Communication

Prognostic Value of Primary Tumor Site in Surgery for Colorectal Liver Metastases

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Prognostic Value of Primary Tumor Site in Surgery for Colorectal Liver Metastases

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Abstract

The compelling study by Liu *et al* delivers a critical verdict: The primary tumor site is not merely an anatomical detail, but a fundamental prognostic imperative in the surgical management of colorectal liver metastases. Their analysis of 178 patients definitively establishes right-sided colonic origin as an independent harbinger of aggressive disease, characterized by significantly higher recurrence rates and inferior survival outcomes compared to left-sided and rectal cancers. This biological dichotomy is further elucidated by the strong association of right-sided tumors with an adverse prognostic profile, including rampant lymph node metastasis, elevated D-dimer (reflecting a pro-thrombotic, pro-metastatic state), hypoalbuminemia, and resistance to neoadjuvant therapy. These findings necessitate an immediate paradigm shift in clinical practice. We can no longer treat colorectal cancer as a monolith. Preoperative risk stratification, surgical decision-making, and adjuvant therapy plans must be tailored according to the primary tumor location. For patients with right-sided primaries, these data suggest a more aggressive multimodal approach and vigilant, personalized surveillance to improve upon the discouraging outcomes this study clearly exposes.

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Core Tip: Primary tumor location is a master prognostic regulator in colorectal liver metastases. Right-sided origin defines an aggressive biologic phenotype, marked by chemoresistance, hypercoagulability, and systemic decline, culminating in a more than 50% 1-year recurrence rate and a 13-month survival deficit. These findings mandate abandoning a one-size-fits-all management approach. Therefore, the immediate implementation of the following site-specific protocols remains paramount: Preoperative risk stratification, therapeutic intensification, and personalized intensive surveillance for right-sided cases.

TO THE EDITOR

The operative management of colorectal liver metastases (CRLM) is evolving. Historically, surgical strategy and prognostication have been guided primarily by the technical resectability and burden of metastatic disease within the liver[1]. Within this paradigm, the primary colorectal tumor has often been considered a historical footnote. The work by Liu *et al*[2] now challenges this established view, providing robust data that position the primary tumor site as a principal determinant of postoperative outcomes. Their evidence compels a critical re-evaluation of our current, relatively uniform treatment approaches. These evolving principles are summarized in Table 1.

Table 1. Evolving paradigms in the management of colorectal liver metastases.

Principle	Traditional paradigm	New, biology-driven paradigm
Defining logic	Technical resectability of metastatic disease	Inherent biological aggressiveness of the primary tumor

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Central prognostic factor	Metastatic burden (number and size of lesions)	Primary tumor location and its associated biologic phenotype
Role of primary tumor	Historical point of origin	Key regulator of metastatic behavior and host systemic response
Therapeutic goal	Standardised application guidelines	Risk-adapted site-specific intensification of multimodal therapy
Implied action	Uniform treatment protocols	Location-defined and molecular-informed treatment algorithms

The analysis by Liu *et al*[2] is methodologically rigorous, moving beyond simple association to identify independent predictors. Through multivariate logistic regression, right-sided origin was isolated as an independent predictor of recurrence (odds ratio: 1.74). This predictive power is contextualized within a syndromic complex of adverse features, positioning the primary tumor site as a central component of a high-risk phenotype[2,3]. The data reveal a consistent pattern: Right-sided tumors are linked to markers of aggressive biology[2,4]. The clinical and biologic profile of right-sided colorectal liver metastases is detailed in Table 2. They exhibit a markedly high rate of lymph node metastases (91%), indicative of advanced metastatic competence. Furthermore, they are associated with a systemic pro-thrombotic state (elevated D-dimer) and cancer-associated systemic decline (hypoalbuminemia), which may impair host immunity and facilitate metastatic progression[2,5]. Notably, these tumors also demonstrate pronounced resistance to neoadjuvant therapy. The clinical consequence of this biologic profile is a 12-month recurrence rate exceeding 55% and a median overall survival of approximately 28.5 months.

Table 2. The clinical and biologic profile of right-sided colorectal liver metastases.

Clinical domain	**Manifestations in right-sided CRLM[1]**	**Proposed biological driver**	**Actionable clinical response**
Metastatic aggression	High lymph node metastasis rate; > 55% 12-month recurrence	CMS4 mesenchymal phenotype; enhanced invasive capacity	Enhanced staging; pursuit of wider surgical margins
Systemic environment	Elevated D-dimer; hypoalbuminemia	Tumor-induced hypercoagulability; cancer-associated systemic inflammation	Consider perioperative anticoagulation; mandatory prehabilitation
Therapeutic resistance	High rate of poor neoadjuvant response	Distinct molecular drivers (*e.g.*, BRAF); enriched chemoresistant pathways	First-line therapy intensification; early biomarker integration

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Ultimate outcome	Diminished median overall survival	Synergistic effect of an aggressive biologic phenotype	Classify as "ultra-high risk"; implement intensive, personalised surveillance

CRLM: Colorectal liver metastases; CMS4: Consensus molecular subtype 4; BRAF: V-Raf murine sarcoma viral oncogene homolog B.

The association between right-sided origin and inferior outcomes is underpinned by well-established biologic distinctions. The embryonic origin, mucosal microenvironment, and immune landscape of the right and left colon are fundamentally different[5]. Carcinomas arising in the right colon are frequently enriched for specific molecular subtypes, particularly the consensus molecular subtype 4. This "mesenchymal" phenotype is characterized by prominent transforming growth factor β signaling, stromal activation, and angiogenesis, which collectively drive invasive capacity and treatment resistance[6]. This molecular framework provides a plausible explanation for the observed clinical aggressiveness.

The translation of these insights into clinical practice necessitates a structured approach. First, primary tumor location should be integrated as a key variable in preoperative risk assessment[5]. Patients with right-sided CRLM may be appropriately classified as high-risk, which could justify enhanced staging with positron emission tomography computed tomography to exclude occult extrahepatic disease[7]. This stratification also supports the implementation of aggressive prehabilitation protocols to address associated systemic vulnerabilities. Second, the observed resistance to neoadjuvant therapy in this subgroup supports the consideration of intensified systemic regimens. For patients with right-sided CRLM, initial therapy should involve the most efficacious available options[8], which may include first-line triplet chemotherapy combined with biologic agents such as bevacizumab[9]. A concerted surgical effort to achieve a parenchymal margin greater than 1 cm is also prudent. Third, the significant recurrence risk mandates a surveillance protocol of heightened intensity. For patients with right-sided primaries, cross-sectional imaging at 3-month intervals for the initial 2-3 years post-operatively is a rational strategy to enable early detection of recurrence.

The primary tumor site is a fundamental prognostic variable in the surgical management of CRLMs. Right-sided origin defines a distinct clinicopathologic entity characterized by an aggressive biological signature and inferior outcomes. The evidence strongly suggests that treatment strategies should be personalized accordingly. The adoption of a site-specific management paradigm represents a critical and necessary step toward improving outcomes for patients with right-sided CRLMs.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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References

1. **Yu W**, Lin Y, Huang M, Du Y, Ye Z. The connection between surgical margins in liver metastases from colorectal cancer and patient prognosis: A mini review. *Curr Probl Surg* 2025; **63**: 101700 [PMID: 39922639 DOI: 10.1016/j.cpsurg.2024.101700]
2. **Liu DM**, Yang XY, Zheng HH, Chen PM, Zeng SK, Wei YF. Impact of primary colorectal cancer site on surgical outcomes for liver metastases: A retrospective study. *World J Gastrointest Surg* 2025; **17**: 111138 [PMID: 41357641 DOI: 10.4240/wjgs.v17.i11.111138]

 doi:10.20944/preprints202601.0160.v1

3. **Liu W**, Wang HW, Wang K, Xing BC. The primary tumor location impacts survival outcome of colorectal liver metastases after hepatic resection: A systematic review and meta-analysis. *Eur J Surg Oncol* 2019; **45**: 1349-1356 [PMID: 31054852 DOI: 10.1016/j.ejso.2019.04.017]
4. **Kitsel Y**, Cooke T, Sotirchos V, Sofocleous CT. Colorectal Cancer Liver Metastases: Genomics and Biomarkers with Focus on Local Therapies. *Cancers (Basel)* 2023; **15**: 1679 [PMID: 36980565 DOI: 10.3390/cancers15061679]
5. **Petrelli F**, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, Passalacqua R, Sgroi G, Barni S. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2017; **3**: 211-219 [PMID: 27787550 DOI: 10.1001/jamaoncol.2016.4227]
6. **Abdel Hamid M**, Pammer LM, Oberparleiter S, Günther M, Amann A, Gruber RA, Mair A, Nocera FI, Ormanns S, Zimmer K, Gerner RR, Kocher F, Vorbach SM, Wolf D, Riedl JM, Huemer F, Seeber A. Multidimensional differences of right- and left-sided colorectal cancer and their impact on targeted therapies. *NPJ Precis Oncol* 2025; **9**: 116 [PMID: 40263545 DOI: 10.1038/s41698-025-00892-y]
7. **Lake ES**, Wadhwani S, Subar D, Kauser A, Harris C, Chang D, Lapsia S. The influence of FDG PET-CT on the detection of extrahepatic disease in patients being considered for resection of colorectal liver metastasis. *Ann R Coll Surg Engl* 2014; **96**: 211-215 [PMID: 24780786 DOI: 10.1308/003588414X13814021679195]
8. **Ashique S**, Bhowmick M, Pal R, Khatoon H, Kumar P, Sharma H, Garg A, Kumar S, Das U. Multi drug resistance in Colorectal Cancer- approaches to overcome, advancements and future success. *Adv Cancer Biology Metastasis* 2024; **10**: 100114 [DOI: 10.1016/j.adcanc.2024.100114]
9. **Loupakis F**, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; **371**: 1609-1618 [PMID: 25337750 DOI: 10.1056/NEJMoa1403108]