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Cohort Study

Survival and prognostic factors of isolated pulmonary metastases originating from colorectal cancer: An 8-year single-center experience

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ABSTRACT

Background: Isolated pulmonary metastasis (IPM) is a rare entity that accounts for 10% of pulmonary metastases seen in colorectal cancer (CRC). This study aims to evaluate the overall 5-year survival of IPM originating from CRC and identify potential prognostic factors affecting the overall survival (OS).

Methods: A retrospective cohort study conducted in a tertiary care center. The study included all patients diagnosed with CRC aged 18–75 years who underwent primary tumor resection with curative intent between 2008 and 2015, and developed IPM. Patients with no follow-up and those with extra-pulmonary metastases were excluded.

Results: The prevalence of IPM in the overall CRC cases was 4.18% (20/478 patients). The mean age of patients with IPM was 52.7 ± 12.9 years. Ten patients had synchronous IPM (50%), thirteen had unilateral (65%), and eleven underwent metastasectomy (55%). The 5-year OS was 40%, and the mean OS was 3.12 ± 1.85 years. Several factors were found to be associated with a favorable outcome, which include unilateral IPM (3.69 vs. 2.07 years; P = 0.024), metachronous (4.25 vs. 2.14 years; P = 0.017), metastasectomy (4.81 vs. 1.83 years; P = 0.005). In addition, mortality was likely to be decreased by more than 90% after metastasectomy (unadjusted odds ratio = 0.071; 95% confidence interval [CI] = 0.01–0.8; P = 0.032).

Conclusions: Forty percent of the included patients survived the 5-year follow-up. Better survival was associated with the metastases being unilateral, metachronous, and metastasectomy. Mortality was lower in patients with pulmonary recurrence after metastasectomy.

1. Introduction

The burden of colorectal cancer (CRC) has been increasing due to the increased incidence of colorectal cancer worldwide [1]. Almost 50% of CRC patients develop distant metastasis, with pulmonary metastasis counting for 15% of them, making it the second most common site for metastasis [2,3]. The liver is considered the primary site of metastases from CRC due to its anatomical venous drainage via the portal system. However, several reports have described metastasis to the lung that bypasses the liver [3–5].

Isolated pulmonary metastasis (IPM) accounts only for 10% of pulmonary metastasis and is usually encountered in patients with rectal cancer [3]. This has been attributed to the rectum's direct hematogenous drainage into the systemic circulation [6,7]. However, IPM that originates from the colon has also been reported in the literature [3]. Factors that are reported to be associated with IPM include left-sided colon cancer, advanced T-stage, mutated genes (e.g., KRAS), presence of nodal disease in rectal cancers, and elevated carcinoembryonic antigen levels [3,8].

IPM is a rare and incompletely understood entity. Countable reports

Abbreviations: CRC, Colorectal cancer; IPM, Isolated pulmonary metastasis; OS, Overall survival; DFI-1, Disease-free interval 1; DFI-2, Disease-free interval 2; CT, Computed tomography; SD, Standard deviation; IQR, Interquartile range; CI, Confidence interval; UOR, Unadjusted odds ratio.

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have been published on IPM with controversial findings. For example, pulmonary metastasectomy has been suggested as a potentially curative option in IPM [9–17]; however, evidence is still controversial in identifying patients who may benefit the most from surgical resection. The lack of consensus regarding the management of affected patients is mainly attributable to its relative rarity and the absence of randomized controlled trials (RCT) comparing therapeutic options. Several barriers exist, which have resulted in the lack of RCTs, including ethical dilemmas and methodological and practical challenges.

Data on the survival of IPM vary considerably between studies. The 5-year survival rates range from 40% to 69.7% [4,5,18–20]. Several predictors of survival have been reported [9,10,13–17,21]; nevertheless, variations have been widely observed on multiple factors [20,22]. Furthermore, the clinical utilization of the proposed prognostic factors has not been implemented for clinical use [22,23]. Moreover, the methodological differences between the available studies limit meaningful comparisons.

Due to the scarcity of evidence, defining the overall survival (OS) and potential prognostic factors of IPM will contribute to the existing evidence. Therefore, this study's primary aim was to evaluate the overall 5-year survival outcome of IPM originating from CRC. The secondary aim was to identify potential prognostic factors affecting the OS rate.

2. Methods

2.1. Study design and setting

This is a retrospective cohort study conducted at a referral tertiary center, King Fahad Specialist Hospital-Dammam (KFSH-D), Saudi Arabia. This study was approved by the institutional board review (IRB) of the KFSH-D. We present this original observational study in accordance with the STROCSS criteria (Strengthening the reporting of cohort studies in surgery) [24]. This study is registered with the Research Registry, and the unique identifying number (UIN) is: researchregistry7598 [25].

The study included all patients who were diagnosed with CRC, between 18 and 75 years old, underwent resection of CRC with curative intent between 2008 and 2015, and developed IPM either at presentation, during treatment, or follow-up. Patients who had an unresectable primary lesion were excluded. Patients with unrecorded post-operative follow-up and patients with metastasis to organs other than the lungs, whether initially or during treatment, were also excluded.

2.2. Data collection

All the variables were pre-defined and collected retrospectively from the hospital's national cancer registry, operation room records, and laboratory records. The variables of interest included the following: patient characteristics (age, gender, and comorbidities), characteristics of both the primary tumor (anatomical location; tumor, nodes, and metastasis [TNM] staging; tumor size; and histopathological reports), and the IPM (anatomical location, disease-free interval [DFI], number of lesions, lymph node involvement, and pulmonary recurrence), laboratory findings (tumor markers and genetic testing), and management of both the primary tumor and IPMs (surgery, chemotherapy, and/or radiotherapy). In addition, two independent authors reviewed the data to ensure the accuracy of data retrieval.

2.3. Five-year surveillance program

All patients who underwent surgery for either colon or rectal cancer were part of a 5-year surveillance program according to the National Comprehensive Cancer Network 2019 guidelines, which are used by all colorectal surgeons at the center. The plan includes follow-up every 3 months, with carcinoembryonic antigen levels for the first 2 years and every 6 months for the following 3 years; surveillance via colonoscopy 1 year after the surgery; and computed tomography (CT) scans of the chest, abdomen, and pelvis every year for 5 years. In addition, a high-resolution CT scan of the chest was performed for those who had newly developed pulmonary lesions on the CT chest, abdomen, and pelvis.

2.4. Definition of colon and rectal cancer and isolated pulmonary metastases

Right-sided colon cancer was defined as a tumor located anywhere between the cecum and the proximal one-third of the transverse colon, while left-sided colon cancer was defined as a tumor in the distal two-thirds of the transverse colon up to the rectosigmoid junction. The rectal cancer classification was based on pelvic magnetic resonance imaging, which divides the rectum into three parts, with the upper third starting from the rectosigmoid junction and spanning of 5 cm, the middle third is the subsequent 5 cm, and the lower third is the remaining distal 5 cm. IPM was defined as the definitive presence of pulmonary metastatic nodules at the time of diagnosis of CRC or during the follow-up period (i.e., 5 years), with the absence of metastasis to other sites. The presence of nodules was confirmed by histopathology or imaging. Metastatic nodules were divided into three categories: solitary nodule, two nodules, and multiple metastases (>2 nodules).

The IPMs were also categorized into either synchronous metastasis (detected within 6 months of the CRC diagnosis) or metachronous metastasis (detected >6 months after CRC diagnosis). The interval between the onset of diagnosis of the CRC and the IPM detection was defined as the first DFI (DFI-1). Thoracic lymph node involvement was determined based on the CT thorax and/or positron emission tomography (PET) scan. Furthermore, the involvement of lymph nodes was divided into mediastinal or other thoracic lymph nodes.

2.5. Statistical analysis

Quantitative data are presented using the mean $\pm$ standard deviation (SD) or the median and interquartile range (IQR). Qualitative data are presented as counts and proportions (%). The relationships between different dependent variables were assessed using Fisher's exact test. Normality tests were conducted using the Shapiro–Wilk test, where a p-value <0.05 was considered to represent skewed data. To compare quantitative variables, the Mann–Whitney U test was used. A p-value of ≤ 0.05 (two-sided) indicated statistical significance for all analyses. Univariate regression analysis was conducted to predict the significant independent factors that were associated with mortality where both the crude ratio and the 95% confidence interval (CI) are reported. Survival analysis (Kaplan–Meier) was performed to measure the survival time between the variable of interest and time (years of survival), including a survival plot and the survival mean and CI of the mean. A log-rank test was used to compare the survival trends between the two groups. All data analyses were performed using the Statistical Package for Social Sciences, version 21 (SPSS, Chicago, IL, USA).

3. Results

Of all patients diagnosed with CRC, 478 patients had a resectable CRC (Fig. 1). After applying the eligibility criteria, 20 patients were included. The prevalence of IPM from resectable CRC in our study population was 4.18%. The primary CRC lesion was colonic in 11 patients (3.24%, 11/339) and rectal in nine patients (6.47%, 9/139). No patient in the study population was lost to follow-up.

The mean age of the patients at the time of CRC diagnosis was 52.7 $\pm$ 12.9 years; 11 patients (55%) were male (Table 1). At the time of CRC diagnosis, ten patients (50%) had a stage 4 disease, while nine patients (45%) had stage 3, and only one patient (5%) had stage 2 disease. The status of the primary tumor's depth of invasion (T) was found to be advanced (T3 or T4) in 19 patients (95%), and nodal involvement ($\geq$N1) was observed in 16 patients (80%). All primary tumors were confirmed

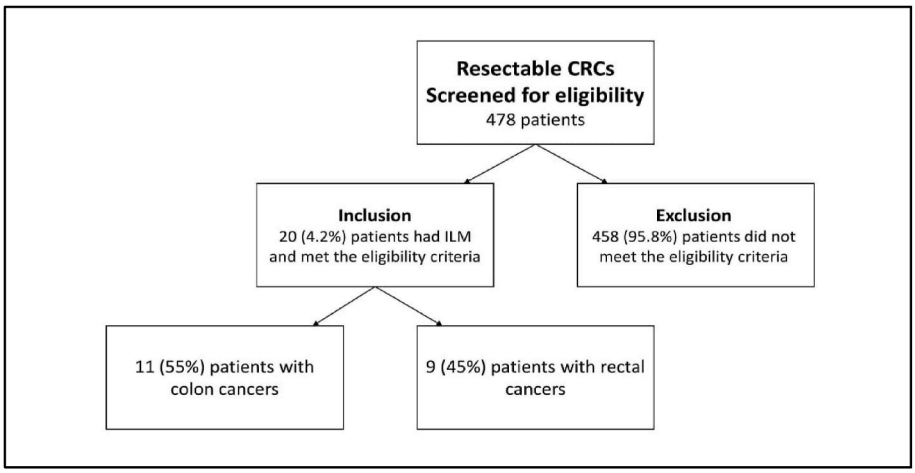

Fig. 1. Flow chart of the study recruitment.

histopathologically to be adenocarcinoma. Genetic screening was available for 18 patients, among whom mutated KRAS was detected in eight patients (44.4%). There was no correlation between the KRAS gene and the TNM classification.

IPM was unilateral in 13 patients (65%) and bilateral in seven patients (35%) (Table 2). Eleven patients had synchronous, and eight patients had metachronous pulmonary metastases. The overall median DFI-1 was 0.5 months (IQR, 0.0–14.75). Most patients (80%) had multiple pulmonary metastases. Six patients (30%) had mediastinal lymph node involvement, two patients (10%) had other thoracic lymph node involvement, and the rest did not have any nodal involvement.

Eleven patients underwent metastasectomy with curative intent, six patients were managed with chemotherapy alone, one patient was managed using palliative chemotherapy, and only two patients were managed conservatively. Among the patients with multiple lesions, 50% underwent metastasectomy. The categorical number of pulmonary metastases, quantitative number of pulmonary metastases, and bilateral metastasis were compared in the metastasectomy and non-operative management groups and showed no statistical difference ($P = 0.591$, $P = 0.904$, and $P = 0.642$, respectively; Table 3). There was no 30-day postoperative mortality among the patients who underwent pulmonary metastasectomy. Among the 11 patients who underwent surgery, six patients (54.5%) developed pulmonary recurrence during surveillance, five of whom received additional chemotherapy. Specifically, four patients were managed with adjuvant chemotherapy with curative intent, while only one patient received adjuvant chemotherapy with palliative intent.

The 5-year OS rate of CRC patients with IPM was 40%, and the overall mean survival was 3.12 ± 1.85 years (95% CI, 2.33–3.91). Specifically, the mean survival of colon cancer patients was 3.41 years (95% CI, 2.26–4.56), while for rectal cancer patients, it was 2.78 (95% CI, 1.77–3.79); with no significant difference ($P = 0.273$; Fig. 2A). In addition, the mean survival of patients <55 years was 2.73 years (95% CI. 1.69–3.77) compared to patients ≥55 years, which was 3.61 years (95% CI = 2.48–4.74). However, this difference was not statistically significant ($P = 0.239$; Fig. 2B).

The mean survival for unilateral pulmonary metastases was 3.692 years (95% CI, 2.684–4.701) compared to bilateral pulmonary metastases, which was 2.071 years (95% CI, 1.205–2.938). Bilateral metastases demonstrated statistically significant worse outcomes compared to unilateral lesions ($P = 0.024$; Fig. 2C). Additionally, the mean survival of patients who underwent pulmonary metastasectomy was 4.182 years (95% CI, 3.524–4.840), which was significantly worse (1.833 years; 95% CI, 0.766–2.900) in patients who did not undergo pulmonary metastasectomy ($P = 0.005$; Fig. 2D).

Additionally, the mean survival of patients with a mutated KRAS gene was 2.375 years (95% CI, 1.081–3.669), while the mean survival of patients with a wild-type KRAS gene was 3.750 years (95% CI, 2.799–4.799). Despite the trends shown by the KRAS status on years of survival, the difference was not statistically significant ($P = 0.119$; Fig. 2E). Patients with metachronous nodules had a mean survival of 4.250 years (95% CI, 3.579–4.921), which was statistically significant for a favorable outcome compared to patients with synchronous IPM (2.136 years; 95% CI, 1.112–3.161; $P = 0.017$; Fig. 2F).

Patients with pulmonary recurrence had significantly better survival compared to patients who had no pulmonary recurrence ($P = 0.018$). However, other variables such as gender, comorbidity, stage at the time of diagnosis, TNM staging, and KRAS gene status had no impact on the OS (Table 4). The correlation between cancer's anatomical origin (colon or rectum) and three different independent variables (KRAS gene status, unilateral metastases, or bilateral metastases) were insignificant. In addition, there was no relationship between KRAS gene status and having metachronous, synchronous, unilateral, or bilateral metastases.

The risk of mortality for patients who had pulmonary metastasectomy was likely to decrease by >90% compared to those who did not undergo metastasectomy (unadjusted odds ratio [UOR], 0.071; 95% CI, 0.006–0.799; $P = 0.032$; Table 5). In addition, we observed that the risk of mortality for patients with pulmonary recurrence was also likely to decrease by 95% compared to those with no pulmonary recurrence (UOR, 0.055; 95% CI, 0.004–0.663; $P = 0.022$).

4. Discussion

In our cohort, the prevalence of IPM was 4.18%. Consistent with the literature, a prevalence of 3.24% was observed for colonic resections compared to 6.4% for rectal lesions. However, Tan et al. showed the incidence of definitive IPM from primary colon and rectal cancer to be 1.3% and 3.1%, respectively, regardless of resectability [3], while Mitry et al. reported a prevalence of IPM of 3.38% [26]. IPM from primary colon cancer is of particular interest because of the precise mechanism by which cancer bypasses its first draining solid organ [1]. Several theories suggest that the differences in the metastasis site could be related to differences in tumor biology, anatomical location, or the "seed-and-soil" hypothesis [3,4,27,28].

Although the DFI is studied frequently as a prognostic factor, a clear and unanimous cut-off value has not been established. The apparent association between the DFI and survival might be because the definition of DFI is variable between different studies in the literature. While some studies define DFI as the interval between the primary tumor's surgery and the detection of pulmonary metastasis [18,19,29,30], others define it as the time interval between the last metastasectomy and recurrence, death, or the last follow-up [4,31]. Additionally, some

Table 1
Demographic and primary tumor characteristics (n = 20).

Study variables	N (%)
Demographics:	
Age at diagnosis (mean ± SD)	52.7 ± 12.9
• <55 years	11 (55.0%)
• ≥55 years	09 (45.0%)
Gender:	
• Male	11 (55.0%)
• Female	09 (45.0%)
Comorbidity:	
• None	10 (50.0%)
• Hypertension	05 (25.0%)
• Diabetes mellitus and hypertension	02 (10.0%)
• Diabetes mellitus	01 (05.0%)
• Inflammatory bowel disease	01 (05.0%)
• Chronic obstructive pulmonary disease (COPD)	01 (05.0%)
Smoking:	
• Yes	03 (15.0%)
• No	17 (85.0%)
KRAS mutation status: [a]	
• Mutated	08 (44.4%)
• Wild	10 (55.6%)
Primary tumor characteristics:	
Pre-operative carcinoembryonic antigen level:	
• ≤5 ng/ml	6 (33.3%)
• >5 ng/ml	12 (66.7%)
Type of resection of the primary tumor:	
• Right hemicolectomy	03 (15.0%)
• Left hemicolectomy	02 (10.0%)
• Low anterior resection	15 (75.0%)
Anatomical location of the primary tumor:	
• Colon:	11 (55.0%)
- Right	03 (27.3%)
- Left	08 (72.7%)
• Rectum:	09 (45.0%)
- Upper	03 (33.3%)
- Middle	03 (33.3%)
- Lower	03 (33.3%)
Size of the primary tumor (mean ± SD)	5.15 ± 2.59
Pathological characteristics:	
Tumor status:	
• T1	0 (0.0%)
• T2	01 (05.0%)
• T3	09 (45.0%)
• T4	10 (50.0%)
Nodal status:	
• N0	04 (20.0%)
• N1	03 (15.0%)
• N2	12 (60.0%)
• N3	01 (05.0%)
Metastasis status:	
• M0	10 (50.0%)
• M1	10 (50.0%)
Grading:	
• Moderate	19 (95.0%)
• Poor	01 (05.0%)
Resection margin:	
• R0	19 (95.0%)
• R1	01 (05.0%)
Staging at time of diagnosis:	
• Stage 1	0 (0.0%)
• Stage 2	01 (05.0%)
• Stage 3	09 (45.0%)
• Stage 4	10 (50.0%)

[a] Missing cases were excluded from the analysis.

studies [18,20,32,33] suggested that a DFI greater than 24 or 36 months is a good prognostic factor, and a DFI of less than 12 months is a poor prognostic factor [9]. Clarity regarding the impact of DFI on metastasectomy outcomes could aid in selecting patients who are most likely to benefit from metastasectomy [9,34,35].

In our study, the median DFI of all patients was 0.5 (IQR, 0.0–14.75) months. This contrasts with the findings of Kumar et al. who reported a

Table 2
Characteristics of isolated pulmonary metastasis (n = 20).

Study variables	N (%)
Pulmonary metastasis location:	
• Unilateral:	13 (65.0%)
- Right	07 (53.8%)
- Left	06 (46.2%)
• Bilateral	07 (35.0%)
Number of pulmonary metastasis:	
• One lesion	04 (20.0%)
• Multiple lesions	16 (80.0%)
Thoracic lymph nodes involvement:	
• Mediastinal lymph node	06 (30.0%)
• Other thoracic lymph node	02 (10.0%)
• No lymph node involvement	12 (60.0%)
Are they operated for pulmonary metastases?	
• Yes	11 (55.0%)
• No	09 (45.0%)
Type of chemotherapy: [a]	
• Adjuvant	05 (27.8%)
• Neoadjuvant	07 (38.9%)
• Neoadjuvant and adjuvant	03 (16.66%)
• None	03 (16.66%)
Type of radiotherapy: [a]	
• Adjuvant	01 (6.25%)
• Neoadjuvant	0 (0.0%)
• None	15 (93.75%)
Pulmonary recurrence:	
• Yes	06 (30.0%)
• No	14 (70.0%)
Time of IPM diagnosis:	
• Synchronous	11 (57.9%)
• Metachronous	8 (42.1%)
Overall disease-Free interval-1, Median (IQR), months	0.5 (0.0–14.75)
Disease free interval of the colon metastases, Median (IQR), months	13 (0.5–18)
Disease free interval of the rectal metastases, Median (IQR), months	0.0 (0.0–21.5)
Disease free interval of the metachronous IPM, Median (IQR), months	15.5 (13.25–25)
Overall-Survival (mean ± SD)	3.12 ± 1.85
•1 year	17 (85.0%)
•3 years	14 (70.0%)
•5 years	08 (40.0%)
Overall outcome (5-years):	
• Non-survivors	12 (60.0%)
• Survivors	08 (40.0%)

[a] Missing cases were excluded from the analysis.

Table 3
Comparison of metastatic characteristics between operative versus non-operative groups.

Factor	Entire study (n = 20)	Metastasectomy N (%) (n = 11)	Non-operative N (%) (n = 9)	P-value
Qualitative Data [a]				
Age:				
• <55 years	11 (55.0%)	5 (54.5%)	5 (45.5%)	1.000
• ≥55 years	9 (45.0%)	5 (55.6%)	4 (44.4%)	
Presence of comorbidity:				
• One or more	10 (50%)	6 (60.0%)	4 (40.0%)	1.000
• None	10 (50%)	5 (50.0)	5 (50.0%)	
Metastasis side:				
• Unilateral	13 (65.0%)	8 (61.5%)	5 (38.5%)	0.642
• Bilateral	7 (35.0%)	3 (42.9%)	4 (57.1%)	
Number of pulmonary metastasis:				
• Single lesion	4 (20%)	3 (75.0%)	1 (25.0%)	0.591
• Multiple lesions	16 (80%)	8 (50.0%)	8 (50.0%)	
Quantitative Data [b]				
Number of pulmonary lesions, median (IQR)	2 (1–3)	2 (1–4)	2.5 (1.25–3)	0.904

[a] P-value has been calculated using the Fischer Exact test.
[b] P-value has been calculated using the Mann Whitney *U* test.

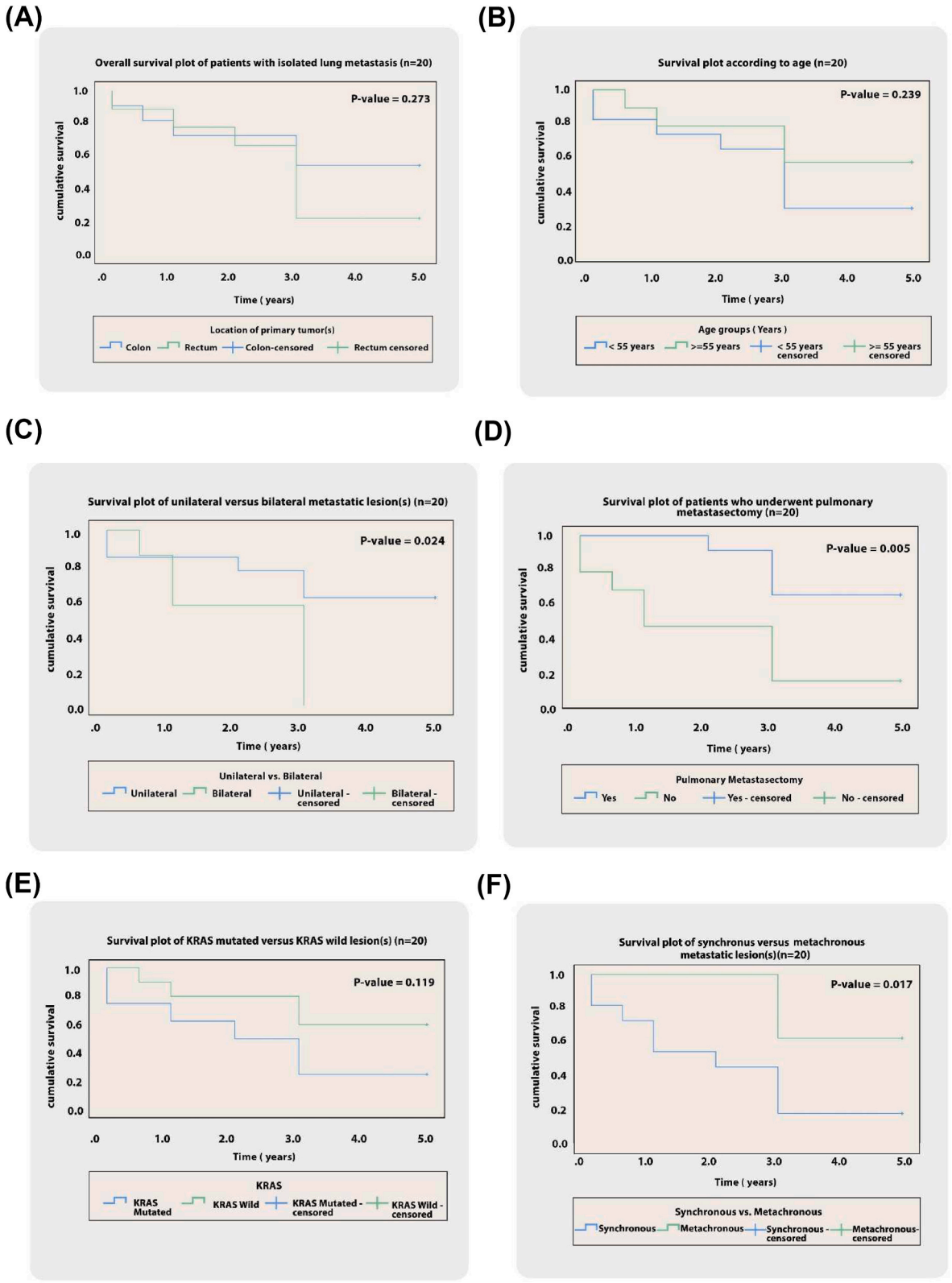

Fig. 2. Kaplan-Meier curves; A, overall survival plot of patients with isolated pulmonary metastasis; B, survival plot according to age; C, survival plot of unilateral versus bilateral metastatic lesion(s); D, survival plot of patients who underwent pulmonary metastasectomy; E, survival plot of KRAS mutated versus KRAS wild type; F, survival plot of synchronous versus metachronous metastatic lesion(s).

median DFI of 20 (IQR, 0–89) months [19]. However, their population included those who had extra-pulmonary metastasis (23%), which might be a confounding factor [19]. Moreover, Chang et al. reported a median DFI of 14.65 (95% CI, 5.56–23.75) months, and Ihn et al. reported a median DFI of 13 (IQR, 0–85) months [29,30].

The overall 5-year survival and the mean OS of our study population were 40% and 3.12 years (37.44 months), respectively. The overall 1-year survival was 85%, and the overall 3-year survival was 70%.

Table 4
Potential predictive factors of survival (n = 20).

Factor	5-years overall Non-survivors N (%) (n = 12)	5-years overall Survivors N (%) (n = 08)	P-value
Qualitative Data [a]			
Age group:			
• <55 years	08 (66.7%)	03 (37.5%)	0.362
• ≥55 years	04 (33.3%)	05 (62.5%)	
Gender:			
• Male	07 (58.3%)	04 (50.0%)	0.999
• Female	05 (41.7%)	04 (50.0%)	
Comorbidity:			
• Yes	04 (33.3%)	05 (62.5%)	0.362
• No	08 (66.7%)	03 (37.5%)	
Smoking:			
• Yes	0 (0%)	03 (37.5%)	**0.049**
• No	12 (100%)	05 (62.5%)	**
Staging at time of diagnosis:			
• Stage 1	0 (0%)	0 (0%)	0 (0%)
• Stage 2	0 (0%)	01 (12.5%)	0.454
• Stage 3	06 (50.0%)	03 (37.5%)	0.617
• Stage 4	06 (50.0%)	04 (50.0%)	0.485
KRAS: *			
• Mutated	06 (60.0%)	02 (25.0%)	0.188
• Wild	04 (40.0%)	06 (75.0%)	
Unilateral vs. Bilateral:			
• Unilateral	05 (41.7%)	08 (100%)	**0.015**
• Bilateral	07 (58.3%)	0 (0%)	**
Side of pulmonary metastasis:			
• Right	02 (28.6%)	05 (71.4%)	0.179
• Left	03 (50.0%)	03 (50.0%)	0.837
• Bilateral	07 (100%)	0 (0%)	**0.027** **
Involvement of mediastinal lymph nodes:			
• Involved	05 (41.7%)	01 (12.5%)	0.325
• Not involved	07 (58.3%)	07 (87.5%)	
Operated for pulmonary metastasis:			
• Yes	04 (33.3%)	07 (87.5%)	**0.028**
• No	08 (66.7%)	01 (12.5%)	**
Pulmonary recurrence:			
• Yes	01 (08.3%)	05 (62.5%)	**0.018**
• No	11 (91.7%)	03 (37.5%)	**
Quantitative Data [b]			
DFI, months (mean ± SD)	13.5 ± 10.7	21.4 ± 12.9	0.358

** Significant at $p < 0.05$ level.
[a] P-value has been calculated using the Fischer Exact test.
[b] P-value has been calculated using the Mann Whitney *U* test.

Table 5
Univariate regression analysis of the significant independent factors with survival outcome (n = 20).

Factor	UOR	95% CI	P-value
Operated for pulmonary metastasis:			
• Yes	0.071	0.006–0.799	**0.032** **
• No	Ref		
Pulmonary recurrence:			
• Yes	0.055	0.004–0.663	**0.022** **
• No	Ref		

UOR – Unadjusted Odds Ratio; CI – Confidence Interval.
** Significant at $p < 0.05$ level.

There is variation in the reported 5-year OS rate in the literature, ranging from 40 to 69.7% [4,5,18–20]. The difference between the reported OS rates in the studies could be due to the difference in the definition of the OS. Specifically, Reijonen et al. [4] and Blackmon et al. [20] considered the OS for CRC patients with IPM to be calculated from the first metastasectomy, while Kumar et al. defined OS as the interval between the surgery for the primary tumor to the last follow-up (i.e., 5-years), which is consistent with our definition of OS [19]. Another factor that might contribute to the difference in the reported outcomes is the variability of the inclusion criteria; Khattak et al. [5] included only patients who had an isolated metastasis at the time of diagnosis, while Goonerate et al. [18] included only patients who had metachronous IPM. In the present study, both groups were included.

Another point to be considered is that Khattak et al. considered pulmonary metastasis to be labeled as isolated in the absence of extra-pulmonary metastases when the primary tumor was diagnosed [5]. Thus, their study population may include non-isolated metastases. Furthermore, Blackmon et al. included patients who had extra-pulmonary metastasis before detecting the lung metastasis, unlike our study population that excluded patients who developed extra-pulmonary metastases before and after detecting the IPM [20].

The favorable survival observed in patients with unilateral IPM is consistent with previous studies [10,13,36]. Saito et al. suggested that poor survival could partly be due to the surgical approach used for bilateral pulmonary metastasis (i.e., median sternotomy), which could limit the complete resection of all nodules [13]. However, the survival rate in our cohort also favored unilateral metastasis, although our patients underwent video-assisted thoracoscopic surgery. Therefore, we suspect that the surgical approach might not explain the worse survival observed in patients with bilateral nodules, but rather it may be due to the tumor biology and tumor progression as hypothesized by Chen et al. [36].

Other parameters such as gender were assessed for their impact on survival because some authors have reported that male sex predicted inferior survival outcome [20], while others [37,38] reported that male patients have a higher risk of developing pulmonary metastasis with no impact on OS. These latter studies showed no difference in survival between men and women, which is consistent with our findings [37,38]. The age of IPM patients when they presented showed that patients who were <55 years had a better OS by > 1 year, but this difference was not statistically significant in our cohort. Another critical parameter that has been associated with aggressive disease behavior and poor survival is the KRAS mutant type [27]. However, this association was not demonstrated in this study.

Despite the lack of level 1 evidence, multiple studies [39,40] showed that surgical resection of pulmonary metastasis is the most efficient treatment, with the 5-year OS ranging from 36% to 45% [41–45]. Similarly, we found that patients who underwent pulmonary metastasectomy had a significantly better survival than their counterparts. When we compared the baseline characteristics of the IPM, we found no statistically significant difference in the number of pulmonary lesions between patients in the metastasectomy and non-surgical groups ($P = 0.904$), which could potentially reject the claim that those patient who underwent metastasectomy had a less severe extent of metastasis. Khattak et al. observed that patients with IPM who underwent curative metastasectomy had better long-term survival than those who did not, with a 4-year survival of 89% and 49%, respectively [5].

A multi-center RCT reported better-estimated survival in patients who underwent pulmonary metastasectomy, whether isolated or not, compared to the control group [46]. Although the study has many limitations, including the small sample size and the abrupt discontinuation of the trial due to poor recruitment, it provides evidence that patients in whom pulmonary metastasis is the only residue of CRC may have better long-term survival after metastasectomy [46].

Mediastinal lymph node involvement was evident in 30% of our patients with no statistically significant difference in OS. However, Hamaji et al. reported lymph node involvement as a significant ominous prognostic factor for survival after pulmonary metastasectomy [47].

Another important issue with CRC metastasis resection is the high relapse rate, ranging from 20% to 68% [12,48,49]. In addition, the role of systemic chemotherapy in those patients remains controversial, although a recent meta-analysis reported better OS for patients with CRC who underwent pulmonary metastasectomy and received peri-operative chemotherapy [50].

Meimarakis et al. observed that the factors affecting survival are different in patients with middle or lower primary rectal cancer compared to patients with upper rectal or colon cancer [51]. Male gender, lymph node involvement for the primary tumor (N1), advanced stage for the primary tumor (III, VI), incomplete resection of the primary tumor (R1, R2), and mediastinal/hilar lymph node involvement were associated with a worse outcome in patients with middle or lower rectal cancer [51]. However, in the second group, incomplete resection of the primary tumor (R1 and R2) and multiple metastases (>2) were associated with lower survival rates [51].

Our secondary outcomes have generated factors that need to be validated in future research. Therefore, prospective large-scale studies are warranted. Future studies need to maintain consistency in methodology and variables' definitions regarding this particular population to reliably validate the findings without confounding effects.

4.1. Strengths and limitations

This study's key strength is the strict application of eligibility criteria to eliminate potential confounding factors. Despite larger sample sizes in the literature, many studies have a mixed population with non-isolated types of metastases, or they included unconfirmed pulmonary metastasis. Moreover, all the included patients were managed uniformly with no change in the treatment protocol across patients. Although this is a single-center experience, ours is a referral and specialized center covering most of the advanced cases of colorectal cancer in the Eastern province of Saudi Arabia. Yet, the generalizability is limited by the narrower range of population and limited geographical inclusion. The primary limitation is the retrospective uncontrolled study design and the small sample size. The databases were limited with respect to the details of the second DFI (DFI-2), which is the interval between metastasis resection and metastatic pulmonary nodule recurrence; thus, this variable was not included in the analysis.

5. Conclusions

The present study showed that multiple factors are associated with a favorable outcome, including metachronous IPM, unilateral IPM, and metastasectomy. In addition, mortality was lower in patients with pulmonary recurrence after metastasectomy. Despite the study's limitations, metastasectomy should be strongly considered during multidisciplinary decision-making because it can offer patients twice the OS of other therapeutic options. Further large-scale multi-center studies should confirm these observations.

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Declaration of competing interest

All authors have completed the disclosure form. The authors have no conflicts of interest to declare.

Data availability statement

The analysed data during this study is available upon reasonable request from the corresponding author. The data does not contain any personal or identifiable data, and the confidentiality of the included patients is fully maintained.

Ethics approval

This study was approved by the KFSH-D ethics committee (Institutional review board number: SUR0331). The institutional review board waived the requirement for individual informed consent. The study was conducted in accordance with the Declaration of Helsinki and with national and international ethics standards.

Authors' contribution

All authors contributed equally in the conception, conduction, and drafting of this study. All authors reviewed and approved the final version of the manuscript. The corresponding author attest that all the listed authors have meet the authorship criteria and no other meeting the authorship criteria were excluded.

Guarantor statement

All authors agreed to be responsible for the accuracy of all the content of the present study and hold accountable for any raised questions or concerns related to the accuracy or integrity of any part of the work is appropriately investigated and resolved.

Reporting checklist

We present this original observational study in accordance with the STROCSS criteria (Strengthening the reporting of cohort studies in surgery).

Peer review file

The authors agree to the publication of the peer review file for transparent peer review.

Provenance and peer review

Not commissioned, externally peer reviewed.

Registration of research

This study is registered with the ResearchRegistry and the unique identifying number is: researchregistry7598.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103559.

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