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Impact of Metastasectomy on Survival Outcomes in Colorectal Cancer: A Single Center Retrospective Study

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ABSTRACT

Aim: Metastasectomy is a significant intervention in metastatic colorectal cancer (mCRC) management. This study uniquely evaluates metastasectomy outcomes by metastatic site and underscores the critical role of R0 resection, offering real-world insights into tailored treatment strategies for mCRC. Our findings align with existing literature, particularly regarding the survival benefits of lung metastasectomy and the importance of achieving complete tumor resection

Methods: This retrospective cohort study included 73 patients with colon cancer who underwent metastasectomy between January 2014 and June 2023. Demographic, clinical, and treatment data were analyzed. Survival outcomes were assessed using Kaplan-Meier analysis.

Results: The median OS for the entire cohort was 40.4 months. Patients undergoing lung metastasectomy demonstrated the longest median survival (53.6 months), followed by liver (41.7 months) and intraabdominal metastasectomy (35.5 months). R0 resections were associated with improved OS (median: 69.6 months), while non-R0 resections had poorer outcomes. Synchronous metastases were linked to shorter OS than metachronous metastases, although the difference was not statistically significant (p=0.09).

Conclusion: Metastasectomy significantly improves survival outcomes in mCRC, with lung metastasectomy showing the most favorable results. Achieving R0 resection is crucial for optimizing survival benefits. These findings underscore the importance of individualized treatment planning in patients undergoing metastasectomy.

Keywords: Colorectal cancer, metastasectomy, prognosis, survival outcomes, treatment planning

Introduction

Metastasectomy, the surgical removal of metastatic tumors, has emerged as a significant intervention for the management of metastatic colorectal cancer (mCRC). The potential benefits of this procedure have been demonstrated in various clinical settings, highlighting its role in improving progression-free survival (PFS) and overall survival (OS) in patients. However, the real-world efficacy of metastasectomy remains a critical area of investigation, as clinical trials may not fully capture the diverse patient populations encountered in everyday practice.

Metastasectomy practices have significantly increased across various cancer types over the past decade. This rise is largely attributed to reports of favorable long-term outcomes, which have sparked growing interest in the procedure despite the limited high-level evidence available [1-3]. Metastasectomy, particularly in the context of renal cell carcinoma and colorectal cancer, has been associated with improved survival outcomes. However, the evidence is primarily based on retrospective studies and registry data rather than randomized controlled trials [1,4,5].

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A comprehensive study involving 1064 patients with mCRC in Türkiye revealed that metastasectomy significantly improved median PFS and OS. Specifically, patients who underwent metastasectomy had a median PFS of 13.5 months compared to 9.9 months for those who did not and a median OS of 47.3 months versus 24.3 months, respectively [6]. This underscores the potential of metastasectomy to extend survival in real-life clinical settings.

Further supporting these findings, a population-based analysis of stage 4 colon cancer patients demonstrated that metastasectomy was associated with improved survival across various age groups and tumor grades. The study found that patients who underwent metastasectomy had a favorable survival outcome, with a hazard ratio (HR) for OS ranging from 0.68 to 0.72, except for those aged 85 years and older [7]. This suggests that metastasectomy can benefit a broad spectrum of patients, although its efficacy may diminish with advanced age.

In elderly patients, the feasibility and benefits of metastasectomy have also been explored. A single-center experience with patients aged 70 years and older indicated that metastasectomy and local ablative treatments could significantly enhance OS. The study reported a median OS of 25.6 months, with metastasectomy being an independent factor associated with improved survival (HR: 0.22, $p<0.001$) [8]. This highlights the potential for surgical interventions to offer substantial survival benefits even in older populations.

The role of metastasectomy in conjunction with primary tumor resection (PTR) has been a subject of debate. An analysis of data from the National Cancer Data Base revealed that while PTR alone significantly improved survival, the addition of metastasectomy did not confer a statistically significant survival advantage over PTR alone. The median OS for patients undergoing PTR with metastasectomy was 20.5 months compared to 21.8 months for those undergoing PTR alone [9]. This finding suggests that while PTR is crucial, the incremental benefit of metastasectomy may vary depending on individual patient factors.

Institutional factors also play a role in the outcomes of metastasectomy. A study examining the impact of the type of treating institution found that patients treated at academic or research hospitals had better survival outcomes. The median survival for patients undergoing metastasectomy at these institutions was 22.4 months, significantly longer than at other types of institutions. Factors such as higher income regions, chemotherapy (ChT), and treatment at academic/research hospitals were positively associated with undergoing metastasectomy and improved survival [10]. This indicates the importance of a multidisciplinary approach and possibly regionalizing care to optimize outcomes for patients with metastatic colon cancer.

In addition to liver and lung metastases, metastasectomy has also been explored for less common metastatic sites such as the spleen. Although data on splenic metastases are limited, studies suggest that metastasectomy for isolated splenic metastases can achieve long-term survival, particularly when performed laparoscopically [11].

Despite the promising outcomes of metastasectomy, its role remains controversial in certain contexts. For example, aggressive surgical resection of the primary tumor without metastasectomy in patients with unresectable liver-only metastases does not appear to provide a survival benefit compared to ChT alone [12]. This indicates that the decision to perform metastasectomy should be carefully considered based on individual patient factors and the extent of the disease.

In summary, metastasectomy has shown significant promise in improving survival outcomes for patients with mCRC. Its benefits are evident across various patient demographics and clinical settings. However, the extent of its efficacy can be influenced by factors such as age, the presence of PTR, and the type of treatment. These findings underscore the need for a tailored approach to the management of mCRC, incorporating metastasectomy as a key component of treatment strategies. In this context, our study provides a unique contribution to the existing literature by offering site-specific survival outcomes and emphasizing the importance of achieving R0 resection within a single-center cohort.

Methods

Study Design and Patient Selection

This retrospective single-center cohort study analyzed the impact of metastasectomy on survival outcomes in patients diagnosed with colon cancer. The study included 73 patients who underwent metastasectomy at our institution between January 2014 and June 2023. Inclusion criteria required patients to have a histopathologically confirmed diagnosis of colon cancer, documented metastasectomy, and available clinical and follow-up data for OS and disease-free survival (DFS). Patients with incomplete clinical data or concurrent malignancies were excluded.

Data Collection

Data were retrospectively extracted from patients' medical records. Demographic details such as age and gender were recorded alongside clinical data, including Eastern Cooperative Oncology Group performance status, primary tumor location, RAS and MSI status, and location of metastases. Treatment data encompassed pre- and post-metastasectomy systemic therapies, such as ChT and targeted therapies. Survival outcomes included OS, defined as the time from metastatic disease to death from any cause.

Statistical Analysis

Descriptive statistics summarized patient demographics, clinical characteristics, and laboratory findings. Categorical variables were compared using chi-square or Fisher's exact tests, while continuous variables were analyzed with independent t-tests or Mann-Whitney U tests based on data distribution. Kaplan-Meier survival analyses were conducted to evaluate OS and DFS, with comparisons between groups assessed using the log-rank test. Cox proportional hazards regression models were used for univariate and multivariate analyses to identify factors

independently associated with survival outcomes. A p value of <0.05 was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences statistics 26.0 (IBM Corporation, Armonk, NY, USA).

Ethical Considerations

This study was conducted in compliance with the principles of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (decision no: 3/11/010.99/2024, date: 25.12.2024). As this was a retrospective study, informed consent was waived; however, all patient data were anonymized to ensure confidentiality.

Results

A total of 73 patients were involved in the study. The median follow-up time was 24 months (range, 1-74), and the median age was 59 years (range, 36-84). Thirty-one (42.5%) patients were women. The proportion of patients with primary right colon cancer was determined to be 35.6%. Synchronous metastasis was detected in 50.7% of those who underwent metastasectomy. Isolated liver metastasectomy was performed in 68.5% of the patients, while 17.8% had lung metastasectomy, and the remaining 13.7% had intraabdominal metastasectomy. It has been shown that 2.3% of the patients have MSI-H, 47.4% have Ras mutation, and 6.9% have a mucinous component. Metastasectomy was performed after conversion therapy in 9.6% of patients (Table 1).

The median OS was 40.4 months [95% confidence interval (CI): 29.0-51.8] in the whole group (Figure 1).

The median survival time for patients with synchronous metastases was 35.5 months (95% CI: 22.3-48.7), compared to 47.5 months (95% CI: 33.2-61.8) for those without synchronous metastases. Although the median survival appeared longer in patients without synchronous metastases, the difference did not reach statistical significance (p=0.09) (Figure 2).

Table 1. Baseline characteristics of patients undergoing metastasectomy

Characteristic	n (%)
Total patients	73
Median follow-up time (months)	24 (1-74)
Median age (years)	59 (36-84)
Female patients	31 (42.5%)
Primary right colon tumors	26 (35.6%)
Synchronous metastasis	37 (50.7%)
Isolated liver metastasectomy	50 (68.5%)
Lung metastasectomy	13 (17.8%)
Intraabdominal metastasectomy	10 (13.7%)
MSI-H	2 (2.3%)
Ras mutation	35 (47.4%)
Conversion therapy before metastasectomy	7 (9.6%)
R0 resection	49 (67.1%)

The analysis of survival outcomes across different metastasectomy sites revealed significant differences in median survival times. Patients who underwent lung metastasectomy had the longest median survival of 53.6 months (95% CI: 2.1-105.1), indicating a more favorable prognosis than metastasectomy at other sites. Liver metastasectomy was associated with a median survival of 41.7 months (95% CI: 24.5-58.9), while intraabdominal metastasectomy showed the shortest median survival of 35.5 months (95% CI: 0.7-70.3). Pairwise comparisons using the log-rank test did not reveal statistically significant differences between the metastasectomy sites, liver vs. lung (p=0.989), liver vs. intraabdominal (p=0.429), and lung vs. intraabdominal (p=0.278). These findings suggest that while there are observable differences in median survival across metastasectomy sites, the variations are not statistically significant (Figure 3).

Among 73 patients, R0 resection was achieved in 52 (71.2%), while 11 (15.1%) had R1, and 10 (13.7%) had R2 resections. Among R0 resections, 48.1% received no targeted therapy, 30.8% were treated with ChT and anti-vascular endothelial growth factors (VEGF), and 21.2% were treated with ChT and anti-epidermal growth factor receptor (EGFR) treatment. In R1-2 resections, ChT with anti-VEGF was most common (76.2%), followed by ChT with anti-EGFR (14.3%) and ChT with no targeted therapy (9.5%).

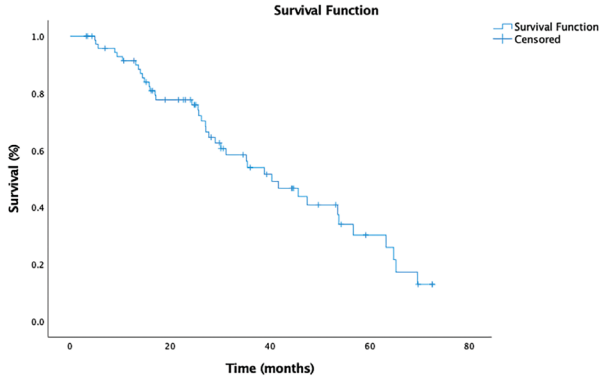

Figure 1. The Kaplan-Meier survival curve displays the overall survival function for the entire cohort

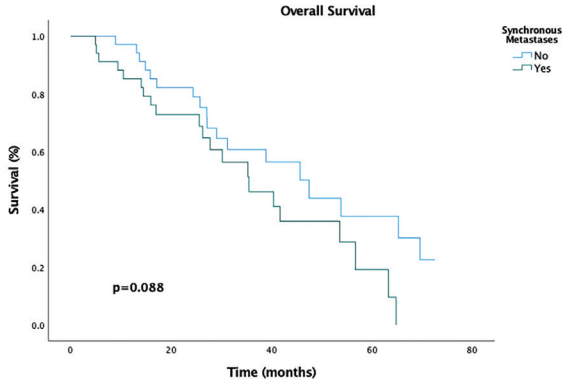

Figure 2. The Kaplan-Meier survival curve illustrates the overall survival of patients stratified by the presence of synchronous metastases

Patients who underwent R0 resection had a median survival of 45.7 months (95% CI: 25.4-66), compared to 35.3 months (95% CI: 19.9-50.7) for non-R0 resection patients. Survival outcomes showed that in R0 resections, non-targeted therapy with ChT had the highest median survival at 69.6 months (95% CI: NA), compared to 45.7 months (95% CI: 31.9-59.5) for anti-EGFR and 35.5 months for anti-VEGF (95% CI: 26.0-45.0) (Figure 4).

Pairwise comparisons using the log-rank test did not reveal statistically significant differences in survival distributions between the treatment groups: no targeted therapy versus anti-EGFR (p=0.66); no targeted therapy versus anti-VEGF (p=0.80); and anti-EGFR versus anti-VEGF (p=0.74). The overall comparison of survival distributions across all groups also yielded no statistically significant differences (p=0.889) (Figure 5).

For R1-2 resections, median survival was lowest with no targeted therapy (4.9 months, n=2), while ChT with either anti-VEGF or anti-EGFR showed 38.9 months (95% CI: 23.4-54.4) and 47.5 months (95% CI: 0-115.2), respectively. There were no significant survival differences between anti-VEGF and anti-EGFR treatments (p=0.08).

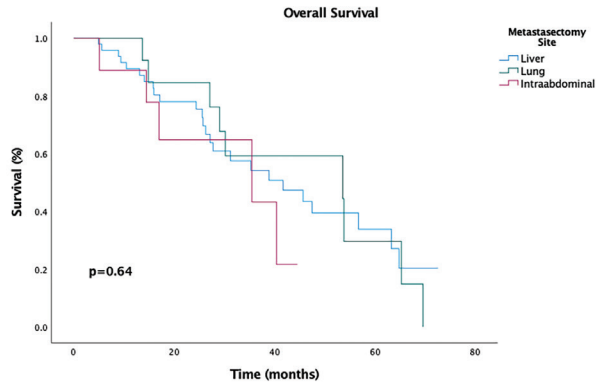

Figure 3. Kaplan-Meier survival curve demonstrates overall survival stratified by metastasectomy site

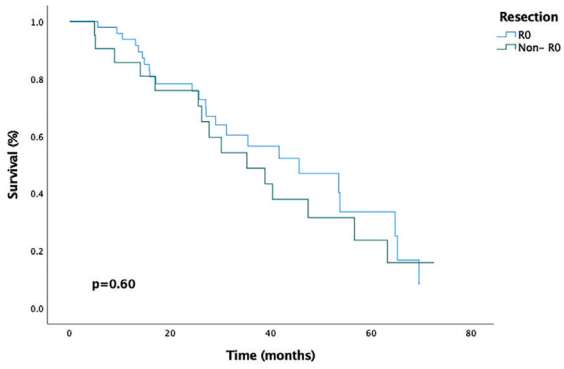

Figure 4. Kaplan-Meier survival curve illustrates OS in patients receiving adjuvant ChT after R0 metastasectomy, stratified by treatment type

OS: Overall survival, ChT: Chemotherapy

Discussion

The survival advantage of metastasectomy in mCRC is well-documented. Patients undergoing metastasectomy, have shown significantly improved OS compared to those who did not undergo the procedure [13,14]. For instance, a study reported that patients who received lung metastasectomy had a median OS that was not reached, compared to 41.4 months for those who did not undergo surgery, with an HR for death of 0.27 (95% CI: 0.14-0.53, p<0.001) [15]. Similarly, another study found that mCRC patients who underwent metastasectomy had a median OS of 54.9 months compared to 28.6 months for those who did not (p<0.001) [16].

The analysis of survival outcomes following metastasectomy in mCRC patients reveals significant benefits, particularly when considering the site of metastasis. Patients undergoing lung metastasectomy exhibit the longest median survival, with a median of 53.6 months (95% CI: 2.1-105.1), suggesting a more favorable prognosis than other metastatic sites. This aligns with findings that highlight the potential for long-term survival in patients with isolated pulmonary metastases, where a 5-year survival rate can exceed 50% in selected cases [17-19]. In a randomized controlled trial, the PulMiCC study, the 5-year survival rate for patients undergoing lung metastasectomy was estimated at 38%, compared to 29% in the control group, suggesting a modest survival benefit [20].

The potential mechanisms underlying the observed survival differences between metastasectomy sites may relate to both anatomical and biological factors. Rectal cancers, for instance, tend to metastasize more frequently to the lungs, while colonic cancers more commonly spread to the liver and peritoneum [21]. The unique microenvironments of these metastatic sites likely play a role in determining treatment outcomes. Lung metastases are often more amenable to complete surgical resection due to their isolated and localized nature than peritoneal metastases, which are often diffuse and associated with a worse prognosis. Furthermore, the liver's

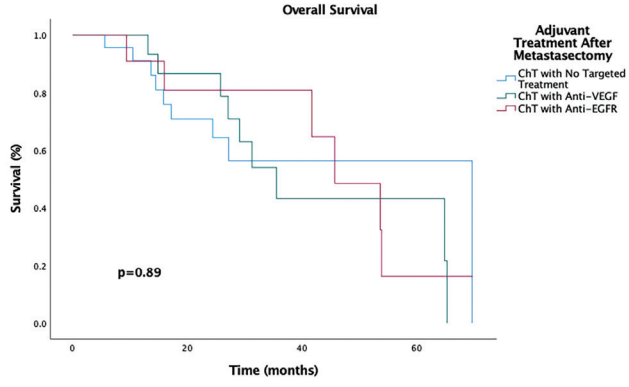

Figure 5. Kaplan-Meier survival curve illustrates OS in patients receiving adjuvant ChT after R0 metastasectomy, stratified by treatment type

OS: Overall survival, ChT: Chemotherapy, VEGF: Vascular endothelial growth factor, EGFR: Epidermal growth factor receptor

dual blood supply and susceptibility to hematogenous spread make it a common metastatic site, but a target for effective interventions like hepatic metastasectomy, which has shown significant survival benefits when feasible.

Another factor is the biology of the metastatic tumors themselves. Lung metastases from rectal cancer may exhibit distinct molecular profiles that make them more responsive to systemic therapies or surgical interventions. For instance, KRAS mutations are more common in liver and peritoneal metastases, correlating with poorer prognosis. In contrast, lung metastases may exhibit molecular features associated with better response to targeted therapies or immunotherapy [21]. Improved surveillance and surgical techniques for lung metastasectomy could also contribute to better outcomes [18,19].

Liver metastasectomy also demonstrates a substantial survival benefit, with a median survival of 41.7 months (95% CI: 24.5-58.9). This is consistent with historical data showing that resection of hepatic metastases can lead to improved outcomes, with 5-year survival rates ranging from 20% to 50% [22]. However, the survival benefit is less pronounced compared to lung metastasectomy, possibly due to the complexity and extent of liver involvement in mCRC [23].

Intraabdominal metastasectomy, however, is associated with the shortest median survival of 35.5 months (95% CI: 0.7-70.3). This may reflect the challenges in achieving complete resection and the aggressive nature of intraabdominal metastases [24]. Despite these challenges, surgical intervention in selected patients can still offer survival benefits, particularly when combined with systemic therapies [22].

The role of metastasectomy is further supported by studies indicating that patients who undergo the procedure have better OS and PFS than those who do not. For instance, patients receiving lung metastasectomy had a median OS benefit, with an HR for death of 0.27, indicating a significant reduction in mortality risk [15]. Similarly, patients undergoing metastasectomy during cetuximab-based therapy showed improved OS and PFS, highlighting the importance of integrating surgical and systemic treatments [16].

The median survival time for patients with synchronous metastases was 35.5 months (95% CI: 22.3-48.7), compared to 47.5 months (95% CI: 33.2-61.8) for those with metachronous metastases. Although a trend toward longer survival was observed in patients with metachronous metastases, the difference did not reach statistical significance (p=0.09). This finding aligns with prior studies reporting poorer outcomes in synchronous metastases than in metachronous cases [25]. However, advancements in surgical techniques and systemic therapies may have narrowed the survival gap between these groups [26].

The success of metastasectomy, particularly R0 resection, is influenced by several factors. Patients with a single metastatic location, metachronous metastatic disease, and no BRAF mutation were more likely to benefit from lung metastasectomy [15]. Additionally, a resected primary tumor and low carcinoembryonic antigen levels were associated with better outcomes [15].

Conversely, factors such as non-R0 resection, multiple metastatic sites, and synchronous metastasis were predictors of worse OS [27]. The importance of achieving R0 resection is underscored by its association with improved survival outcomes, as incomplete resection (non-R0) is linked to poorer prognoses [27].

Despite the promising outcomes, the decision to perform metastasectomy must be carefully considered. Factors such as the site of metastasis, the patient's performance status, and the potential for complete resection play crucial roles in determining the likelihood of success [24]. Moreover, while metastasectomy offers survival benefits, the risk of recurrence remains high, necessitating a comprehensive treatment approach that may include systemic therapies [28].

Study Limitations

This study has several limitations. First, its retrospective single-center design may limit the generalizability of the findings to broader patient populations and healthcare settings. The relatively small sample size of 73 patients reduces the statistical power to detect subtle differences, particularly in subgroup analyses, such as those stratified by metastasectomy site or synchronous versus metachronous metastases. Additionally, the lack of randomization introduces potential selection bias, as patients undergoing metastasectomy may inherently differ in baseline characteristics or disease biology compared to those not undergoing the procedure. To address selection bias, future studies should incorporate prospective designs with predefined inclusion and exclusion criteria, focusing on comprehensive patient stratification.

Moreover, detailed data on post-metastasectomy systemic therapies were not comprehensively analyzed, which could influence survival outcomes. The study also did not account for potential confounders such as comorbidities or socioeconomic factors that might impact treatment decisions and survival. Finally, while Kaplan-Meier and Cox regression analyses were employed to evaluate survival outcomes, the observational nature of the study precludes definitive conclusions about causality between metastasectomy and improved survival.

Conclusion

Metastasectomy significantly improves survival in metastatic colorectal cancer, particularly in patients undergoing lung metastasectomy and achieving R0 resection. Further multicenter, prospective studies are warranted to validate these findings and explore the potential mechanisms underlying the survival benefits associated with metastasectomy.

Ethics

Ethics Committee Approval: Approval was obtained from the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2024/010.99/11/3, date: 25.12.2024).

Informed Consent: Retrospective study.

Declaration Regarding the Use of AI and AI-Assisted Technologies: In the preparation of this manuscript, AI tools, including Translate GPT and Paperpal-AI, were utilized for translation and grammar checks. Their incorporation primarily impacted the language refinement process, ensuring accuracy, clarity, and consistency in the presentation of the text. After carefully reviewing and editing the content as necessary, the authors take full responsibility for the publication's content.

Footnotes

Authorship Contributions

Concept: O.K., Design: O.K., D.I., Data Collection or Processing: G.A., S.Y., H.Ş.Y., A.D., Analysis or Interpretation: Y.E.A., U.Ö., S.Ö., A.T., Literature Search: O.K., T.B., S.A., H.O., N.T., H.S., Writing: O.K.

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