

Individualized Adjuvant Chemotherapy Guided by Pharmacogenomic Testing in a 14-Year-Old with Undifferentiated Embryonal Sarcoma of the Liver

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Case Report

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Abstract

Background

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare, aggressive mesenchymal tumor in children, with historically poor prognosis. No standardized adjuvant chemotherapy exists. Pharmacogenomic testing can individualize treatment by predicting drug efficacy and toxicity based on genetic polymorphisms, but its application in UESL has not been reported.

Case presentation

We report a 14-year-old male presenting with right upper quadrant pain and fever. Imaging revealed a large mixed cystic-solid mass in the right hepatic lobe. He underwent R0 right hemihepatectomy. Histopathology and immunohistochemistry confirmed UESL with a Ki-67 index of 40%. Postoperative multigene pharmacogenomic testing (84-gene panel) identified key polymorphisms in TP53, ABCB1, and ERCC1, which guided selection of an individualized adjuvant chemotherapy regimen (VDC/IE: vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide). The patient completed six cycles without dose reduction or delay, experiencing only grade 1–2 myelosuppression. At 36 months postoperatively, imaging showed no recurrence or metastasis, and the patient had returned to all normal activities.

Conclusions

This is the first report of systematic multigene pharmacogenomic testing to guide adjuvant chemotherapy in UESL. The patient achieved 36-month disease-free survival with favorable tolerability, a result comparable to or better than historical outcomes with empirical therapy. This case supports the integration of pharmacogenomic testing into individualized treatment strategies for rare sarcomas.

Clinical trial number: not applicable.

INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is an extremely rare malignant mesenchymal tumor, accounting for less than 1% of primary hepatic malignancies in children¹. The disease predominantly occurs in childhood, with a peak incidence between 6 and 10 years of age, although sporadic cases in adolescents and adults have been described, often presenting with more aggressive biological behavior^{2,3}. The present case involves a 14-year-old male, whose age slightly exceeds the typical range, further highlighting the potential diversity in UESL onset.

The clinical management of UESL is challenging due to its aggressive biology. Historically, even after gross total resection, rates of local recurrence and distant metastasis remained high, with 5-year overall survival (OS) ranging from 30% to 50% with surgery alone⁴. In recent years, the combination of radical surgical resection and postoperative adjuvant chemotherapy has become the cornerstone for improving prognosis⁵. With contemporary multidrug regimens borrowed from pediatric sarcomas (e.g., VAC or

VDC/IE), pooled analyses have reported 5-year OS of 65–75%¹⁴, and selected patients undergoing R0 resection in specialized centers have achieved 2-year OS as high as 90%¹³. However, due to the rarity of UESL, no standardized adjuvant chemotherapy regimen exists. Clinicians must extrapolate from other sarcomas, leaving them without reliable biomarkers to guide regimen selection for individual patients — particularly adolescents with large tumors and high recurrence risk — making it difficult to achieve an optimal balance between efficacy and toxicity⁶.

The emergence of pharmacogenomics offers a new perspective to address this gap. This discipline predicts drug efficacy and toxicity by analyzing patients' genetic polymorphisms and has enabled individualized therapy in several common cancers, with growing applications in sarcoma^{7,8}. However, in UESL — an ultra-rare disease — the use of pharmacogenomics remains virtually unexplored, with no established testing panel or clinical guidelines available⁹. Against this backdrop, each case that successfully applies genetic testing to guide treatment holds significant value for accumulating evidence and identifying potential patterns.

The core value of this case report lies in three aspects: (i) the patient is a 14-year-old male with an age at onset beyond the typical range, adding to the known spectrum of UESL presentation; (ii) it represents the first systematic application of multigene pharmacogenomic testing in UESL, providing molecular evidence — based on polymorphisms in TP53, ABCB1, and ERCC1 — to guide the selection of an individualized adjuvant chemotherapy regimen (VDC/IE); and (iii) the patient achieved 36-month disease-free survival postoperatively, offering empirical evidence for precision treatment of rare tumors. By presenting the entire process from diagnosis to gene-guided decision-making and long-term follow-up, this article aims to demonstrate the potential of pharmacogenomics to overcome the limitations of traditional empirical therapy in rare tumors such as UESL, providing a basis for integrating individualized treatment strategies.

CASE PRESENTATION

Presenting symptoms and physical examination

A 14-year-old previously healthy male presented with a 21-day history of right upper quadrant pain and intermittent fever (maximum 38.5°C). He denied nausea, vomiting, jaundice, or weight loss. His past medical, family, and psychosocial history was unremarkable, with no known genetic disorders or malignancies in first-degree relatives. On physical examination, the patient was afebrile at presentation, with normal vital signs. A firm, non-tender, mobile mass approximately 10 cm in diameter was palpable in the right upper quadrant, extending to the midclavicular line. No hepatosplenomegaly, ascites, or peripheral lymphadenopathy was noted.

Laboratory findings

Complete blood count and liver function tests were normal. Serum alpha-fetoprotein (AFP) was within normal limits (<10 ng/mL), while CA125 was mildly elevated at 26.6 U/mL. Hepatitis B/C serologies

were negative.

Imaging findings and diagnostic challenges

Abdominal ultrasound revealed a hypoechoic lesion with indistinct margins measuring 152.6 mm × 124.4 mm × 142.7 mm in the right hepatic lobe, containing punctate and flocculent hypoechoic areas. The initial interpretation suggested possible early liquefaction of a liver abscess. However, contrast-enhanced CT (Fig. 1A) demonstrated a large mixed cystic-solid mass (16.0 × 15.0 × 11.0 cm) with tortuous intratumoral vessels and progressive enhancement of the solid components in the venous and delayed phases — features highly atypical for an abscess. MRI (Fig. 1B) further showed heterogeneous long T1/long T2 signal with peripheral restricted diffusion on DWI. The mass compressed the inferior vena cava but caused no vascular invasion. These findings raised suspicion of a primary hepatic sarcoma rather than a benign inflammatory process.

A differential diagnosis was established including: (i) undifferentiated embryonal sarcoma of the liver (UESL), (ii) hepatoblastoma (less likely given age and normal AFP), (iii) hepatocellular carcinoma (unlikely without underlying liver disease), and (iv) mesenchymal hamartoma (less consistent with solid components and vessel tortuosity). Given the strong imaging suspicion of a malignant mesenchymal tumor, upfront surgical resection without preoperative biopsy was planned to avoid the risk of tumor seeding and bleeding.

Surgical treatment and histopathology

The patient underwent right hemihepatectomy with cholecystectomy. Intraoperatively, the tumor measured 16 × 15 × 11 cm, had an intact capsule, and was closely adherent to but not invading the inferior vena cava. No peritoneal seeding or ascites was present. A macroscopically complete (R0) resection was achieved. Estimated blood loss was 200 mL, no transfusion was required, and the operative time was 230 minutes. Postoperative recovery was uneventful, and the patient was discharged on postoperative day 10.

Gross examination showed a gray-red to gray-white, mixed cystic and solid cut surface. Microscopically (Fig. 2), the tumor exhibited diverse cell morphology including spindle, giant, and undifferentiated small cells with marked atypia. The stroma was loose and myxoid in most areas. Immunohistochemistry revealed: vimentin (+), focal CK (+), CD56 (+), BCL-2 (+), P16 (+), and a Ki-67 proliferation index of approximately 40%. AFP, GPC3, CD34, SMA, CK8/18, CD10, HepPar-1, S-100, myogenin, and MyoD1 were negative. These findings confirmed the diagnosis of undifferentiated embryonal sarcoma of the liver (UESL). The resection margin was free of tumor. No pathogenic germline variants were identified in the 84-gene panel (see Pharmacogenomic Testing section).

The study was approved by the Institutional Review Board (Approval No. CYFYLL2026005). Written informed consent for publication of the clinical and molecular data was obtained from the patient and his guardian.

Pharmacogenomic testing and individualized treatment decision-making

Rationale. Although postoperative adjuvant chemotherapy is critical for reducing recurrence risk in UESL, no standardized regimen exists, and clinical practice often relies on protocols borrowed from other pediatric sarcomas (such as the VAC/VDC-IE regimen for rhabdomyosarcoma), with significant inter-individual variability in efficacy and toxicity. The patient had a postoperative Ki-67 proliferation index of approximately 40%, indicating high recurrence risk. To optimize the adjuvant chemotherapy strategy and avoid potential toxicities, we performed multigene pharmacogenomic testing postoperatively to provide molecular evidence for individualized treatment.

Testing methods. Genomic DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue. A custom-designed 84-gene panel was used for library preparation and sequenced on an Illumina NextSeq 500 platform with a mean depth of coverage $>500\times$. Raw sequencing data were aligned to the human reference genome (hg19) using BWA-MEM. Variant calling was performed using GATK4, and variants were annotated using ANNOVAR. All identified polymorphisms were cross-referenced against dbSNP (v155), ClinVar, and PharmGKB databases. Only variants with a population frequency $\geq 1\%$ (based on gnomAD) were considered potentially pathogenic. Germline status was assessed by comparing tumor variants to a matched peripheral blood sample; no pathogenic germline variants (including in TP53) were identified.

Individualized decision-making based on genetic testing. The test results revealed that multiple genetic polymorphisms were closely associated with drug response to the VDC/IE regimen (vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide). Importantly, no pathogenic germline TP53 mutation was identified in the patient's peripheral blood or tumor tissue, effectively excluding Li-Fraumeni syndrome.

The key findings are summarized in Table 1.

- - TP53 rs1042522 CC: This polymorphism is associated with impaired p53 function. While this might increase sensitivity to some DNA-damaging agents, it has also been linked to an increased risk of cisplatin-induced nephrotoxicity in some adult solid tumor studies¹⁰. Given the lack of clear efficacy data for cisplatin in UESL and the potential for enhanced toxicity, we elected to avoid a cisplatin-based regimen.
- - ABCB1 rs1045642 AA: This genotype reduces P-glycoprotein efflux activity, potentially leading to higher intracellular accumulation of doxorubicin and improved efficacy.
- - ERCC1 rs11615 GG: This genotype indicates a deficiency in nucleotide excision repair (NER), which may confer relative resistance to platinum agents but increase sensitivity to other DNA-damaging drugs such as doxorubicin.

Table 1
Summary of relevant polymorphisms and their clinical implications

Drug	Gene	Variant	Genotype	Efficacy/Toxicity Implication	Clinical Implication
Doxorubicin	<i>ABCB1</i>	rs1045642	AA	Reduced efflux, increased intracellular drug accumulation (efficacy score 63.3)	Preferred
Doxorubicin	<i>ERCC1</i>	rs11615	GG	NER deficiency, enhanced sensitivity to DNA-damaging agents	Evidence for efficacy
Cyclophosphamide	<i>CYP2C19</i>	rs4244285	GG	Slowed metabolism (toxicity score 66.6)	Caution – enhanced monitoring
Etoposide	<i>TP53</i>	rs1042522	CC	Impaired p53 function (efficacy score 60.0)	Alternative, mechanism-matched
Cisplatin	<i>TP53</i>	rs1042522	CC	p53 deficiency increases nephrotoxicity risk	Avoided

Adjuvant treatment and follow-up outcomes

Chemotherapy regimen. The patient received six cycles of adjuvant chemotherapy with the VDC/IE regimen (alternating VDC and IE cycles, 21-day cycles). VDC cycle (day 1): vincristine 1.5 mg/m² (max 2 mg), doxorubicin 75 mg/m² (6-hour infusion), cyclophosphamide 2.2 g/m² (1-hour infusion). IE cycle (days 1-5): ifosfamide 1.8 g/m²/day (2-hour infusion), etoposide 100 mg/m²/day (1-hour infusion). Supportive care included mesna for hemorrhagic cystitis prophylaxis (20% of cyclophosphamide dose at 0, 4, and 8 hours post-agent), 5-HT₃ receptor antagonists for antiemesis, and hydration therapy (≥ 2000 mL/m²/day).

Toxicity and tolerability. According to CTCAE version 5.0, the main adverse effects were grade 1-2 myelosuppression: grade 2 neutropenia (nadir absolute neutrophil count $0.8 \times 10^9/L$) after cycle 3, and grade 1 thrombocytopenia (nadir platelet count $85 \times 10^9/L$) after cycle 4; no febrile neutropenia or bleeding events were observed. These were managed with short-term G-CSF support (filgrastim 5 µg/kg/day). Grade 1 nausea and vomiting (<10% incidence) was noted, with no abnormalities in liver or renal function (ALT/AST and creatinine within normal limits), no cardiotoxicity (left ventricular ejection fraction >55% on echocardiography), and no hemorrhagic cystitis. The patient tolerated the regimen well, and all six cycles were completed without dose reduction or treatment delay.

Follow-up and survival outcomes. Postoperative follow-up included contrast-enhanced chest and abdominal CT every 3 months for the first year, every 6 months for the second year, and annually

thereafter. At 3, 6, 12, and 36 months post-surgery, imaging consistently showed no evidence of local recurrence or distant metastasis, and tumor markers remained within normal limits. As of the last follow-up (36 months postoperatively), the patient remained alive and disease-free, with a good quality of life, having returned to full-time school activities and sports. This outcome supports the potential long-term efficacy of R0 resection combined with this gene-guided adjuvant chemotherapy approach in this patient with UESL.

DISCUSSION

We report a 14-year-old male with a large UESL who achieved 36-month disease-free survival after R0 resection followed by adjuvant chemotherapy guided by multigene pharmacogenomic testing. This case provides three novel contributions: (1) it extends the age spectrum of UESL beyond the typical 6-10-year peak, (2) it is the first systematic application of an 84-gene pharmacogenomic panel in UESL to tailor chemotherapy selection based on TP53, ABCB1, and ERCC1 polymorphisms, and (3) it offers real-world evidence that a genotype-guided VDC/IE regimen can achieve favorable outcomes in this ultra-rare sarcoma.

Pharmacogenetic testing revealed the TP53 rs1042522 CC genotype, which is associated with impaired p53 function and increased risk of cisplatin-induced nephrotoxicity¹⁰. Although this association is not definitively established in pediatric sarcomas, we considered it as an additional safety consideration when choosing between platinum-based and anthracycline-based regimens; consequently, cisplatin was avoided. The ABCB1 rs1045642 AA genotype reduces P-glycoprotein efflux activity, leading to higher intracellular accumulation of doxorubicin and potentially improved efficacy¹¹. The ERCC1 rs11615 GG genotype indicates deficiency in nucleotide excision repair; although this may confer resistance to platinum agents, it increases sensitivity to other DNA-damaging drugs such as doxorubicin, creating a synthetic lethality effect when combined with p53 impairment¹². Together, these molecular findings provided a strong rationale for selecting the doxorubicin-containing VDC/IE regimen while avoiding cisplatin-based therapy.

Historically, UESL carried a poor prognosis with 5-year OS of 30-50% with surgery alone⁴. With the addition of adjuvant multidrug chemotherapy borrowed from pediatric sarcomas, reported 5-year OS has improved to 65-75% in pooled analyses¹⁴. More recent series reported a 2-year OS of up to 90% in highly selected patients undergoing R0 resection with modern chemotherapy¹³. Our patient's 36-month disease-free survival is therefore comparable to or better than these benchmarks. The notable contribution of our case is the precision application of an existing regimen – using genetic polymorphisms to maximize efficacy and minimize toxicity, which is particularly important for adolescent patients in whom long-term treatment-related morbidities must be weighed against oncologic benefit.

In this case, we opted for direct surgical resection without preoperative biopsy or neoadjuvant chemotherapy. The rationale was: (i) imaging strongly suggested a resectable primary hepatic sarcoma

with no evidence of metastatic disease; (ii) an image-guided core needle biopsy carried risks of tumor seeding and bleeding; (iii) there is no established role for neoadjuvant chemotherapy in UESL; and (iv) the patient's symptoms warranted prompt source control. This approach aligns with the current standard of care at many high-volume pediatric centers¹³.

The major strengths of this report are: (a) detailed, transparent application of a multigene pharmacogenomic test in a rare tumor, (b) 36-month follow-up with comprehensive imaging and laboratory data, and (c) adherence to CARE guidelines. Limitations include: (i) this is a single case, providing only level-IV evidence; (ii) follow-up is limited to 36 months; UESL can recur late, and longer surveillance (≥ 5 years) is needed to confirm cure; (iii) we did not perform functional validation (e.g., in vitro drug sensitivity assays or gene expression analysis) to directly link the genotypes to drug response; and (iv) the pharmacogenomic panel did not include all potentially relevant variants (e.g., CYP3A4, GSTP1).

This case demonstrates that even for ultra-rare tumors, modern molecular diagnostics can transform empirical chemotherapy into a more individualized strategy. We suggest that for patients with UESL, consideration be given to multigene pharmacogenomic testing as part of the pre- or postoperative workup. Larger, prospective registries are needed to validate the predictive value of individual polymorphisms and to establish evidence-based cutoff scores for treatment recommendations.

Conclusion

For a 14-year-old with large UESL undergoing R0 resection, pharmacogenomic testing enabled the selection of an individualized VDC/IE regimen, resulting in 36-month disease-free survival with favorable tolerability. This precision approach illustrates a potential paradigm that warrants further investigation in collaborative registries.

Patient perspective

The patient has returned to normal life, participating in full-time school activities and sports. He reported no tumor-related symptoms and expressed satisfaction with the treatment process. His guardian provided written informed consent for publication and noted appreciation for the transparent communication throughout the clinical course.

Declarations

Competing Interests:

The authors declare that they have no competing interests.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to disclose.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical Approval: “The study protocol was approved by the Institutional Review Board of the Affiliated Hospital of Chengde Medical University (Approval No. CYFYLL2026005), in accordance with the Declaration of Helsinki.”

Consent to participate: “Informed consent to participate was obtained from the patient's legal guardian.”

Consent to publish: “Informed consent to publish was obtained from the patient's legal guardian.”

Author Contribution

M.L. and J.L. conceived and designed the study. J.L., J.W., and C.H. acquired the clinical data and performed the follow-up assessments. M.L. drafted the manuscript and prepared the figures and tables. C.H. performed the pharmacogenomic data interpretation. A.Y. supervised the surgical treatment and provided critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

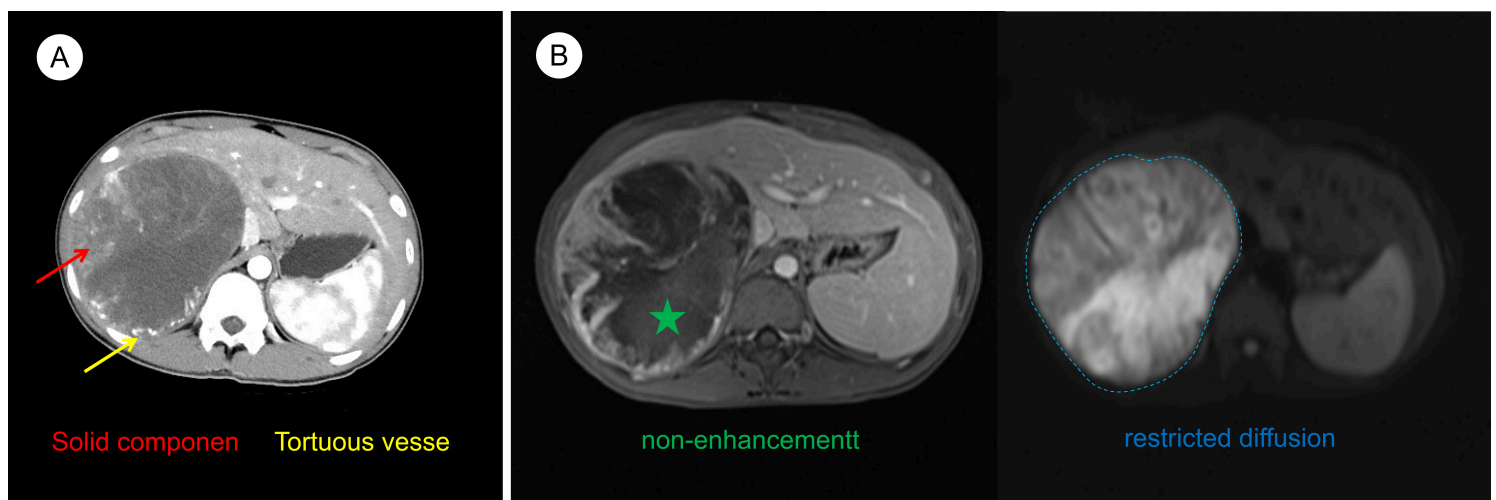


Figure 1

Combined imaging panel – CT (A) showing mixed cystic-solid mass with tortuous intratumoral vessels; MRI (B) demonstrating heterogeneous signal with peripheral restricted diffusion.

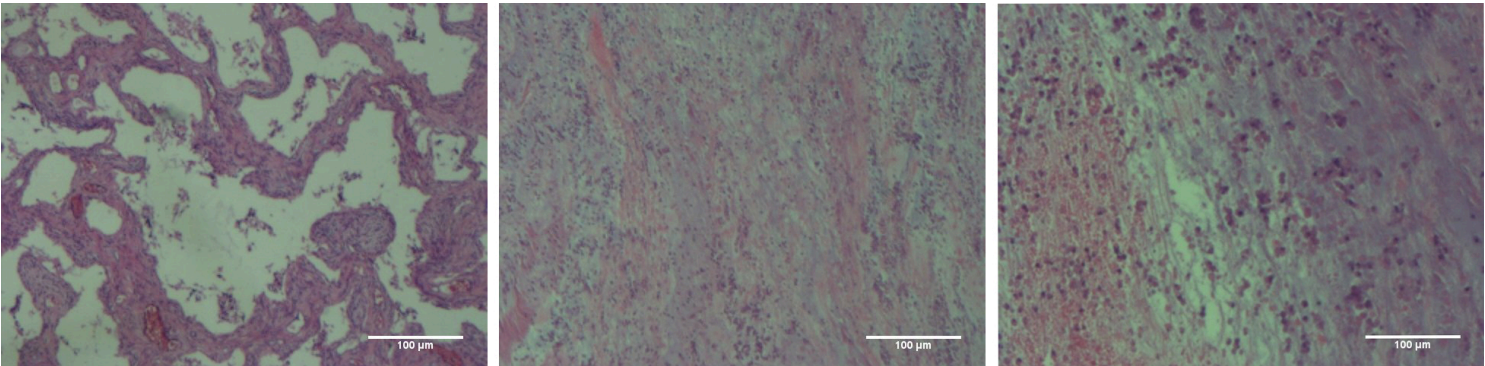


Figure 2

HE staining (×100) showing diverse tumor cell morphology including spindle-shaped, giant, and undifferentiated small cells, with loose stroma and myxoid matrix.

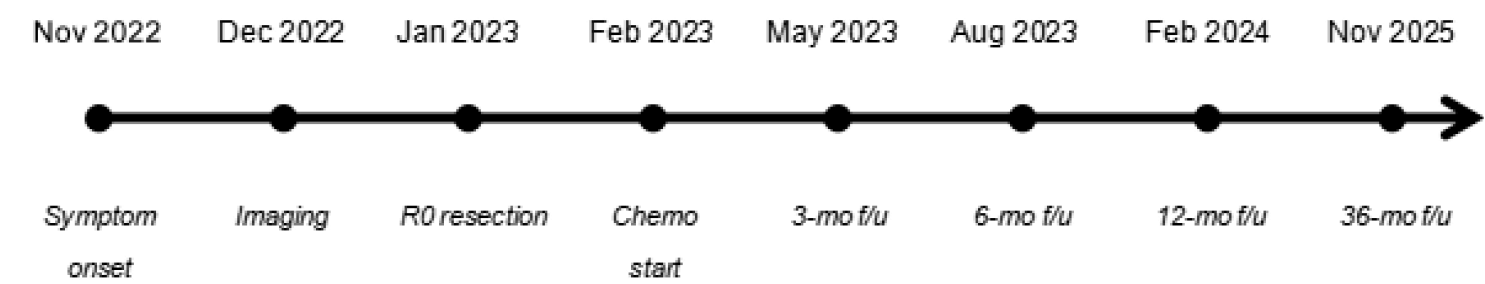


Figure 3

Clinical timeline summarizing the full course from presentation through 36-month follow-up.