Original Article

Colorectal Cancer Liver Metastasis Trends in the Kingdom of Saudi Arabia

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ABSTRACT

Background/Aim: To elucidate colorectal cancer (CRC) disease patterns, demographics, characteristics, stage at presentation, metastases, and survival rates of patients, particularly those with liver metastases, at our center as the first report from the Kingdom of Saudi Arabia. **Patients and Methods:** We performed a retrospective, single-center database study based on the histological diagnosis of CRC in patients seen at the King Khalid University Hospital between 2007 and 2011. **Results:** 427 cases of CRC with a mean age at diagnosis of 55.47 ± 12.85 years, out of which 96% were resected. Stage II was predominant at presentation, followed by both stage III and IV, with the remainder being stage I. One hundred patients had distant metastases, of which the liver was the only location in 54 patients. Mean survival was 3.0 years. Overall survival rates for CRC patients with liver metastases who underwent resection were 30% at 2 years and 17% at 5 years, and the mean survival rate was 1.4 years. **Conclusions:** Both the mean survival rate of our CRC patients with resectable liver metastases and the 5-year survival rate of these patients are lower than global averages. This discrepancy is likely due to late diagnoses rather than more aggressive disease.

Key Words: Colon cancer, metastasis, Saudi Arabia, survival

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Colorectal cancer (CRC) is considered to be the third most common malignancy worldwide.[1] It affects roughly 30–50 people per 100,000 individuals in the USA and Europe,[2] and roughly half of these patients develop metastases during the course of the disease.[3,4] The liver is the predominant site of metastasis in CRC, and 25% of patients present with metastases at the time of diagnosis (synchronous).[4-6] Throughout the course of the disease, in particular after resection of the primary tumor, approximately half of all CRC patients develop liver metastases.[4-6] CRC rates are markedly lower in Africa and the Middle East, occurring at an estimated rate of 3–11 per 100,000 individuals.[7] Specifically, in the Kingdom of Saudi Arabia (KSA), the incidence of CRC is increasing from 6.6 per 100,000 individuals in 2003[8] to over 12 per 100,000 individuals in 2008.[9]

In a recent meta-analysis by Kanakas *et al*., the global 3 and 5-year mean survival rates of CRC were estimated to be 57.6 and 40.3%, respectively;[10] however, 5-year survival rates in the USA are estimated to be greater than 65%.[11] In comparison, the 5-year survival rate of CRC in the KSA is reported to be 44.6%.[12] Survival rates have improved tremendously for CRC due to early detection, application of total mesorectal excision, and addition of radiochemotherapy.[13,14] With respect to CRC patients with liver metastases, the estimated global mean 5-year survival is 38%, although this number varies dramatically from region to region.[10] Survival improvement for metastatic CRC is majorly due to the aggressive surgical approach in resecting all metastasis and the addition of effective systemic

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chemotherapy.[15] Despite increasing data pertaining to CRC incidence and survival in the KSA, information relating to the leading cause of death from this disease, namely liver metastasis, is currently scarce.[16] Therefore, the aim of this study is to elucidate CRC disease pattern and survival rates, particularly of patients with liver metastases, in the KSA population and to compare these figures to the global averages.

PATIENTS AND METHODS

This study was a retrospective, single-center database study based on the histological diagnosis of CRC. Inclusion criteria included all patients diagnosed with primary CRC between 2006 and 2012 at the King Khalid University Hospital, KSA. Data including patient demographics; location of primary tumor; tumor, node, and metastasis (TNM) staging at presentation and grading; surgical intervention; disease-free period and recurrence; and final status of the patient at last follow-up were collected. Descriptive statistics were analyzed using JMP 11 statistical software (SAS Institute Inc, Cary, NC, USA). In this study, we used a marginal structural model to understand whether metastasis location and timing had an effect on the survival rate. Probability of metastasis was predicted using age, stage, site, and vascular invasion. The inverse of these probabilities were used as weights to construct an exponential survival model adjusted for metastasis location (lungs, liver, or both).

RESULTS

We conducted a retrospective analysis of histological diagnosis of CRC for primary CRC between 2007 and 2011. We retrieved 427 cases of CRC with a mean age ± standard deviation at diagnosis of 56 ± 13 years, with a slight male predominance (240 patients; 56.2%). With respect to the location of the primary tumor, the rectum was the least common site, occurring in 120 patients (28.1%), followed by the sigmoid colon (140 patients; 32.3%), and the remaining colon (148 patients; 37.7%); in 19 patients, localization data was missing. The mean size of the primary tumor was 5.1 ± 3.0 cm [Table 1].

Stage II was most common at presentation (127 patients; 31%), followed by stage III with 122 patients (30%) and stage IV with 100 patients (25%), with the remainder being stage I (59 patients; 14%) and unknown (19 patients; 4.46%). With respect to tumor differentiation, the majority of the tumors were moderately-differentiated adenocarcinomas (304 patients; 71.3%), followed by poorly-differentiated carcinomas (23 patients; 5.3%), well-differentiated adenocarcinoma (14 patients; 3.28%), and undocumented (86 patients; 20.8%). Vascular invasion was present in 81 patients (20.7%).

Of the 427 patients, 409 underwent resection (96.0%), and 320 of these patients were followed up after surgery (computerized tomography [CT] scan and colonoscopy) for a mean of 3 years and a minimum of 1 year; there was no evidence of recurrence in 241 patients (75.31%), 79 (24.68%) patients among our follow-up patients had metastatic recurrence.

Patients had distant metastases on presentation (23.7%), and of these, the liver was the only location in 54 patients (54%). Other metastatic locations included the lung (20 patients; 20%), concomitant liver and lung (20 patients; 20%), and others (5 patients; 5%) [Figure 1]. Among the 54 patients with liver metastases, additional 12 patients developed liver metachronous disease, 35 underwent liver resection, and 9 underwent pulmonary metastatectomy for curative intent with available follow-up data.

A Kaplan–Meier estimator was used to estimate the survival curve. Patients with missing follow-up data were removed from the analysis. The overall survival rates for CRC patients with resected liver metastasis were 30% at 2 years (77/192) and 17% at 5 years (38/192) [Figure 2]. The mean overall

Table 1: Patients characters and results

	Counts	Percentage
Gender		
Male	240	56.2
Female	187	43.8
Location of Pirmary		
Colon	148	37.7
Sigmoid	140	32.3
Rectum	120	28.1
Missing Data	19	1.9
AJCC Stage		
Stage I	59	14
Stage II	127	31
Stage III	122	30
Stage IV	100	25
Vascular Invasion		
Present	81	20.7
Absent	346	79.3

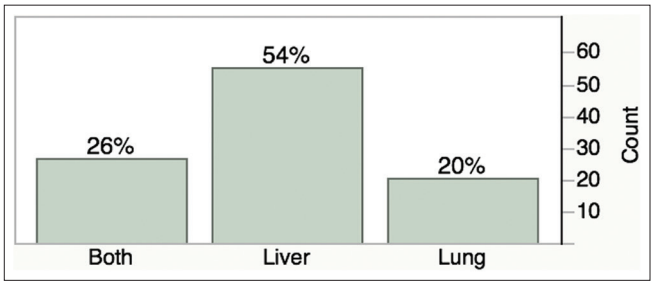

Figure 1: Distribution of metastatic locations in our colorectal cancer patients (percentage)

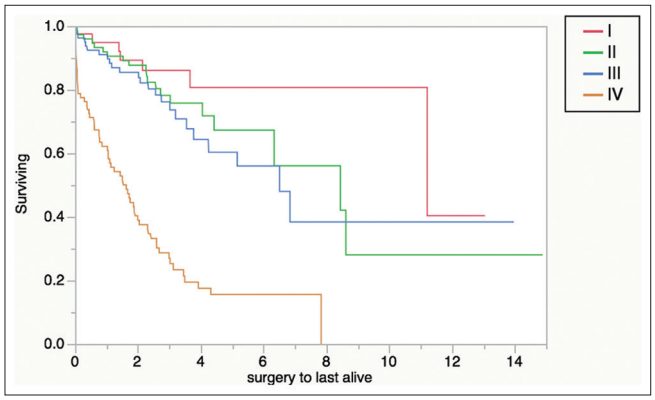

Figure 2: Survival curve plot between stage on presentation

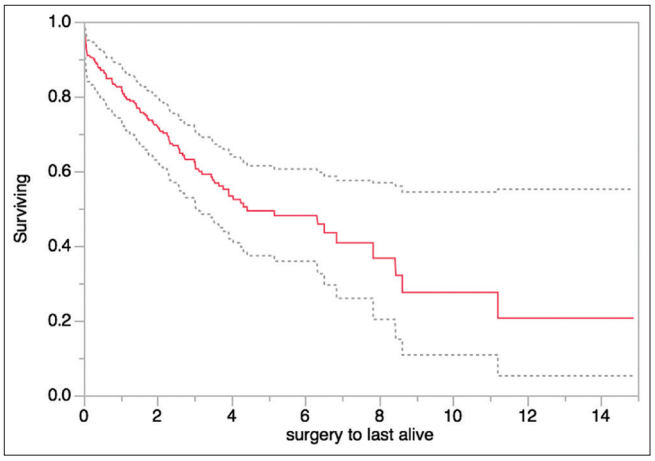

Figure 3: Overall survival curve plot between males and females

survival of CRC patients with resected liver metastases was 1.8 years [Figure 3].

The survival rates between males and females showed no statistically significant differences. However, on univariate analysis, survival had a significant correlation with tumor grade, age group at presentation, and timing of metastasis ($P < 0.05$).

An exponential survival model was constructed to estimate survival adjusted for age, cancer stage (localized, regional, or distant), colon vs. rectal cancer, and whether or not there was vascular invasion. Stage was only significant with a negative effect on survival ($P = 0.005$) [Appendix Table 1a]. We also calculated the coefficient estimates to predict the hazard rates and its standard deviation, which in turn predicts the survival at time t [S (t)] [Appendix Table 1b].

To determine the time of metastasis, we present [Appendix Table 2] a description of stage and metastasis by survival rate.

For patients with metastasis, a subanalysis of a probability of metastasis location effect on survival calculations is shown in Appendix Table 3. The data suggests that the location has an effect on survival rate ($P = 0.0001$ for location and $P < 0.0001$ for timing).

DISCUSSION

Several studies have attempted to determine the prognostic factors and provide recommendations for the treatment of CRC. In terms of allocation of new cases, CRC is the third most common cancer worldwide.[17] The incidence of this devastating disease is increasing each year in Asian countries and particularly in KSA.[18] However, data pertaining to the main cause of death from CRC—liver metastasis—from this region is sparse in the literature. In this study, we determined the mean survival rate of CRC patients in the KSA with resectable liver metastases.

Our cohort revealed a younger age of patients at the time of presentation, similar to the findings of other studies reported from the same region;[19] however, this is very different from published data from the Western society. Although a clear explanation is yet to be identified, one factor could be the general younger age of our population.[20]

We found the mean survival rate of CRC patients in our cohort to be approximately 2.94 (95% confidence interval (CI): 2.69–3.1) years. However, it does not meet the global survival rate of 3.6 years.[10] Surprisingly, in our study, the 5-year survival rate of patients with resected liver metastasis was 17% whereas other studies have reported a survival rate of 50%.[21-23] Moreover, in the USA, survival of patients with resectable CRC liver metastasis is over 60%.[24] It is noteworthy that the survival rates of CRC liver metastasis patients in the KSA region are exponentially improving despite this discrepancy. In corroboration with the recent reports, our current study (2006–2012) supports the fact that the 5-year survival of CRC patients with metastasis is higher than a previous study from KSA (14.7%) conducted between 1994–2004.[12]

It is interesting to note that the current study had more stage I CRC cases (13.8% versus 10.1%) and far fewer stage II CRC cases (29.8% versus 63.9%). This suggests that CRC tumors are being detected earlier in the KSA population compared to older studies. This is supported by the report from Al-Ahwal *et al.*, where 25.9% of patients presented with advanced disease at the time of diagnosis.[12] However, despite the increase in stage I CRC diagnosis in the KSA over the past 5 years, in the USA, over 25% of patients with CRC are diagnosed at stage I,

a factor that undoubtedly contributes to their increased relative survival rates.[25]

One important caveat to this study is that the global synchronous metastasis rates for CRC patients is approximately 25%, which is higher than that reported for our cohort patients (13.3%).[26,27] However, in contrary, a recent study reported that there is no significant prognostic benefit for patients with metachronous metastases compared to synchronous metastases, where synchronous metastases developed within the first 12 months from diagnosis.[28] Furthermore, recent studies suggest that metachronous metastases may be present at the time of initial diagnosis (i.e., metachronous metastases are actually the result of growth of subclinical synchronous metastases). If this hypothesis is correct, the total number of synchronous/metachronous metastases in the present study is approximately 30% (5 synchronous and 4 metachronous), which is roughly at par with global averages.[26-28] Other reasons for this aforementioned discrepancy may simply be different diagnostic criteria or sensitivity to detect the presence of synchronous metastases varying by region. In addition, in this study, 33.5% of patients developed metastasis, which is lower than the global average, suggesting that the shorter survival rates in KSA patients is more likely due to late diagnosis rather than more aggressive disease.[29]

The current study has been conducted in a tertiary hospital, a referral center for CRCs from all over the country, and all the samples are relevant to the study being exclusively from the Saudi population. However, we acknowledge that small sample size is a limitation of this study, with a potential bias in selecting more resectable patients when undergoing selection via the admission office. Current data that have been presented here are still preliminary, and thus, one has to be careful while extrapolating the results presented here to the entire KSA population. In addition, because no consideration was made regarding chemotherapy and its survival, it is possible that the varying chemotherapeutic modalities used in individual patients may influence the survival rates reported here. CRC is considered a preventable tumor because the lesions arise from precancerous polyps and other recognizable processes.[7] Thus, every effort should be made to identify both the presence of these lesions and also patients—such as those with inflammatory bowel disease—that are at a risk of developing CRC.[30] To further improve the trend of diagnosing CRC and to raise the survival rates globally, it is recommended to adopt a national screening program in the KSA region. In Australia, such a program resulted in significantly early diagnoses, and it is hypothesized that this translated into a reduction in CRC mortality.[31] Further evidence supporting this ideology is a recent study reporting that pathological markers corresponding to earlier detection, such as staging, tumor size, and tumor differentiation, are most likely to impact survival.[32] For CRC, early detection is critical; 5-year survival rates are well over 90% if detected at stage I.[24,33]

CONCLUSION

While the survival rates for patients with resectable CRC liver metastases in the KSA are lower than what is reported globally, we suggest that increased attention to surgical techniques and significant improvements in surgical care over time has possibly led to improvements in the survival rates of CRC patients in the country. Even though the long-term results for these patients are not yet known, our preliminary results indicate that early detection of CRC will increase survival rates. Continued efforts are necessary to elucidate the long-term results. Future studies should, therefore, compare the long-term results between the patients who received an early diagnosis with those who received a late diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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Appendix Tables

Table 1a: Exponential survival mode, multivariate study

	Chi-square	df	*P*
Age	1.71	1.00	0.19
Stage	54.22	2.00	0.005
Site	0	1.00	0.94
Vascular invasion	1.86	1.00	0.17
Total	63.19	5.00	0.005

df, degree of freedom

Table 1b: Coefficient estimates

	Coefficient estimates	Standard error
Intercept	3.2477	0.4716
Age	−0.0098	0.0075
Stage=Regional	−0.3019	0.2942
Stage=Distant	−1.646	0.2472
Site=Rectum	0.0156	0.2242
Vascular Invasion=Yes	−0.3211	0.2354

Table 2: Marginal structural model testing metastasis location and timing had an effect on survival

	N	Alive (*N*=173)	Dead (*N*=115)
Stage: localized	403	54% (91)	25% (27)
Regional	54.22	35% (58)	22% (24)
Distant	0	11% (18)	54% (59)
Developed metastasis: No	421	82% (142)	36% (41)
Developed metastasis: Yes	63.19	18% (31)	64% (74)

Table 3: Exponential survival model adjusted for metastasis location

	Chi square	df	*P*
Metastasis location	17.62	2.00	0.005
Total	17.62	2.00	0.005
Metastasis timing	11.89	1.00	0.005
Total	11.89	1.00	0.005

df: Degree of freedom