first choice treatment for early-stage endometrial MLA. However, due to the rarity of the endometrial MLA, there is still a lack of standard and effective therapeutic options for patients with advanced stage and recurrence. Besides, the prognosis of endometrial MLA at advanced stage is still poor.

The precise diagnosis of MLA relies on a combination of clinical, radiological, and histopathological assessments, such as immunohistochemical analysis to differentiate it from other endometrial malignancies. Endometrial MLA histologically exhibits various architectural patterns and cytological features including tubular, solid, ductal, papillary, retiform, and sex cord-like(15). Immunohistochemical staining for MLA-associated markers often shows GATA binding protein 3 (GATA3) positive, transcription termination factor 1 (TTF1) positive, calretintin positive, and cluster of differentiation 10 (CD10) positive(10). Notably, estrogen receptor (ER) and progesterone receptor (PR) are often negative. Molecular studies have detected mutations in KRAS, NRAS, PIK3CA, and ARIDIA in MLA tissues(10,16). However, the clinicopathological features and pathogenesis remain unclear. Considering the limited information on MLA, there is a need to elucidate its clinical behavior, optimal management strategies, and prognostic factors.

This work retrospectively investigated clinicopathological features and prognosis of 11 endometrial MLA patients. By better understanding the clinical features, histopathological characteristics, and treatment outcomes of MLA, we hope to improve diagnostic accuracy, customized treatment intervention, and prognostic prediction for patients with endometrial MLA. Ultimately, this study aims to provide valuable insights that may guide future research efforts and clinical decision-making for patients with MLA.

MATERIALS AND METHODS

Ethical approval

Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2023-KY-0563-001). All patients and/or their families had signed informed consent.

Study design

This is a single-center retrospective study by the Department of Obstetrics and Gynecology, The First Affiliated Hospital of Zhengzhou University. We enrolled11 patients diagnosed with MLA (confirmed by preoperative biopsy or postoperative pathological examination). The hematoxylin-eosin (HE) and immunohistochemical (IHC) stained slides were evaluated by two experienced pathologists in gynecological pathology at the Department of Pathology, The First Affiliated Hospital of Zhengzhou University. We obtained and analyzed all the clinicopathological data.

Clinicopathological data collection

Clinicopathological data were collected and recorded by corresponding gynecological oncologists. These data included age at diagnosis, primary symptoms, tumor biomarkers, pathologic findings, tumor metastasis, type of surgery, adjuvant treatment, FIGO stage, presence or absence of recurrences, recurrence site, tumor progression, and survival. PFS was computed from the date of diagnosis to that of recurrence or death (if no recurrence occurred) and follow-up time was defined as the date of last-known follow-up or death.

Immunohistochemical staining evaluation

All tissue samples were fixed in paraformaldehyde and embedded in paraffin. Then paraffin-embedded blocks were sectioned into 4 μm slices. IHC staining processes were performed using an automated slide staining system (BenchMark Ultra, Roche) and ultraView universal DAB detection kit. The IHC staining results were evaluated

by two experienced pathologists in gynecological pathology. Table 1 presents the antibody information.

KRAS mutation test

Slices of 4 μm thickness were used to isolate DNA using a nucleic acid extraction kit (FFPE DNA, Omega Bio-Tek, USA). KRAS mutation was tested using the Human KRAS Gene Mutation Detection Kit (Amoy Diagnostics Co., Ltd. Xiamen, China). Protocols were executed following the kit instructions(17,18). The quantitative real-time PCR was performed based on protocols from previous studies(19,20).

Statistical analysis

Clinicopathological data were summarized using descriptive statistics. Non-normally distributed variables were expressed as medians, and normally distributed continuous variables were expressed as means ± standard deviation (SD). All statistical analysis were performed using the Graphad Prism 10.1 software. Survival analyses were performed using SPSS version 26.0 and GraphPad Prism version 10.1 Kaplan-Meier curves were generated to estimate PFS using GraphPad Prism version 10.1, and two-sided 95% confidence intervals were calculated.

RESULTS

This study enrolled 11 patients. The mean age of all patients was 62.18±9.24 years (range, 48-74). Over half of the patients were overweight (n=5, 25<BMI≤30) or obese (n=1, 30<BMI≤40) . All cases (excluding case 3 and case 6) were classified according to FIGO stages. 78% (7/9) of patients were diagnosed at advanced FIGO stage (stage II-IV). Case 3 could not be staged due to a lack of lymph node dissection, and lymph node metastasis could not be determined. Case 6 was diagnosed with MLA by biopsy and declined any treatment, hence we could not stage. Seven cases were under pelvic lymph node dissection, 6 of whom were confirmed to have lymph node metastasis by postoperative pathology. At the initial hospital visit, 4 cases had distant metastasis. Table 2 and Table 3 show the results.

Postmenopausal bleeding, lower abdominal pain, pelvic mass, cough, productive cough, and blood-tinged sputum were the most common clinical manifestations. Of these, postmenopausal bleeding (55%, 6/11) was the most common clinical manifestation. Case 9 presented cough, productive cough, and blood-tinged sputum due to lung metastasis. Of cases who received lymph node dissection, 86% (6/7) of cases presented lymph node metastasis. One case (case 6) declined any treatment. One case (case 9) received first treatment at another hospital. Therefore, the presence of lymph node metastasis was unclear due to the missing information. Total 6 cases (cases 3, 4, 5, 7, 8, and 9) presented distant recurrence during the follow-up, of which two cases (case 4 and case 9) presented distant recurrence at their first visit to our hospital. Notably, case 9 presenting lung recurrence received basal segment of the left lower lobectomy and mediastinal lymph node dissection for 5 years after initial surgery. Multivisceral metastases were identified in 3 cases (Case 3, 4, and 8). Lung metastases (45%,5/11) was the most common distant metastases. The median PFS was 16 months (95% confidence intervals: 6-26). All the 11 patients are alive and well at present. These results were showed in Table 3 and Figure 1-3. Kaplan–Meier curves were showed in Figure 6.

The plasma samples of all cases were obtained for tumor biomarker analysis. Elevated cancer antigen 125 (CA125) and cancer antigen 199 (CA199) were detected in 55% and 36% (4/11) of cases, respectively. Notably, vascular endothelial growth factor (VEGF) was elevated in 67% (4/6) of cases. Further, 30% (3/10) and 27% (3/11) of cases presented elevated human epididymis protein 4 (HE4) and carcinoembryonic antigen (CEA), respectively. All these results are shown in Table 4.

All tumors were negative for progesterone receptor (PR). The vast majority of cases (10/11) were negative for estrogen receptor (ER). Most cases were positive for “mesonephric-like” markers GATA-3 (100%, 11/11), TTF-1 (91%, 10/11), and CD 10 (82%, 9/11). All patients were positive for “Müllerian marker” PAX-8; 90% (9/10) of patients exhibited positive for P16; 91% (10/11) of patients showed wild-type P53 immunostaining pattern. P53 mutation was detected in only one case (case 3). Figure

4 shows the pathology features from case 5. Figure 5 shows ER weakly positive and PR negative from case 6. Among the 11 cases, 5 cases underwent KRAS mutation test where KRAS mutation was detected in all of them (p.G12D, 2/5; p.G12A, 1/5; p.G12V, 1/5; p.G13D, 1/5). These results are shown in Table 5.

DISCUSSION

Endometrial MLA is one of the rare gynecological malignancies first described in 2016 by McFarland M *et al*(7). The World Health Organization (WHO) approved MLA as a novel pathological classification of female genital tumors(8). Due to its rarity, clinical behavior, pathological features, treatment options, and prognosis of endometrial MLA remain poorly understood. This single-center retrospective study examined the clinicopathological features and prognosis of 11 endometrial MLA patients to further understand the molecular mechanisms of endometrial MLA.

One previous study reported 7 cases of endometrial MLA in endometrial cancer; this was out of 237 consecutive endometrial carcinoma cases(21), representing an incidence of 3% (7/237); another retrospective study identified the incidence of 0.7% (4/570)(9). However, the precise incidence of endometrial MLA remains unknown. In this study, we collected 11 endometrial MLA cases with ages ranging from 48 years to 74 years. Although endometrial MLA can occur at any age, the majority of patients are still post-menopausal females(15,22). Most patients initially visited the hospital presenting with postmenopausal irregular vaginal bleeding(23). Our data showed that 55% (6/11) of cases comprised visits for postmenopausal bleeding. Previous studies also indicated that 67% (6/9) of patients had postmenopausal bleeding(23,24). Additionally, over half of cases were overweight (n=5) or obese (n=1). Results revealed that obesity might be the high-risk factors for endometrial MLA; however, this warrants validation by additional studies.

Furthermore, we diagnosed 78% (7/9) of patients at an advanced FIGO stage (stage II-IV). We could not establish stages for case 3 (without lymph node dissection) and

case 6 (diagnosed MLA by biopsy and declined any treatment). In case 8, preoperative imaging analysis demonstrated no lymph node or distant metastasis. Therefore, total hysterectomy and bilateral salpingo-oophorectomy were performed without pelvic lymph node dissection and para-aortic lymph node dissection. Multiple bone metastases were identified 2 months after surgery through positron emission tomography-computed tomography (PET-CT) (Figure 4). These findings indicate that endometrial MLA is highly malignant and prone to early metastasis. The median PFS was 16 months (95% confidence intervals: 6-26). All patients are alive and well at present. Pors et al. reported 58% (25/43) of patients with an advanced FIGO stage(10), with a median PFS of 21 months. Kim et al. reported 57% (4/7) of patients at an advanced FIGO stage with a median PFS of 8 months(16). Elsewhere, the prognosis of 23 endometrial MLA patients was analyzed and median PFS of 18.2 months, and 70.6 months were reported in endometrial endometrioid carcinoma(25). All these results indicated that endometrial MLA might be more aggressive than endometrioid carcinoma. Till date, there was still no well-documented evidence. Although age might be a high-risk factor for endometrial MLA, it was not significantly different for OS and PFS between stage I-II and stage III-IV(10). All these results indicate that endometrial MLA might present at an advanced stage, have a worse prognosis, and can recur. Owing the rarity and limited cases reported, outcomes of endometrial MLA is still unclear. It is still need further investigation and require more evidence-based medicine from the clinical experience.

Elevated CA125 and CA199 were observed occurred in 55% (6/11) and 36% (4/11) of cases, respectively. Therefore, CA125 and CA199 might influence early diagnosis in endometrial MLA. Previous studies also indicated that CA125， CA199, and ubiquitin-specific protease 31 (USP31) might be associated with prognosis(20,24,26). Notably, elevated VEGF was observed in 67% (4/6) of cases. Nevertheless, additional studies are important to investigate whether they can be applied as biomarkers for diagnosis and prognosis.

Case 9 was diagnosed with endometrial cancer 4 years earlier and underwent surgical treatment at another facility. As a result, the postoperative pathological findings revealed uterine endometrial endometrioid carcinoma. The patient developed lung recurrence a few months earlier and received surgical treatment. Pathology findings revealed that MLA originated in the female genital tract. In this case, we believed the initial pathological diagnosis might have been misdiagnosis. Due to lack the initial slides of the primary tumor, we can not reevaluated the pathological types of the primary tumor. The probability of emerging new pathological type 4 years after surgical treatment is very low. As endometrial MLA is a rare histologic subtype, and identified as a novel pathological classification in recent, misdiagnosis could occurred for insufficient understanding of this rare subtype. Based all of these, we consider that the initial pathological diagnosis might have been misdiagnosis.

According to previous studies, endometrial MLA displays varied architecture including ductal, tubular, papillary, retiform, solid, and sex cord-like, which might result in misdiagnosis(10,24,27,28). Table 5 summarizes the results of immunohistochemical staining. All the tested cases had “mesonephric-like” marker GATA-3 and “Müllerian marker” PAX-8 positive. “Mesonephric-like” markers TTF1 and CD10 were positive in 91% (10/11) and 82% (9/11) of patients, respectively. Furthermore, all the tested patients were PR-negative, and 91% of patients were ER-negative. Weakly ER-positive was found in case 6 (Figure 5). In line with previous literature, ER could be focal or partial positive in a small number of endometrial MLA patients. These findings indicate that ER-positive could not be the criterion for excluding MLA. Additionally, WT1 was negative in nearly all patients which is consistent with previous findings(20). Recent study indicated papillary and ductal patterns were the most often overlooked, and recommend a low threshold to perform GATA3, TTF1 and ER in this scenario(29). Some patients underwent testing for P53 mutation. Only 1 case (case 3) had a P53 mutation. Previous studies summarized 25 cases of endometrial MLA and 19 cases of ovarian MLA, and found a

wild-type P53 expression pattern in nearly all patients; besides, few patients had P53 mutation(20,30).

In addition, 5 patients underwent KRAS mutation test, and all 5 patients (100%) presented KRAS mutation p.G12D, 2/5; p.G12A, 1/5; p.G12V, 1/5; p.G13D, 1/5). Previous research revealed that 83% (5/6) of endometrial MLA patients had KRAS mutation(16). Besides, KRAS mutations were found in 82% (23/28) of ovarian MLA patients(20). Several larger series have reported that KRAS mutations occur in 76% to 89% of patients(5,10,25,31). These results indicate that KRAS mutations are prevalent in endometrial MLA and may play a key role in the onset and development of endometrial MLA.

Although most patients are diagnosed at an advanced stage, surgical resection remains the first choice for patients who meet the surgical requirements. Postoperative chemoradiotherapy helps in improving prognosis. The progress in molecular classification of EC has led to more precision treatment(32). At present, platinum and paclitaxel combination is the primary chemotherapeutic treatment for endometrial MLA. Common KRAS mutation in endometrial MLA indicates that targeted KRAS therapy might improve the prognosis. However, there is still no effective KRAS Targeted therapy due to “undruggable”. Scholars have proposed that the selective inhibition of downstream targets of KRAS may represent a promising therapeutic approach(33). Recent study showed that T-cellreceptor engineered T-cell therapy targeting mutant KRAS proteins may be another potential therapeutic option for patients with MLAs and there are ongoing trials in other KRAS-mutated solid tumors(34). However, more studies are necessary.

CONCLUSION

This work retrospectively investigated clinicopathological features and prognosis of 11 endometrial MLA patients and found that endometrial MLA might have a worse prognosis. All patients who underwent KRAS mutation test had KRAS mutation. This shows that KRAS might be a promising target. Our findings improve the

understanding of endometrial MLA. However, this research has compelling limitations, including a small sample size, and the retrospective and single-center design. Therefore, the applicability of the results is limited. Future research should therefore consider prospective studies with a large sample size and multi-center design.

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TABLES AND FIGURES WITH LEGENDS

Table 1. List of antibodies

Antibody	Manufacture	Cloning information	Cat No.
Anti-ER antibody	Roche, Germany (RTU)	SP1	790-4325
Anti-PR antibody	Roche, Germany (RTU)	1E2	790-4296
Anti-GATA3 antibody	Jie Hao, China (RTU)	L50-823	GM-0091
Anti-CD10 antibody	Zhongshan Goldenbridge, China (RTU)	polyclonal	ZM-0283
Anti-TTF1 antibody	Maixin Biotech, China (RTU)	MX011	MAX-0677
Anti-PAX8 antibody	Zhongshan Goldenbridge, China (RTU)	OTI6H8	ZM-0468
Anti-AE1/AE3 antibody	Maixin Biotech, China (RTU)	AE1/AE3	Kit-0009
Anti-Vimentin antibody	Zhongshan Goldenbridge, China (RTU)	UMAB159	ZM-0260
Anti-P53 antibody	Zhongshan Goldenbridge, China (RTU)	DO-7	ZM-0408
Anti-P16 antibody	Roche, Germany (RTU)	E6H4	705-4713
Anti-Ki-67 antibody	Gene Tech, China (RTU)	GM027	GT209407

Abbreviations: ER: Estrogen receptor; PR: Progesterone receptor; GATA3: GATA-binding protein 3; TTF-1: Thyroid transcription factor-1; PAX8: Paired box 8.

Table 2. Demographics and clinical charaterstics in patients with MLA

	Total (*n*=11, Mean ±SD, range)
Age (years)	11 (62.18±9.24, range, 48-74)
<60	4 (52.25±3.50, range, 48-56)
≥60	7 (67.86±5.73, range, 60-74)
BMI	
Underweight (<18.5)	0
Normal (18.5> , ≤ 25)	5
Overweight (25> , ≤30)	5
Obese (30> , ≤40)	1
Morbidly obese (≥40)	0
FIGO stage (at initial diagnosis)	
I	2
II	0
III	3
IV	4
Metastasis	
Lymph node metastasis	6

Distant metastasis	4
Survival	
Alive	11
Dead	0

Abbreviations: MLA: Mesonephric-like adenocarcinoma; BMI: Body mass index; SD: Standard deviation; FIGO: International Federation of Gynecology and Obstetrics; LNM: Lymph node metastasis; DM: Distant metastasis.

Table 3. Clinical charaterstics in patients, treatment and prognosis with endometrial MLA

Case	Age	Symptom	Initial stage	Metastasis	Surgery	Adjuvant treatment	PFS (mo)	Recurrence	Alive/ Dead	Follow-up time (mo)
1	72	Postmenopausal bleeding	IIIC1	PLN	TH, BSO, PLND	No	NA	NA	Alive	36
2	64	Postmenopausal bleeding	IIIC1	PLN	TH, BSO, PLND, PALND	Yes	NA	NA	Alive	36
3	70	lower abdominal pain	NA	NA	TH, BSO	Yes	10	liver, lung, bone	Alive	30
4	54	Postmenopausal bleeding	IVA	PLN, PALN, bladder	TH, BSO, PLND, PALND	Yes	16	lung, liver, spleen, brain	Alive	41
5	51	lower abdominal pain	IVA	PLN, rectum	TH, BSO, PLND, PALND, RSE	Yes	10	lung	Alive	15
6	74	Postmenopausal	NA	NA	NA	No	NA	NA	Alive	5

		bleeding								
7	62	intrauterine space-occupying lesion	IA	No	TH, BSO, PLND, PALND	Yes	27	lung	Alive	32
8	73	Postmenopausal bleeding	IA	NA	TH, BSO	Yes	2	multiple bone metastases	Alive	7
9	56	Cough, productive cough, blood-tinged sputum	IVB	lung	BSLLL, MLND	NA	48	lung	Alive	56
10	60	lower abdominal pain, Postmenopausal bleeding	IIIC1	PLN	TH, BSO, PLND	Yes	8	No	Alive	8
11	48	pelvic mass	IVB	RO, PLN, PALN, LFT,	TH, BSO, PLND,	Yes	1	No	Alive	1

				PE	PALND, OM					

Symptom: Symptom onset to first medical visit. Adjuvant treatment: chemotherapy with or without radiation. Chemotherapy is platinum-based therapies combined with paclitaxel. Abbreviations: TH: Total hysterectomy; BSO: Bilateral salpingo-oophorectomy; PLND: Pelvic lymph node dissection; PALND: Para-aortic lymph node dissection; RSE: Rectosigmoidectomy; RO: Right ovary; LFT: Left fallopian tube; PE: Peritoneum; OM: Omentectomy; BSLLL: Basal segment of the left lower lobectomy; MLND: Mediastinal lymph node dissection.

Table 4. Serum tumor biomarkers in patients at initial diagnosis

Case	CA-125 U/ml (0.01-35)	CA-199 U/ml (0.01-37)	CEA ng/ml (0-5)	HE4 pmol/L (0-140)	SCC ng/ml (<2.5)	VEGF pg/ml (0-160)	AFP ng/ml (0-10)
1	30.57	23.87	0.94	127	0.796	754.89↑	1.61
2	106.30↑	43.14↑	10.31↑	107.80	1.222	20.80	2.38
3	738.00↑	48.60↑	2.64	456↑	9.064↑	683.11↑	4.52
4	182.70↑	4.387	0.31	127.10	0.87	NA	3.70
5	151.00↑	937.00↑	5.09↑	777.00↑	0.971	330.20↑	1.30
6	29.80	8.47	0.81	114.00	1.02	NA	1.77
7	7.23	6.22	0.81	101.20	1.40	54.30	1.84
8	15.40	15.20	3.57	75.90	0.371	NA	4.61
9	10.40	15.00	1.82	NA	NA	NA	2.04
10	73.10↑	570.00↑	7.64↑	147.00↑	0.198	＞800↑	3.44
11	378.00↑	3.75	0.43	87.90	NA	NA	0.97

Abbreviations: CEA: Carcinoembryonic antigen; HE4: Human epididymis protein 4; SCC: Squamous cell carcinoma antigen; VEGF: Vascular endothelial growth factor; AFP: Alpha-fetoprotein.

Table 5. Histopathological features, immunohistochemical staining and targeted sequencing results

	Case										
	1	2	3	4	5	6	7	8	9	10	11
ER	-	-	-	-	-	W	-	-	-	-	-
PR	-	-	-	-	-	-	-	-	-	-	-
GATA3	F	+	+	P	F	F	W	P	+	Fe	F
TTF1	F	+	F	F	F	P	-	P	+	P	F
CD10	-	+	+	W	+	F	P	P	+	+	-
PAX8	+	+	+	+	+	+	+	+	+	+	+
P16	P	P	+	P	-	P	+	P	NA	P	P
P53	WT	WT	+	WT	WT	WT	WT	WT	WT	WT	WT
AE1/AE3	+	+	NA	+	+	+	+	+	+	+	+
WT1	-	-	-	-	-	NA	-	-	NA	-	-
Vimentin	P	P	+	NA	P	NA	-	P	+	-	-
Ki-67	15% +	10% +	60% +	70% +	20% +	80% +	60% +	60% +	25% +	30% +	30% +
KRAS mutation	NA	NA	p.G12D	NA	p.G12D	p.G12A	NA	NA	p.G12V	NA	p.G13D

Abbreviations: ER: Estrogen receptor; PR: Progesterone receptor; GATA3: GATA-binding protein 3; TTF-1: Thyroid transcription factor-1; CD10: Cluster of differentiation 10; PAX8: Paired box 8; WT1: Wilms tumor 1; WT: Wild type; NA:

Not available; P: Partial positive; F: Focal positive; W: Weakly positive; Fe: Few positive.

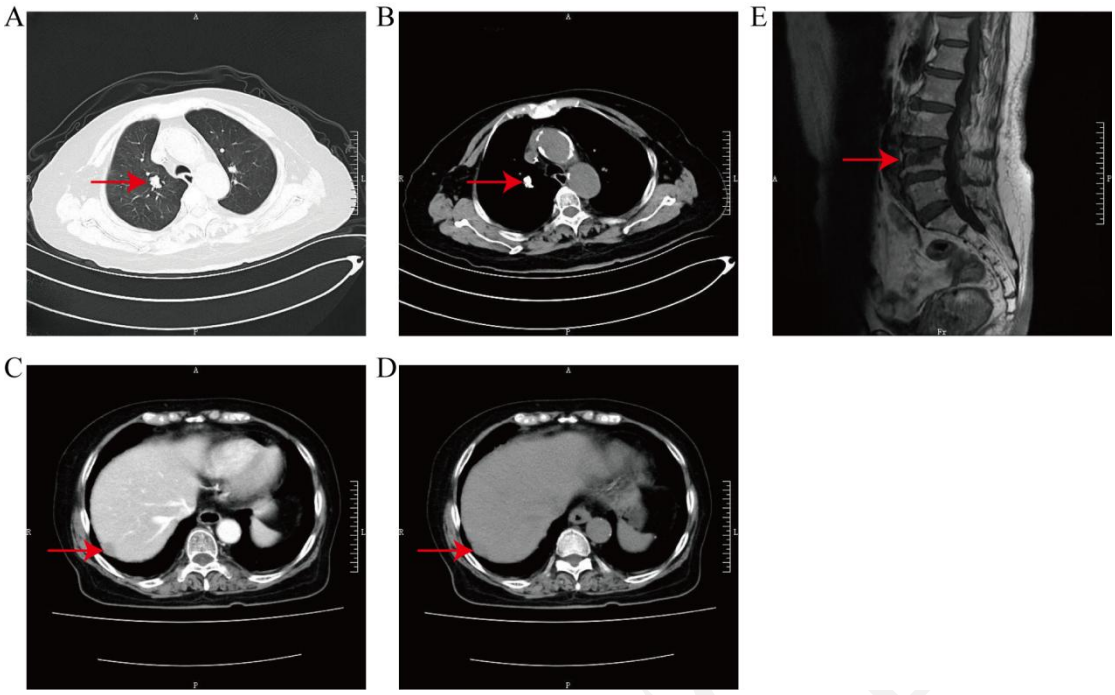

Figure 1. Radiographic data from case 3 - Computed tomography (CT) and magnetic resonance imaging (MRI) images. These radiographic data demonstrate that metastasis occurred in the liver, lung, and bone. (A) CT image in lung window. Metastasis can be observed in the lung (arrow). (B) CT image in the mediastinal window. Metastasis can be observed in the lung (arrow). (C) Cross-sectional contrast-enhanced arterial phase CT of the abdomen. Metastasis can be observed in the liver (arrow). (D) Cross-sectional contrast-enhanced venous phase CT of the abdomen. Metastasis can be observed in the liver (arrow). (E) Sagittal images of MRI. Metastasis can be observed in vertebrae (arrow).

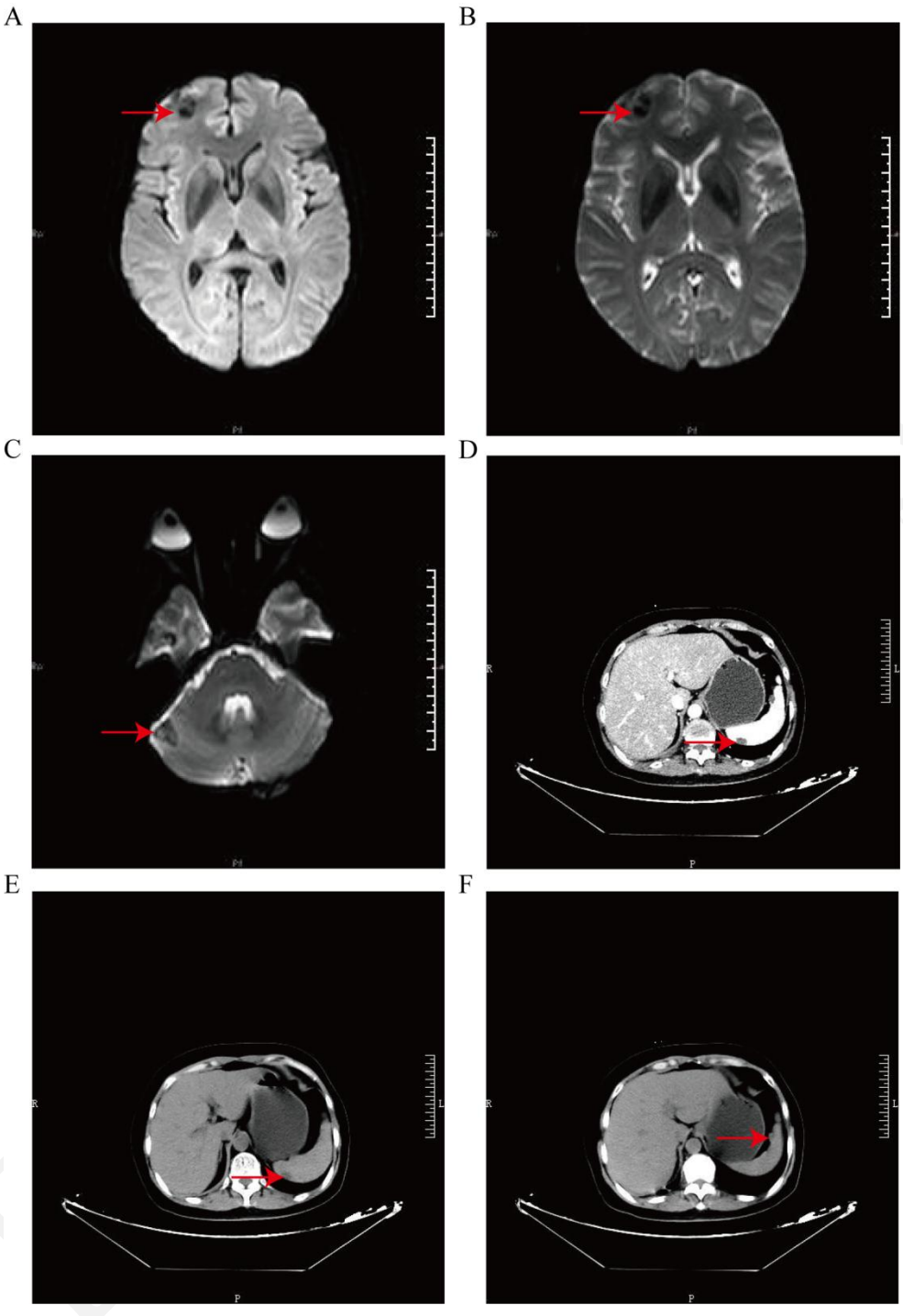

Figure 2. Radiographic data from case 4. CT and MRI images. These radiographic data demonstrate that metastasis occurred in the brain and spleen. (A-C) MRI images indicate metastasis occurred in the brain. (D) Cross-sectional contrast-enhanced arterial phase CT of the abdomen. Metastasis can be observed in the spleen (arrow). (E-F) Cross-sectional contrast-enhanced venous phase CT of the abdomen. Metastasis can be observed in the spleen (arrow).

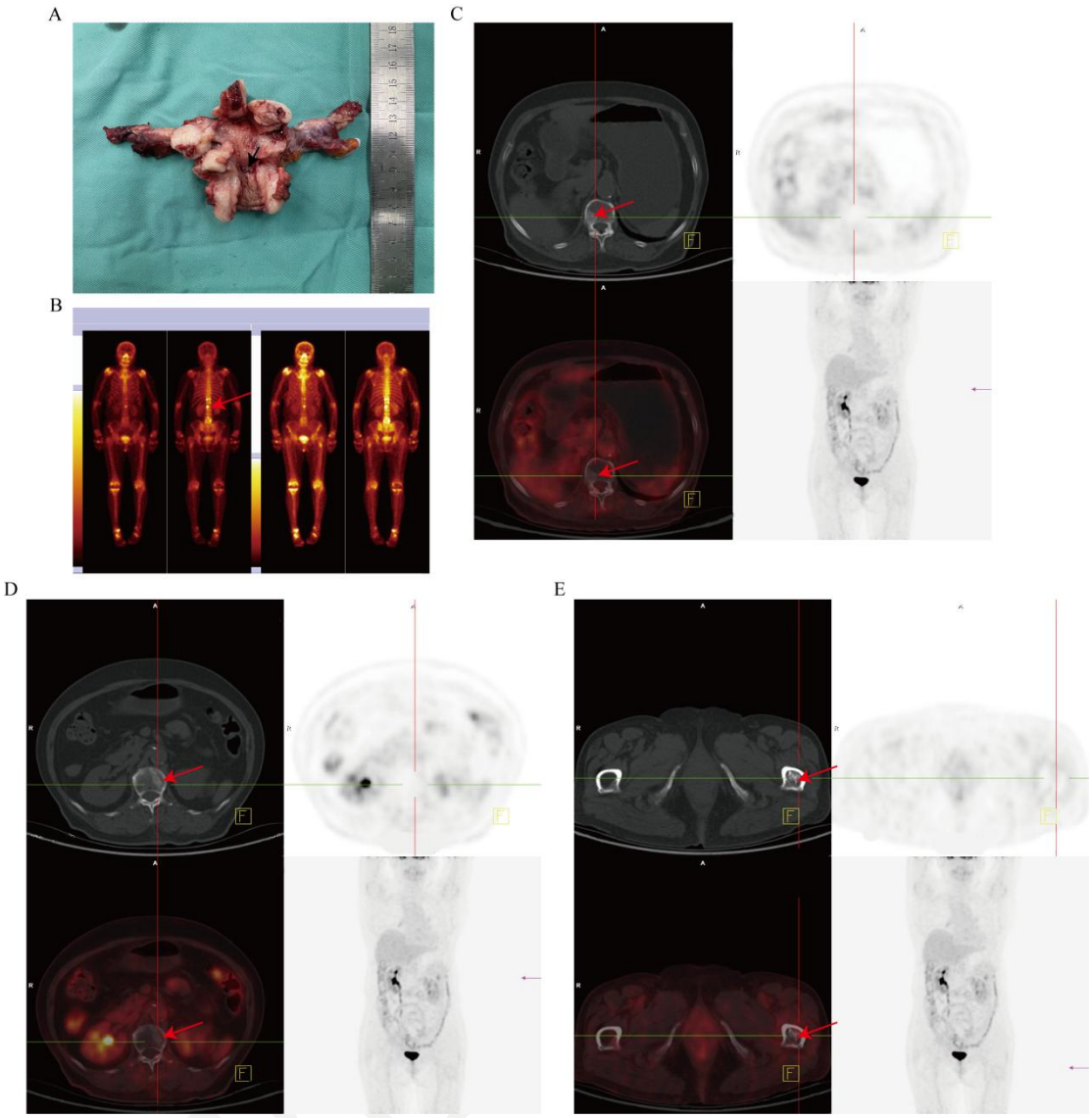

Figure 3. Surgical resection specimen and radiographic data from case 8. Single photon emission computed tomography (SPECT) and PET-CT images. These radiographic data demonstrate that metastasis occurs in bone. (A) Hysterectomy and bilateral salpingo-oophorectomy. Lesions can be observed (arrow). (B) SPECT image demonstrates multiple metastasis occurs in bone. (C-E) PET-CT images demonstrate multiple metastasis occurs in bone.

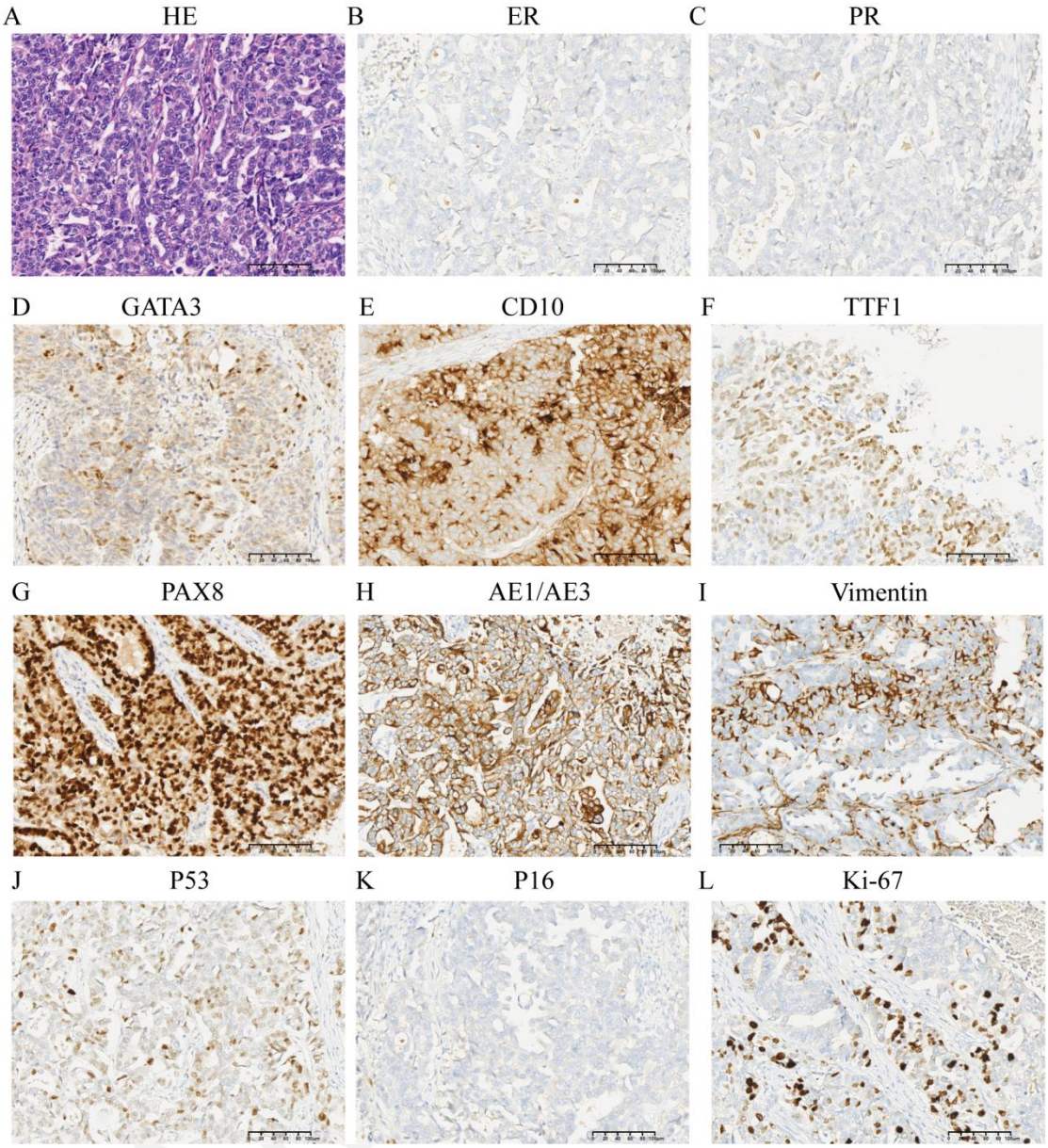

Figure 4. HE staining and immunohistochemical staining of case 5. ER and PR were negative. (A) HE staining. (B) ER negative. (C) PR negative. (D) GATA3 positive. (E) CD10 positive. (F) TTF1 positive. (G) PAX8 positive. (H) AE1/AE3 positive. (I) Vimentin positive. (J) P53 wild type. (K) P16 negative. (L) Ki-67 20% positive. Abbreviations: ER: Estrogen receptor; PR: Progesterone receptor; GATA3: GATA-binding protein 3; CD: Cluster of differentiation; TTF-1: Thyroid transcription factor-1; PAX8: Paired box 8; HE: Hematoxylin and eosin.

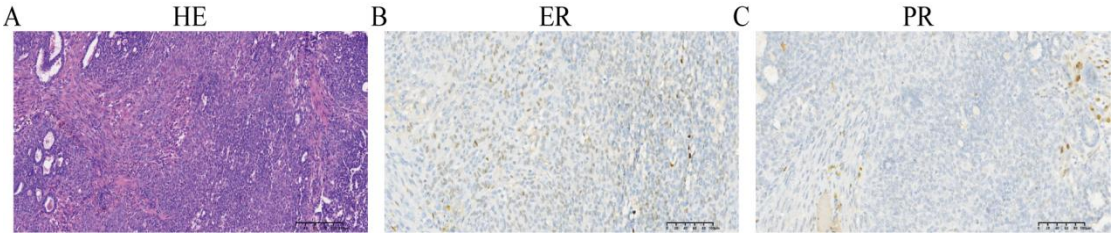

Figure 5. HE staining and immunohistochemical staining of case 6. PR was negative, and ER was weakly positive. (A) HE staining. (B) ER weakly positive. (C) PR negative. Abbreviations: ER: Estrogen receptor; PR: Progesterone receptor.

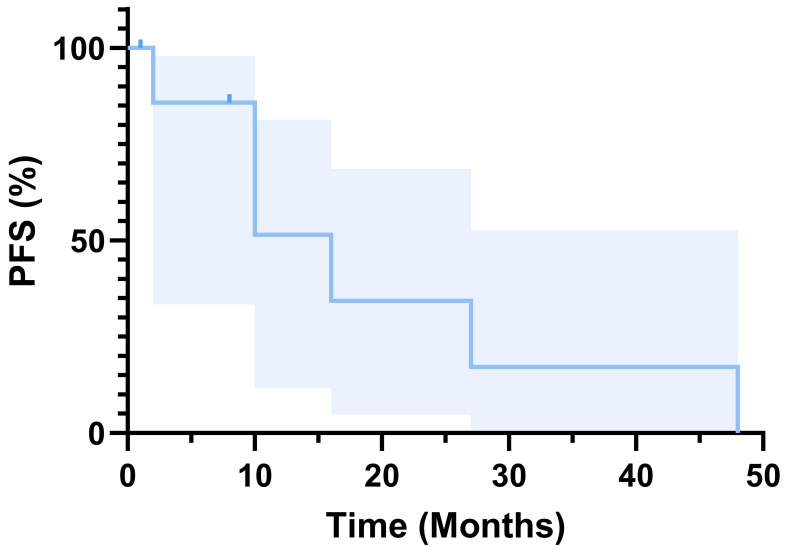

Figure 6. Kaplan–Meier curve for progression-free survival (PFS) over time. Survival analysis was performed using the Kaplan–Meier method to estimate PFS.