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Cohort Study

Colorectal cancer survival rates in Makassar, Eastern Indonesia: A retrospective Cohort Study

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ABSTRACT

Background: The 5-year overall survival (OS) rate for colorectal cancer (CRC) has been reported as 39%, and the 5-year recurrence-free survival (RFS) rate has been reported as 14%. Various prognostic factors have been associated with differences in survival rates among CRC patients. This study investigated the difference between several prognostic factors and the OS and RFS rates of CRC patients at the Dr. Wahidin Sudirohusodo General Hospital Makassar in Indonesia.

Materials and methods: The study group comprised all CRC patients treated at the Division of Digestive Surgery from 2014 to 2016. Prognostic factor data were collected from medical records for 293 patients. The OS and RFS rates were analyzed using the bivariate Kaplan–Meier method and log-rank tests.

Results: Log-rank analysis of the association of age, histopathology, stage, definitive surgery, chemotherapy, and radiotherapy with the OS rate showed *p*-values of 0.031, 0.009, 0.014, 0.000, 0.343, and 0.381, respectively. Log-rank analysis of the association of these prognostic factors with the RFS rate showed *p*-values of 0.282, 0.006, 0.008, 0.020, 0.002, and 0.000, respectively.

Conclusion: There were significant differences in the OS rate according to age, histopathology, stage, and history of definitive surgery. Histopathology, stage, history of definitive surgery, and chemotherapy and radiotherapy were significantly associated with differences in the RFS rate.

1. Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and the fourth most common cause of death worldwide. The incidence and mortality rates of CRC vary geographically [1–4]. The global burden of CRC is predicted to increase by 60%, corresponding to more than 2.2 million new cases and 1.1 million deaths by 2030 [5]. CRC is one of the most common cancers in Indonesia, and its incidence is slowly increasing [3,6].

According to the International Agency for Research on Cancer (IARC) Global Cancer Observatory's GLOBOCAN 2018 database, the incidence of CRC in Indonesia was 30,017 out of 348,809 cancer cases, and it had the fifth-highest mortality rate (7.7%) among all cancers [3,7]. The differences in survival rates observed in clinical trials may have been due to variations in patients' characteristics and prognostic factors [2].

The rising incidence of CRC has been suggested to be associated with the improving socioeconomic status and increasingly westernized lifestyle [8–10]. Other risk factors such as an ageing population, uncontrolled tobacco usage and alcohol intake, and physical inactivity could also contribute to the prevalence of CRC [10].

Surgery is the primary treatment for CRC with no metastasis. The outcome depends on the quality of surgery, the tumor stage, and further therapy. In more severe cases, neoadjuvant therapy (such as

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perioperative chemotherapy for T4 cancer lesions and [chemo]radiotherapy for local lesions) may reduce tumor stage and increase resection success [11].

The cumulative death risk of CRC at 0–74 years is 0.66% in males and 0.44% in females, with a mortality rate of 8.9 per 100,000 cases. The survival rate is the best index for evaluating the effectiveness of healthcare, diagnostic, and curative interventions in CRC patients. The survival rate is defined as the proportion of cancer patients who have survived at a specific period after the diagnosis of cancer [12–14]. In the United States, the 5-year life expectancy for CRC patients is 92% for stage I, 87% for stage IIA, 65% for stage IIB, 90% for stage IIIA, 72% for stage IIIB, 53% for stage IIIC, and just 12% for metastasis [15].

Most cases of CRC in Indonesia are diagnosed at an advanced stage for a range of educational, cultural, social, and economic reasons. The incidence of CRC at the Dr. Wahidin Sudirohusodo General Hospital in Makassar, a referral center in Eastern Indonesia, is relatively high. So far, the survival rate in this institution has remained unclear. The current study investigated the relationship between several prognostic factors and the overall survival (OS) and recurrence-free survival (RFS) rates in CRC patients at the Dr. Wahidin Sudirohusodo General Hospital Makassar in Indonesia.

2. Methods

This retrospective cohort study was conducted in the Division of Digestive Surgery at the Dr. Wahidin Sudirohusodo General Hospital and the Division of Digestive Surgery at the Faculty of Medicine of Hasanuddin University Makassar, Indonesia. The protocol was approved by our institution's review board and was registered with the Research Registry (no. 7354). Between February and June 2021, data were from the medical records of all CRC patients presenting between 2014 and 2016. Patients who had incomplete medical records or died from causes other than cancer were excluded from the study group. We carried out the work in line with the "Strengthening the Reporting of Cohort Studies in Surgery" (STROCSS) criteria [16].

The OS rate was calculated based on the time interval between the date of diagnosis and the date of either death from any cause or last follow-up. The RFS rate was calculated based on the time interval between the date of initial treatment and the date of either the first recurrence of CRC or death from any cause. The analysis included the following factors that might affect the disease prognosis: age, stage, histopathology, history of definitive surgery, history of chemotherapy, and radiotherapy.

The subject's characteristics were investigated using univariate analysis. The Kaplan–Meier method was used for univariate survival-rate analysis. The log-rank test was used to compare differences between groups of variables. Analyses were performed using the Statistical Product and Service Solution Software for Windows 22 (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY).

3. RESULTS

3.1. Univariate analysis

The majority (57.3%) of the patients (168/293) were aged 50 years or above (Table 1). Histopathological analysis revealed that the most common cancer type was adenocarcinoma (AC) at 75.1% (220 patients), followed by mucinous AC (MAC) at 14.0% (41 patients). The most common stage was IV (34.8%; 102 patients), followed by stage II (31.4%; 92 patients), and stage III (33.8%; 99 patients). In the history of chemotherapy, 42.0% (123 patients) underwent chemotherapy and 58.0% (170 patients) did not. In the history of radiotherapy, 29.0% (85 patients) underwent radiotherapy and 71.0% (208 patients) did not.

Within the 5-year observation period, among the 293 subjects, 115 (66.7%) survived while 178 (33.3%) died, and 253 (28.6%) experienced recurrence while 40 (71.4%) had no recurrence.

Table 1
Patient's characteristics ($n = 293$).

Variable	Category	*n*	Percentage (%)
Age (years)	<50	125	42.7
	≥50	168	57.3
Histopathology	MAC	41	14
	AC	220	75.1
	Other	32	10.9
Stage	II	92	31.4
	III	99	33.8
	IV	102	34.8
Definitive surgery	Yes	234	20.1
	No	59	79.9
History of Chemotherapy	Yes	170	58
	No	123	42
History of radiotherapy	Yes	85	29
	No	208	71
Recurrence	Yes	253	28.6
	No	40	71.4
Five-year survival	Yes	115	66.7
	No	178	33.3

Fig. 1 shows that of the 293 CRC patients, 178 died with an average OS rate of 3.973 years (95% CI 3.835–4.110). There were 253 patients who experienced recurrence during the observation period with an average RFS rate of 3.179 years (95% CI 3.048–3.310).

3.2. Bivariate analysis

Log-rank analysis was used to determine the correlation of each prognostic factor variable with the OS and RFS rates.

Fig. 2 shows a significant relationship between age and OS rate ($p = 0.043$): the average OS rate was 4.052 years in patients aged >50 years and 3.861 years in patients aged <50 years. The relationship between age and the RFS rate was not statistically significant ($p = 0.782$): the average RFS was 3.190 years for patients aged >50 years and 3.163 years for those aged <50 years.

We found significant relationships between histopathology and both OS ($p = 0.009$) and RFS ($p = 0.006$) (Fig. 3). The average OS was 3.282 years in patients with MAC histopathology and 4.158 years in patients with AC histopathology. There was a statistically significant relationship between histopathology and the RFS rate ($p = 0.006$), with an average RFS of 2.611 years in patients with MAC histopathology and 3.348 years in patients with AC histopathology.

Fig. 4 shows a significant relationship between stage and OS ($p = 0.014$). The average OS was 4.410 years in patients with stage II, 3.837 years in patients with stage III. and 3.710 years in patients with stage IV. There was a statistically significant relationship between stage and RFS ($p = 0.008$), with an average RFS of 3.588 years in patients with stage II, 3.053 years in patients with stage III, and 2.931 years in patients with stage IV.

Fig. 5 shows a significant relationship between definitive surgery and OS ($p = 0.000$). Additionally, there was a significant relationship between histopathology and RFS ($p = 0.006$). The average OS was 4.151 years for patients receiving definitive surgery and 3.265 years for patients who did not receive definitive surgery. There was a significant relationship between histopathology and RFS ($p = 0.020$), with an average RFS of 3.306 years in patients receiving definitive surgery and 2.673 years in patients who did not receive definitive surgery.

Fig. 6 shows a statistically insignificant relationship between chemotherapy history and OS ($p = 0.343$). The mean OS was 4.002 years in chemotherapy patients and 3.932 years in patients who did not undergo chemotherapy. However, there was a significant relationship between chemotherapy history and RFS ($p = 0.002$), with an average RFS of 3.307 years in patients who had undergone chemotherapy treatment and 3.001 years in patients without a history of chemotherapy.

Fig. 7 shows a statistically insignificant correlation between radiotherapy history and OS ($p = 0.381$). The mean OS was 3.996 years in

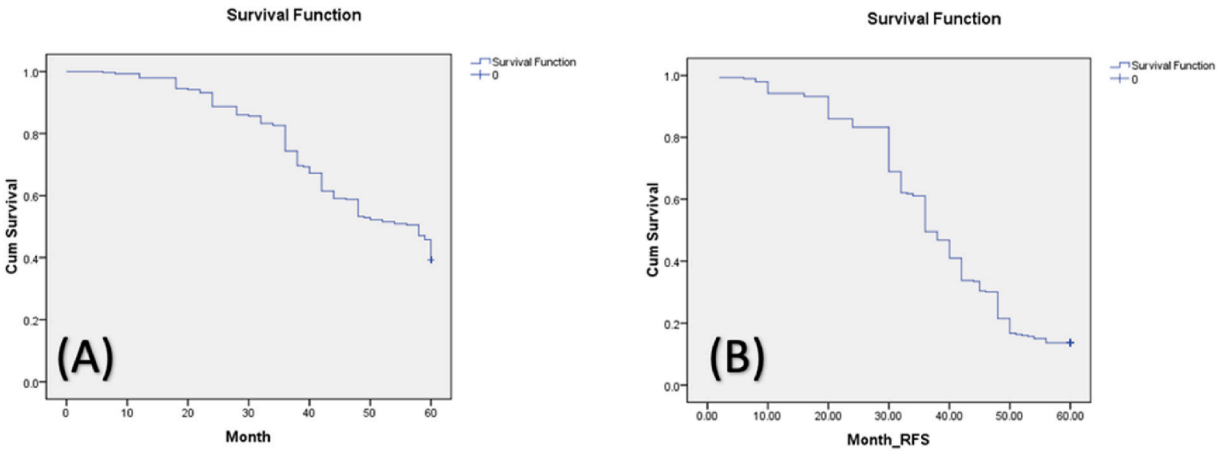

Fig. 1. (A) OS and (B) RFS rates of CRC patients.

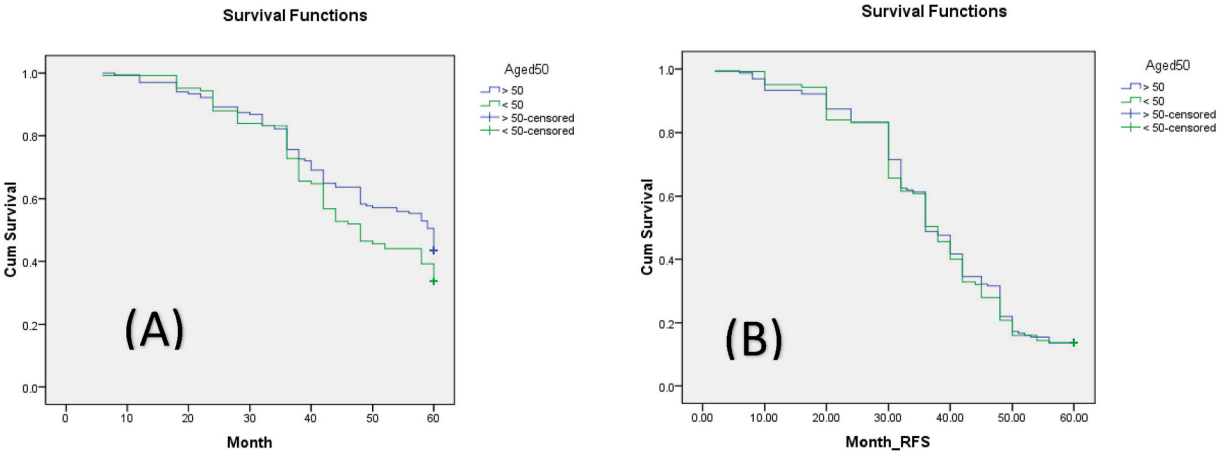

Fig. 2. Log-rank analysis between age and (A) OS and (B) RFS rates of CRC patients.

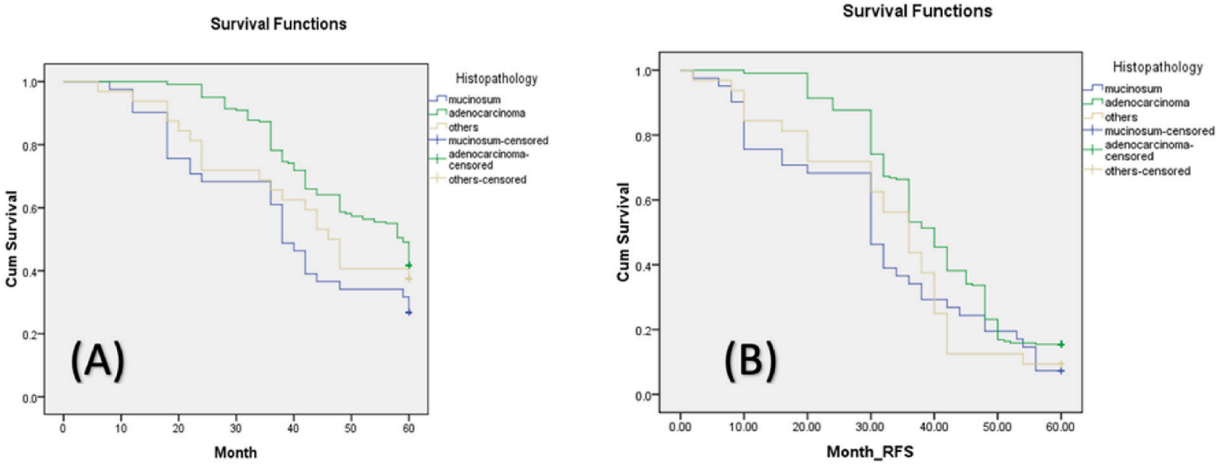

Fig. 3. Log-rank analysis between histopathology and (A) OS and (B) RFS rates.

patients with a history of radiotherapy and 3.911 years in patients who had not undergone radiotherapy. By contrast, the correlation between radiotherapy history and RFS was statistically significant (p=<0.001). The mean RFS was 3.294 years in patients with a history of radiotherapy and 2.898 years in patients who had not undergone radiotherapy.

4. Discussion

In this study, OS was defined as the period from the date of diagnosis to the date of either death from any cause or last follow-up. The average OS rate for CRC was 3.973 years (95% CI 3.835–4.110). RFS was defined as the period after the end of primary care during which the patient survived without any signs or symptoms of tumors. In clinical trials,

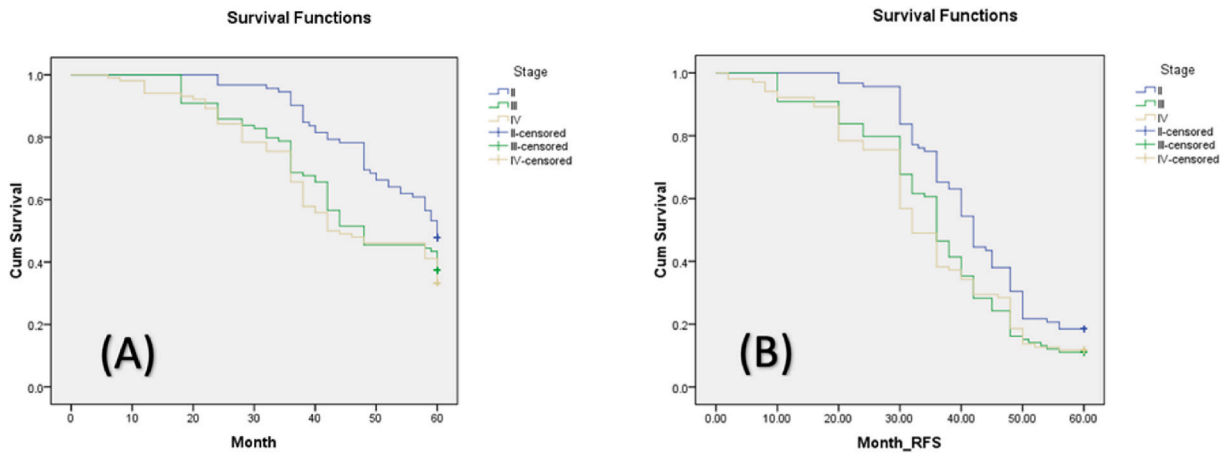

Fig. 4. Log-rank analysis between stage and (A) OS and (B) RFS rates.

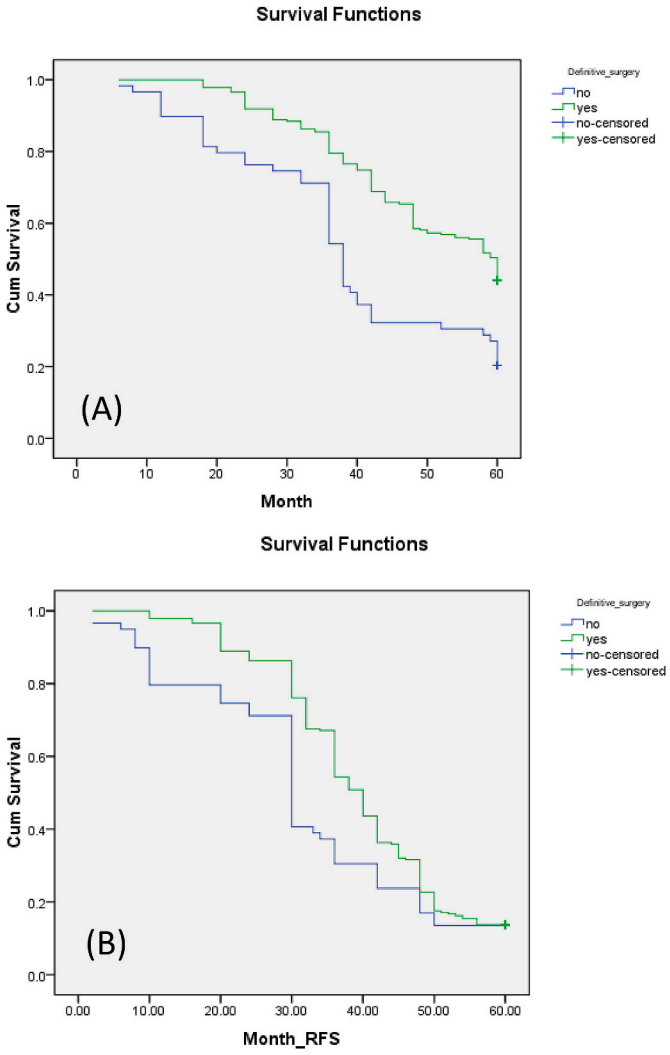

Fig. 5. Log-rank analysis between definitive surgery and (A) OS and (B) RFS rates.

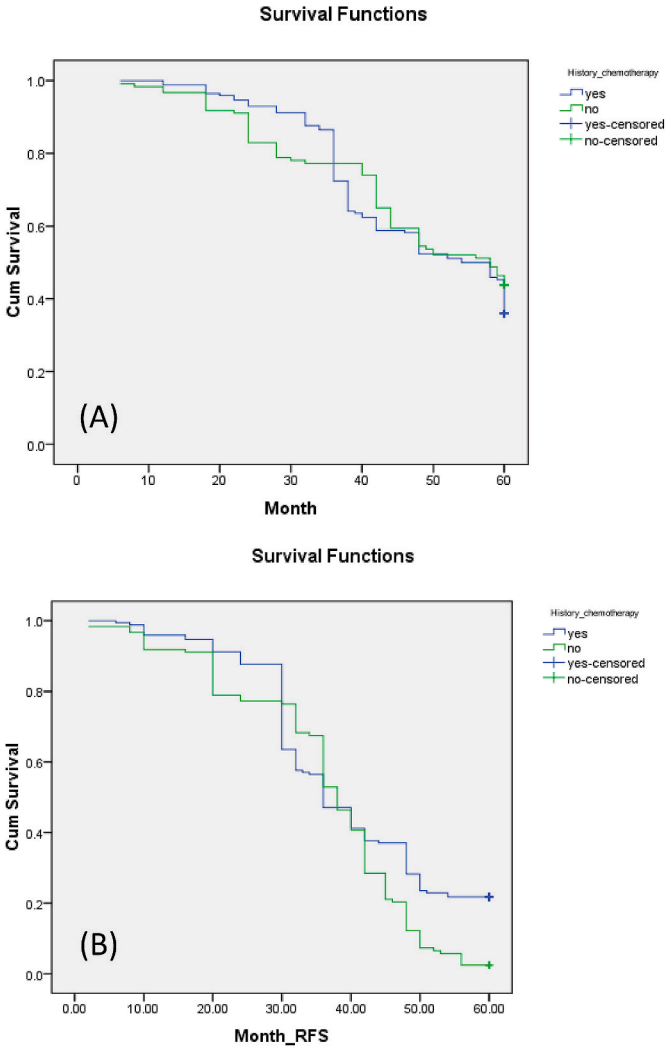

Fig. 6. Log-rank analysis between chemotherapy history and (A) OS and (B) RFS rates.

assessing RFS is one way of determining how the treatment is working. In this study, the average RFS of CRC was 3.179 years (95% CI 3.047–3.310) [17].

There was a significant relationship between OS and age ($p = 0.043$). Overall survival in patients aged >50 years was better than in patients aged <50 years (4.052 vs 3.861 years). The relationship between age and RFS was not statistically significant ($p = 0.782$). In a study by Li et al. (2018), older people (according to age at the time of diagnosis) had a higher risk of death than those of younger ages [18]. Moreover, Sinaga

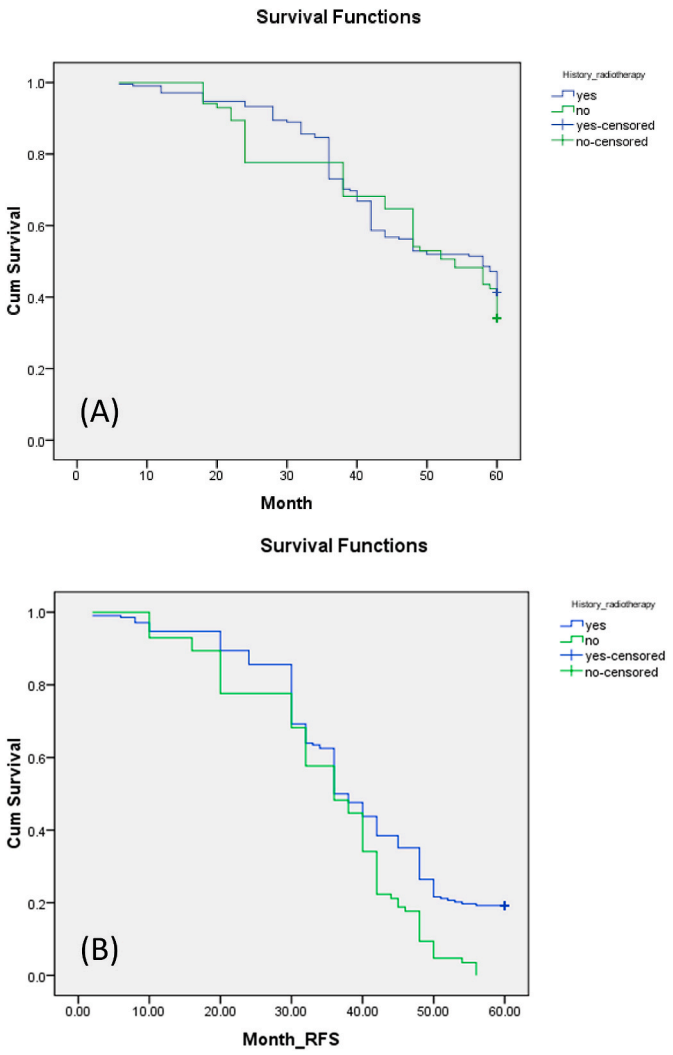

Fig. 7. Log-rank analysis between radiotherapy history and (A) OS and (B) RFS rates.

et al. (2017) reported that age at diagnosis was related to the 5-year survival of CRC patients and that the risk of death in CRC patients in the <50 year age group was 3.64 times greater than that in the group aged ≥50 years [19]. Some studies have also suggested the poorer OS in younger patients could be since their cancer tends to be more aggressive and less responsive to treatments [18–22].

The results showed a significant relationship between histopathology and both OS ($p = 0.009$) and RFS ($p = 0.006$); these findings were similar to a study of CRC patients, which reported that patients with MAC had a poor OS and overall response rate to chemotherapy compared to patients with AC [23]. The prognosis of CRC is usually poor, and MAC has an even lower OS rate [15].

The cancer stage is the most important predictor of CRC patients' survival [24–26]. There was a significant relationship between stage and OS ($p = 0.014$). The relationship between stage and RFS was also statistically significant ($p = 0.008$). Research by Yin et al. (2016) showed that the tumor–node–metastasis (TNM) staging level was highly correlated with OS results. The TNM staging is divided into several levels—namely 0, I, IIA, IIB, IIIA, IIIB, IIIC, and IV—that are assessed according to the primary tumor (T), regional lymph nodes (N), and distant metastases (M) [18,27].

The results showed a significant relationship between receiving definitive surgery and both OS (p=<0.001) and RFS ($p = 0.020$). Subjects who received definitive surgery, which comprised tumor resection after diagnosis, had significantly better survival. Patients who received resection showed a 5-year survival rate of 35.2% compared with 4.1% in those who did not. However, the OS rate in those receiving definitive surgery was 4.151 years. This finding was similar to a study by Duraker et al. that showed a better survival rate in patients receiving tumor resection [28].

History of chemotherapy treatment had a statistically insignificant relationship with OS ($p = 0.343$). However, chemotherapy and RFS had a significant relationship ($p = 0.002$). There was no difference in the average OS in patients who received chemotherapy and surgery alone [29]. This contrasted with the results of a randomized trial that found an increase in the benefits of OS and RFS in patients receiving neoadjuvant therapy [18]. The OS rate in patients who received chemotherapy was better than in those who did not (4.002 years vs 3.932 years). Other factors might have influenced this, such as the cancer stage or the therapy combination. Papamichael et al. showed that 5-fluorouracil (5-FU)/leucovorin (LV) intravenous treatment led to a 29% 5-year mortality risk. Different regimens may have been responsible for the diverse findings. Several characteristics, particularly those associated with stage IV (34.8%), such as renal salt-washing syndrome (RSWS), may lead to a poor prognosis [29]. Several study subjects did not complete the recommended therapy program, so their data were not recorded and examined in this study.

The relationship between radiotherapy treatment history and OS was statistically insignificant($p = 0.381$). However, patients who underwent radiotherapy treatment significantly improved RFS (p=<0.001). Compared to a randomized controlled trial, there was a significant reduction in local cancer recurrence. However, no significant difference in metastasis or OS time has been demonstrated [30].

The survival rate of CRC is affected by a combination of factors. Moghimi-Dehkordi et al. showed that differences in the method of initial diagnosis, history of alcohol use, initial treatment methods, and history of metastasis could predict CRC mortality, although economic status, education, and other comorbid factors were not included in the analysis [13].

This was a retrospective cohort study, which limited the amount of data obtained. Although the researchers attempted to contact the study subjects individually, the data were limited due to the irregular follow-up of patients during the 5-year period. Future prospective studies are needed so that data and follow-up can be better assessed. It may be possible to do future research with a larger sample size, or it could be done in some digestive surgery centers in Indonesia.

Several factors could have biased the current study results, including incomplete medical record data and some personal characteristics of the research subjects. Cancer patients tend to differ from the general population in individual factors that can influence death from other causes (socioeconomic status, health status, and health behaviors such as smoking), thereby biasing relative survival rates.

5. Conclusion

There were significant differences in OS rate associated with the prognostic factors of age, histopathology, tumor stage, and history of definitive surgery. Histopathology, tumor stage, history of definitive surgery, and chemotherapy and radiotherapy treatments significantly affected recurrence-free survival rate. These factors may influence one another; therefore, future studies need to be carried out to examine the effect of prognostic factors on survival rates using prospective research methods with a longer duration both at digestive surgery centers and in other settings.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

All procedure for human experiment has been approved by Ethics Commission Faculty of Medicine, Hasanuddin University.

Sources of funding

None.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective data base and files for research work.

Author contribution

Ibrahim Labeda, Ronald Erasio Lusikooy, Mappincara, Muhammad Iwan Dani, and Arham Arsyad wrote the manuscript and participated in the study design. Ibrahim Labeda, Ronald Erasio Lusikooy, Muhammad Ihwan Kusuma, Julianus Aboyaman Uwuratuw, Erwin Syarifuddin, and Muhammad Faruk drafted and revised the manuscript. Ibrahim Labeda, Ronald Erasio Lusikooy, Mappincara, Muhammad Iwan Dani, Samuel Sampetoding, Muhammad Ihwan Kusuma, Julianus Aboyaman Uwuratuw, Erwin Syarifuddin, and Arham Arsyad performed treatment and surgery. Ibrahim Labeda, Arham Arsyad, and Muhammad Faruk performed bioinformatics analyses and revised the manuscript. All authors read and approved the final manuscript.

Registration of research studies

This study is registered with the Research Registry and the unique identifying number is: researchregistry7354.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103211.

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