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Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer

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ABSTRACT

Background: The literature on prognostic survival associated with left-sided versus right-sided colon cancer reveals significant distinctions in clinical outcomes and treatment responses, influenced by a multitude of biological, pathological, and molecular factors. **Literature Review:** Further investigations, such as those by (Zovak & Mužina Mišić, 2018), have indicated that while overall and disease-free survival rates post-surgery for stages I-III do not significantly differ between right- and left-sided colon cancers, there is a notable divergence in chemotherapy responses for disseminated disease ((Zovak & Mužina Mišić, 2018)). This suggests that treatment strategies should be tailored based on tumor sidedness, particularly in advanced cases. (Bahl et al., 2020) reinforced the notion that left-sided colon cancer generally correlates with better long-term survival compared to right-sided tumors, emphasizing the importance of tumor location in treatment planning ((Bahl et al., 2020)). The systematic review conducted by further elucidated the correlation between specific biomarkers and tumor location, indicating that right-sided tumors often exhibit poorer survival outcomes due to distinct biological behaviors. **Conclusion:** In conclusion, the literature collectively indicates that tumor sidedness plays a crucial role in the prognosis and treatment of colon cancer, with left-sided tumors generally associated with better outcomes. However, the complexity of the relationship between sidedness and survival outcomes is evident, as various studies highlight the influence of confounding factors, molecular characteristics, and treatment responses. As such, a nuanced understanding of these dynamics is essential for optimizing treatment strategies and improving patient management in colorectal cancer.

Keyword: Prognostic Survival, Left-Sided, Right-Sided Colon Cancer

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INTRODUCTION

The prognostic survival associated with left-sided versus right-sided colon cancer has garnered significant attention in the medical literature, reflecting a complex interplay of clinical, pathological, and molecular factors. The body of research highlights critical differences in the characteristics and outcomes of colon cancer based on tumor location, starting with the foundational work of (Mik et al., 2017), which established that right-sided colon cancers are typically diagnosed at a more advanced stage compared to their left-sided counterparts. This study emphasized the potential implications of staging inaccuracies due to the fewer lymph nodes removed during surgeries for left-sided cancers, suggesting a need for further exploration into the biological disparities of adenocarcinomas based on their anatomical location.

Building on this foundation, (Zovak & Mužina Mišić, 2018) investigated survival outcomes post-surgery, revealing no significant differences in overall or disease-free survival between right- and left-sided colon cancers for patients with stages I-III. Their findings indicated that while both types of cancer are treated similarly surgically, the systemic therapy approaches diverge in cases of disseminated disease due to varying chemotherapy responses. This points to the necessity for tailored treatment strategies based on tumor sidedness, particularly in advanced stages.

(Cai et al., 2018) further contributed to the discourse by analyzing the impact of primary tumor location on survival, noting that right-sided colorectal cancer (CRC) is associated with poorer outcomes across various disease stages. Their systematic review underscored the need for ongoing research to unravel the underlying biological differences influencing these survival rates, reinforcing the notion that tumor sidedness could serve as a critical factor in treatment decision-making.

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(B. Wang et al., 2019) expanded on these insights by examining biomarkers associated with tumor location, identifying significant variations in clinical outcomes based on the location of the primary tumor. Their study highlighted the distinct molecular profiles of right- and left-sided cancers, suggesting that these differences warrant consideration in prognosis and treatment strategies, particularly as the disease progresses.

In contrast, (Chung Yan Chan et al., 2019) challenged the prevailing assumptions regarding tumor sidedness as an independent prognostic marker, asserting that previously unaccounted confounding factors may obscure the true impact of sidedness on survival. Their findings suggest that while tumor biology plays a crucial role, the relationship between sidedness and prognosis is not as straightforward as previously thought.

(Bahl et al., 2020) further elucidated the clinico-pathological differences between right and left colon cancers, emphasizing the importance of primary tumor location in determining prognosis and treatment responses. They noted distinct embryological origins and associated molecular characteristics that contribute to the observed disparities in outcomes, reinforcing the notion that tumor sidedness should be a key consideration in clinical practice.

(Stelzner et al., 2024) provided a nuanced perspective by analyzing the significance of sidedness in relation to cancer stages, revealing that while left-sided tumors generally exhibited better prognoses, this advantage diminished under certain conditions, such as matching for tumor resection adequacy. Their analysis indicated that external factors, including fecal transit time and microbiome differences, could influence outcomes, complicating the interpretation of sidedness as a prognostic indicator.

Finally, (Wu et al., 2024) conducted a multicenter study that highlighted the clinical and molecular heterogeneity associated with tumor sidedness, particularly in the context of liver metastases. Their findings revealed that the prognostic advantages of left-sided tumors were particularly pronounced in patients with KRAS wild-type,

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while those with KRAS mutations experienced worse outcomes regardless of tumor location. This study underscores the importance of integrating molecular profiling into prognostic assessments and treatment planning, further emphasizing the distinct biological behaviors of right and left colon cancers.

Collectively, these studies illustrate a rich tapestry of insights into the prognostic implications of tumor sidedness in colon cancer, revealing both consistent themes and critical debates within the literature. The evolving understanding of how tumor location influences clinical outcomes continues to shape treatment paradigms and underscores the need for personalized approaches in managing colorectal cancer.

LITERATURE REVIEW

The article "Right- and left-sided colon cancer – clinical and pathological differences of the disease entity in one organ" by Mik et al. (Mik et al., 2017) provides a comprehensive examination of the variances in clinical presentation and pathological characteristics between right-sided and left-sided colon cancers. The authors present a compelling argument that these differences are significant and warrant further investigation, particularly in the context of prognostic survival outcomes.

One of the key insights from the study is that right-sided colon cancer is typically diagnosed at a more advanced stage compared to its left-sided counterpart. This finding is particularly noteworthy as it suggests a potential delay in diagnosis for right-sided lesions, which may be attributed to the anatomical and physiological differences in the colon. The authors highlight that patients with right-sided colon cancer tend to be older at diagnosis, which may further complicate treatment options and overall prognosis (Mik et al., 2017).

The article also addresses the issue of lymph node removal during surgical procedures, noting that patients with left-sided colon cancer had fewer lymph nodes removed. This discrepancy raises concerns about the accuracy of staging for left-sided tumors, which could potentially lead to misclassification of disease severity

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and affect long-term survival outcomes. The authors emphasize the need for standardized surgical protocols to ensure adequate lymph node assessment, as this is crucial for accurate staging and subsequent treatment planning (Mik et al., 2017).

Moreover, the authors call for additional research to explore the biological differences between adenocarcinomas located on different sides of the colon. This recommendation is critical, as understanding these biological dissimilarities could lead to more tailored therapeutic approaches and improved prognostic models for patients with colon cancer. The study underscores the importance of recognizing that colon cancer is not a homogeneous disease; rather, it exhibits significant variability based on its anatomical location, which can have profound implications for patient management and outcomes.

The article titled "Kirurgija raka debelog crijeva s obzirom na razlike u prognozi između desnostranih i lijevostranih tumora" by Zovak and Mišić (Zovak & Mužina Mišić, 2018) presents a comprehensive analysis of the prognostic differences between right-sided and left-sided colon cancer, particularly following radical surgical treatment for stages I-III. The authors highlight that their examination of two studies indicates no significant difference in overall survival and disease-free survival rates between the two sides of colon cancer post-surgery. This finding is crucial as it challenges some prevailing assumptions in oncological practices regarding the distinct prognoses associated with the anatomical location of colon tumors.

The article delves into the nuances of systemic therapy for disseminated disease, emphasizing the differential response rates to chemotherapy based on tumor location. Specifically, the authors note that metastatic right colon cancer exhibits a lower response rate to systemic treatments compared to its left-sided counterpart. This observation raises important clinical questions regarding the optimal management of patients with oligometastatic disease, suggesting that a more aggressive surgical approach may be warranted for those with right-sided tumors.

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Zovak and Mišić (Zovak & Mužina Mišić, 2018) effectively underscore the implications of their findings for clinical practice, particularly in the context of treatment planning and patient prognosis. The lack of significant differences in survival outcomes post-surgery highlights the need for a tailored approach to systemic therapy, taking into account the unique characteristics of right-sided colon cancer. Their work calls for further investigation into the biological and molecular differences that may influence treatment responses and outcomes, thereby providing a foundation for future research aimed at improving therapeutic strategies for patients with colon cancer.

The article "The effect of the primary tumor location on the survival of colorectal cancer patients after radical surgery" by Cai et al. (Cai et al., 2018) provides a comprehensive examination of the prognostic implications associated with the primary tumor location in colorectal cancer, specifically contrasting left-sided and right-sided colon cancers. The authors present a systematic review that highlights significant differences in survival outcomes and clinicopathological features between these two groups of patients.

One of the key insights from the study is the observation that patients with left-sided colon cancer generally exhibit better long-term survival rates compared to those with right-sided colon cancer. This finding aligns with previous research suggesting that the biological behavior of tumors may differ based on their anatomical location, which could influence treatment responses and overall prognosis (Cai et al., 2018). The authors effectively synthesize data from multiple studies, reinforcing the notion that right-sided colon cancer is associated with a worse prognosis, particularly in stages I to III.

The article also delves into the prognostic and predictive relevance of primary tumor location, specifically in patients with RAS wild-type metastatic colorectal cancer. This aspect is crucial, as it underscores the need for tailored therapeutic approaches based on tumor laterality. The authors emphasize that right-sided colon cancers often present with distinct clinicopathological characteristics, which may

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necessitate different treatment strategies compared to left-sided cancers (Cai et al., 2018).

Furthermore, the systematic review outlines the implications of tumor laterality on recurrence rates and survival, drawing attention to the necessity for ongoing research into the molecular features that differentiate these cancer types. The authors advocate for a more nuanced understanding of how primary tumor location can impact treatment decisions and patient management.

The article "Impact of Tumor Location and Variables Associated With Overall Survival in Patients With Colorectal Cancer: A Mayo Clinic Colon and Rectal Cancer Registry Study" by Wang et al. presents a comprehensive analysis of the prognostic implications of tumor location in colorectal cancer (CRC). The authors emphasize the distinct biological behaviors and survival outcomes associated with left-sided versus right-sided colon cancers, highlighting the necessity of considering tumor sidedness as an independent variable in treatment planning.

One of the key insights from the study is the correlation between specific biomarkers and tumor location. Notably, the research identifies a significant association between elevated levels of C-reactive protein (CRP) and right-sided colon cancer. This finding suggests that inflammatory markers may play a role in the prognosis of CRC, particularly for patients with right-sided tumors, which tend to exhibit poorer survival outcomes compared to their left-sided counterparts . Furthermore, the expression of caudal-type homeobox transcription factor 2 (CDX2) is shown to be less prevalent in metastatic right-sided colon cancers, indicating a potential mechanism behind the differential metastatic behavior observed in these tumors.

The article also delves into the implications of microsatellite instability (MSI) on overall survival, revealing that the survival rates differ significantly between proximal and distal tumor locations. This aspect underscores the heterogeneity of CRC and suggests that MSI status may interact with tumor location to influence patient outcomes . The authors advocate for further investigations into the

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biological factors contributing to these disparities, which could ultimately enhance the understanding of tumor biology and improve therapeutic strategies.

In the article titled "Tumor sidedness is not an independent prognostic marker of colorectal cancer patients undergoing curative resection: A retrospective cohort study" by Chan et al. (Chung Yan Chan et al., 2019), the authors critically evaluate the role of tumor sidedness in determining the prognosis of colorectal cancer (CRC) patients who have undergone curative resection. The study's premise revolves around the ongoing debate regarding whether left-sided or right-sided colon cancer presents differing prognostic outcomes.

A key aspect of the study is its methodological approach, which included rectal cancer patients in the left-sided cancer group. This inclusion is justified by the authors as a means to align their findings with previous meta-analyses, particularly the work by Petrelli et al. (2017), which posited that sidedness could be a significant prognostic factor. However, the authors conducted a sensitivity analysis excluding rectal patients, and the results consistently indicated that tumor sidedness does not serve as an independent prognostic marker. This finding is critical, as it challenges the prevailing notion that the location of the tumor within the colon can singularly dictate survival outcomes.

The authors acknowledge several limitations inherent in their retrospective study design. Notably, the lack of comprehensive chemotherapy data due to fragmented patient record-keeping across multiple sites raises concerns about the robustness of their findings. Additionally, incomplete data on clinicopathological variables further complicates the interpretation of the results. These limitations underscore the necessity for caution when generalizing the findings to broader populations. The authors also point out that retrospective analyses inherently carry limitations when compared to prospectively validated studies, which are often more reliable in establishing causative relationships.

Moreover, the authors emphasize the importance of previously unaccounted biological factors that may influence survival outcomes. They suggest that future

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research should incorporate critical confounders, such as RAS mutation status, to provide a more comprehensive understanding of the relationship between tumor sidedness and prognosis. The call for further investigation into the continuum model of colorectal cancer is particularly noteworthy, as it acknowledges the complexity of the disease and the potential for significant regional differences in mutation profiles and cancer molecular subtypes (CMS).

The article "Primary Tumor Location as a Prognostic and Predictive Marker in Metastatic Colorectal Cancer (mCRC)" by Bahl et al. (Bahl et al., 2020) provides a comprehensive examination of the clinico-pathological differences between right-sided and left-sided colorectal adenocarcinomas and their implications for prognosis and treatment response. The authors effectively argue that the location of the primary tumor significantly influences both the biological behavior of the cancer and the patient's clinical outcomes.

One of the key insights presented in the article is the differential gene expression and mutation profiles associated with the two tumor locations. Right-sided colonic tumors are characterized by a higher incidence of microsatellite instability and are often linked to specific genetic signatures, such as RAS or BRAF mutations, and a serrated pathway of tumorigenesis. Conversely, left-sided tumors exhibit distinct molecular characteristics, including the activation of WNT and MYC pathways, along with beta-catenin activation and upregulation of growth factor receptors such as EGFR and HER2 (Bahl et al., 2020). This molecular divergence underscores the necessity for tailored therapeutic approaches based on tumor sidedness.

Furthermore, the article highlights that the prognostic implications of tumor location become increasingly significant as the disease progresses. The authors emphasize that while both right and left-sided tumors may initially present similarly, their clinical trajectories can diverge markedly, necessitating different management strategies. The evidence presented suggests that patients with right-sided tumors may have a poorer prognosis compared to those with left-sided

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tumors, which could be attributed to the underlying biological differences and the distinct pathways involved in tumor progression.

Moreover, the review discusses the clinical data supporting the impact of primary tumor location on treatment efficacy. For instance, the authors note that left-sided tumors tend to respond better to anti-EGFR therapies, while right-sided tumors may be less responsive due to their unique genetic profiles (Bahl et al., 2020). This finding is crucial for oncologists when considering treatment options for metastatic colorectal cancer, as it reinforces the importance of personalized medicine based on tumor characteristics.

The article titled "Sidedness is not a prognostic factor in an unselected cohort of patients with colon cancer but prognosis for caecal carcinoma is worse – A multivariate analysis of a large single institution database" by Stelzner et al. (Stelzner et al., 2024) presents a comprehensive examination of the prognostic implications of tumor sidedness in colon cancer, particularly focusing on the caecum and its associated outcomes.

The authors conducted a detailed multivariate analysis using a substantial dataset, which allows for robust statistical conclusions. They observed that tumors located in the caecum were generally more advanced, correlating with poorer prognostic outcomes. In contrast, tumors in the ascending colon tended to be less advanced, indicating a potential disparity in disease progression based on tumor location. Notably, the splenic flexure tumors exhibited the highest relative mortality, underscoring the complexity of colon cancer's anatomical variations and their implications for patient survival.

A critical aspect of the findings is the nuanced role of tumor sidedness in different stages of colon cancer. The authors highlight that while right-sided cancers (particularly those classified as T4 and N2) were associated with worse outcomes, the prognostic significance of sidedness diminished after statistical matching, particularly in stage III cancers. This suggests that while initial observations may

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indicate a trend favoring left-sided tumors, these differences may not hold when controlling for confounding variables, such as tumor stage and treatment factors.

Interestingly, the article underscores that sidedness does not serve as a reliable prognosticator for relapse-free survival in stage III tumors. However, once relapse occurs, patients with right-sided cancers face a significantly poorer prognosis. This finding aligns with previous literature suggesting that right-sided colon cancers may exhibit more aggressive biological behavior, which could contribute to their inferior outcomes post-relapse.

Furthermore, the authors emphasize the importance of adjuvant chemotherapy as an independent prognostic factor, reinforcing its role in improving survival outcomes in colon cancer patients. The analysis also references a national database study that corroborates the inferior outcomes associated with right-sided cancers, particularly when fewer than 22 lymph nodes are harvested during surgical intervention. This detail is crucial, as it suggests that surgical and pathological factors may also play a significant role in the overall prognosis of colon cancer.

The article titled "Clinical and molecular heterogeneity associated with tumor sidedness in colorectal liver metastasis: a multicenter propensity cohort study" by Wu et al. (Wu et al., 2024) offers a significant contribution to the understanding of prognostic survival differences between left-sided and right-sided colon cancer, particularly in the context of liver metastases. This multicenter study provides a comprehensive analysis of clinical and molecular characteristics that distinguish these two tumor types, revealing critical insights into their divergent prognoses.

One of the key findings of the study is the statistically significant positive prognostic impact of left-sided tumors, which was specifically noted in patients with KRAS wild-type tumors. This contrasts sharply with patients harboring KRAS mutations, who exhibited poorer outcomes regardless of the tumor's sidedness. This observation underscores the importance of molecular profiling in colorectal cancer (CRC), as it appears that the prognostic value of tumor sidedness is significantly influenced by KRAS mutational status. The authors emphasize that when molecular

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markers are included in multivariate analyses, the significance of sidedness diminishes, suggesting that KRAS mutations may serve as a more reliable prognostic indicator than tumor location alone (Wu et al., 2024).

Additionally, the study highlights the distinct molecular patterns associated with right-sided tumors, which were found to have a higher prevalence of somatic mutations in genes such as TP53, APC, KRAS, and BRAF. The increased frequency of these mutations, along with a higher incidence of pathogenic germline variants, points to a more complex biological behavior in right-sided tumors compared to their left-sided counterparts. The authors also note that right-sided tumors tend to present at a higher tumor stage and are more common in females, further contributing to the observed differences in clinical outcomes (Wu et al., 2024).

The authors propose that the embryological origins of the proximal and distal colon may help explain these disparities in tumor behavior and patient prognosis. This perspective is crucial for clinicians, as it suggests that left-sided and right-sided colorectal cancers should be approached as distinct clinical entities. The integration of tumor sidedness into treatment decision-making could enhance personalized therapeutic strategies, particularly in light of the findings regarding KRAS mutations and their implications for treatment efficacy (Wu et al., 2024).

CONCLUSION

The literature on prognostic survival associated with left-sided versus right-sided colon cancer reveals significant distinctions in clinical outcomes and treatment responses, influenced by a multitude of biological, pathological, and molecular factors. The foundational study by (Mik et al., 2017) established that right-sided colon cancers are often diagnosed at a more advanced stage, which raises concerns regarding the adequacy of surgical staging and lymph node assessment ((Mik et al., 2017)). This highlights the necessity for standardized surgical protocols to avoid misclassification of disease severity, which can impact long-term survival outcomes.

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Further investigations, such as those by (Zovak & Mužina Mišić, 2018), have indicated that while overall and disease-free survival rates post-surgery for stages I-III do not significantly differ between right- and left-sided colon cancers, there is a notable divergence in chemotherapy responses for disseminated disease ((Zovak & Mužina Mišić, 2018)). This suggests that treatment strategies should be tailored based on tumor sidedness, particularly in advanced cases.

(Bahl et al., 2020) reinforced the notion that left-sided colon cancer generally correlates with better long-term survival compared to right-sided tumors, emphasizing the importance of tumor location in treatment planning ((Bahl et al., 2020)). The systematic review conducted by further elucidated the correlation between specific biomarkers and tumor location, indicating that right-sided tumors often exhibit poorer survival outcomes due to distinct biological behaviors ().

Conversely, (Chung Yan Chan et al., 2019) challenged the idea of tumor sidedness being an independent prognostic marker, suggesting that confounding factors may obscure its true impact on survival outcomes ((Chung Yan Chan et al., 2019)). This perspective is echoed by (Stelzner et al., 2024), who noted that while right-sided tumors often present with worse outcomes, the prognostic significance of sidedness diminishes when controlling for other variables, such as tumor stage and treatment factors ((Stelzner et al., 2024)).

The study by (Bahl et al., 2020) highlighted the differential gene expression and mutation profiles associated with tumor location, reinforcing the need for personalized treatment approaches based on these biological differences ((Bahl et al., 2020)). Additionally, (Wu et al., 2024) emphasized that the prognostic advantages of left-sided tumors are particularly pronounced in patients with KRAS wild-type tumors, underscoring the importance of molecular profiling in prognostic assessments ((Wu et al., 2024)).

In conclusion, the literature collectively indicates that tumor sidedness plays a crucial role in the prognosis and treatment of colon cancer, with left-sided tumors generally associated with better outcomes. However, the complexity of the

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relationship between sidedness and survival outcomes is evident, as various studies highlight the influence of confounding factors, molecular characteristics, and treatment responses. As such, a nuanced understanding of these dynamics is essential for optimizing treatment strategies and improving patient management in colorectal cancer.

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