Relationship between Age and The Histopathological Features to Chemotherapy Response in Colorectal Cancer Patients: A Prospective Observational Study

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Abstract

Introduction Chemotherapy response in early age-onset colorectal cancer patients is still controversial, and the results of chemotherapy response are unknown. Therefore, the purpose of this study is to determine the relationship between the age of colorectal cancer patients and histopathological features and chemotherapy response.

Methods This is a prospective observational study. The subjects in this study were colorectal cancer patients in the Digestive Surgery division at Tertiary Hospital in West Java from September 2021 to September 2022.

Results There were 86 subjects who underwent chemotherapy in accordance with the inclusion and exclusion criteria. Consisting of 39 patients of early age onset and 44 female patients. The most common histopathological feature in early age onset (EAO) and late age onset (LAO) was adenocarcinoma (25% and 46%, respectively). Stage III colorectal cancer affected 38 patients, while stage IV affected 48 patients. There was a significant relationship between early age onset and late age onset with histological features ($p < 0.001$). The patients with the highest chemotherapy response had stable diseases in EAO (17 patients) and LAO (20 patients). There was no statistically significant relationship between age, histological features, and stage of colorectal cancer and chemotherapy response ($p > 0.05$). The results of the ordinal logistic regression test showed no systematic relationship between chemotherapy response and age, histopathological features, gender, or cancer stage ($p > 0.05$).

Conclusion There was no association between age and histopathologic features with chemotherapy response and there is no difference in chemotherapy response between early and late age onset.

Keywords
- early-onset
- chemotherapy
- histopathological features
- late-onset

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Introduction

Colorectal cancer is a malignancy that originates from the surface of the lumen of the colon. The most common locations are the descending colon (40%–42%), rectosigmoid and rectum (30%–33%), cecum and ascending colon (25%–-30%), and transverse colon (10%–13%).[1] Colorectal cancer is the third-largest type of cancer in the world after breast and lung cancer. According to the American Cancer Society, the incidence rate of colorectal cancer in men is 44.4 per 100,000 people, while in women it is 34 per 100,000 people. By race, the incidence of colorectal cancer was higher in non-hypnotic blacks (45.7 per 100,000 population), which was nearly 20% higher than in non-Hispanic whites (38.5 per 100,000 population), and least in Asian Americans and Pacific Islanders (30 per 100,000 population).[2]

In Indonesia, the incidence of colorectal cancer ranks fourth after breast cancer, cervical cancer, and lung cancer. The mortality rate of colorectal cancer is 9.1% of the total death cases of 16,002,075; the incidence in Indonesia is 8.6% of the population of all ages from 396,914 cases of malignancy. The number of males was 11.9% out of a total of 183,368, and the number of females was 5.8% out of a total of 213,546 cases. Based on the age of incidence of colorectal cancer in Indonesia, aged 0-49 years, as many as 5.7% of the total number of cases (5,319,887) age over 50 years, as much as 11.2% of the total number of cases (23,873,526).[3] The incidence of colorectal cancer is influenced by various factors, including family history of colorectal cancer, inherited syndromes such as familial adenomatous polyposis (FAP), racial background, ethnicity, age, male gender, history of polyps, previous history of colorectal cancer, history of inflammatory bowel diseases, diabetes mellitus, obesity, high consumption of alcohol, and a diet high in fat and meat and low in fiber.[1]

Histopathologic colorectal cancer, according to the WHO (World Health Organization), is classified into adenocarcinoma, cribriform comedo-type adenocarcinoma, medullary carcinoma, micropapillary carcinoma, mucinous adenocarcinoma, serrated adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma, neuroendocrine carcinoma (large NEC and small NEC), and mixed adenoendocrine carcinoma.[4] Most colorectal cancers originate from the glandular mucosa; histopathologically, 90% are adenocarcinomas; the rest are mucinous carcinomas or signet ring cell carcinomas.[3,5] In 2018, 36 patients with adenocarcinoma rectum were studied in Bandung-West Java, with three patients diagnosed at stage II, ten diagnosed at stage IIIA, twenty diagnosed at stage IIIB, and three diagnosed at stage IIIC. According to the histopathological picture, there were 19 patients who were well differentiated, 15 patients who were moderately differentiated, and two patients who were poorly differentiated.[6]

Colorectal cancer management is multidisciplinary; the choice of therapy such as surgery, chemotherapy, and radiotherapy depend on several factors such as the stage of cancer, histopathology, possible side effects, the patient's condition, and the patient's preferences.[5] Patients with stage III should be given surgical therapy and adjuvant chemotherapy. In patients with stage IV treatment with chemotherapy, surgery is performed if there is uncontrolled feeding bleeding, obstruction, or perforation. For decades, the standard first-line therapy was fluorouracil and leucovorin (5FU/LV), but with the introduction of irinotecan, oxaliplatin, and biological agents targeting angiogenesis and epidermal growth factor receptors, it has been shown to increase life expectancy. Today, first-line agents such as folinic acid, fluorouracil, and oxaliplatin (FOLFOX), oxaliplatin and capecitabine (XELOX), and folinic acid, fluorouracil, and irinotecan hydrochloride (FOLFIRI) are widely used in potentially resectable patients.[7]

There are factors that play a role in the efficacy and toxicity of chemotherapy, both clinically, in the laboratory, and molecularly.[8] Some influential factors include age, gender, performance status, histopathology type, cancer location, and circulating cell tumor levels.[9–11] Based on American Cancer Society research, the incidence of early age-onset (EAO) colorectal cancer has increased while the incidence of late age-onset (LAO) colorectal cancer tends to decrease.[12] In colorectal cancer, early age onset is significantly associated with the microsatellite instability pathway and the development of hereditary cancer syndrome, better known as Lynch syndrome. In several other studies, it is stated that early age onset is associated with stable and sporadic microsatellite pathways. Research has been conducted on the relationship between risk factors, microsatellite instability status, and P53 expression in adenocarcinoma colorectal carcinogenesis in Indonesians.[13]

The response of chemotherapy in patients with early age-onset colorectal cancer is still a debate; some studies say the outcome of patients who do adjuvant and neoadjuvant chemotherapy has worse outcomes compared to patients with late age-onset colorectal cancer. Although therapy is carried out to optimal standards, patients with colorectal cancer with early onset and metastases have worse outcomes than expected. There is an inverse relationship between age and treatment outcomes at early onset and metastasis.[12]

In early-stage colorectal cancer, the most histologically onset type is adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma. Early-onset colorectal cancer is diagnosed with aggressive tumor characteristics. Each histopathological picture has a different chemotherapy response. Based on histopathological features, the degree of differentiation of colorectal carcinoma is divided into well differentiated, moderately differentiated, and poorly differentiated. Based on research, there is a significant relationship between the degree of differentiation and the chemotherapy response. In patients suffering from colorectal malignancy at a young age, poor differentiation is found compared to patients of old age. In patients with histopathological features, poorly differentiated adenocarcinoma has a poor chemotherapy response to neoadjuvant chemotherapy. Patients who underwent chemotherapy and surgery saw their 5-year survival rate increase by 13%, from 50% to 63%.[12,13]

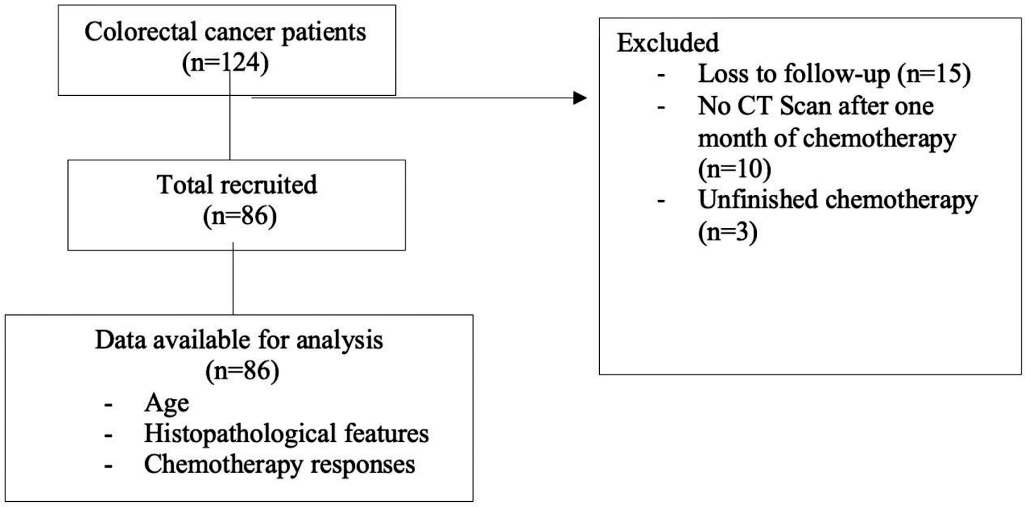

Fig. 1 The flowchart of the study selection process.

There is still controversy about chemotherapy response in patients with colorectal cancer (early age onset), as described in several studies abroad, where the outcome is worse than in patients of old age (late age onset). In Indonesia, the incidence of colorectal cancer at a young age and through mostly sporadic pathways has increased, but the results of the chemotherapy response are still underreported. This study aims to assess the relationship between the age of colorectal cancer patients and histopathological features and chemotherapy response so that an evaluation of therapy options in chemotherapy can be carried out considering histopathological factors and age, which have different tumor biology.

Material and Methods

The research design is a prospective observational study in the West Java, Indonesian population, and follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[14,15] This study compares the age of colorectal cancer patients and histopathological features with chemotherapy response. The subjects in this study were colorectal cancer patients who sought treatment at the Division of Digestive Surgery in the Tertiary Hospital in West Java, Indonesia, during September 2021–August 2022, as seen in ►**Figure 1**. The inclusion criteria in this study were colorectal cancer patients who had been clinically, radiologically, and histopathologically diagnosed and had been treated with systemic chemotherapy. Patients who have finished chemotherapy are then carried out for clinical examinations, laboratory examinations, and computed tomography (CT) scan examinations within one month after the completion of chemotherapy. The exclusion criteria in this study were patients who had not finished a standard cycle of chemotherapy. Patients were divided by age (50 years and $>$ 50 years) and based on histopathological features. Determine chemotherapy response from the assessment of an abdominal CT-scan in patients who have completed chemotherapy.

In this study, the data collected were secondary data. Secondary data is obtained from patient data that has been entered into the colorectal cancer registry. After the data is

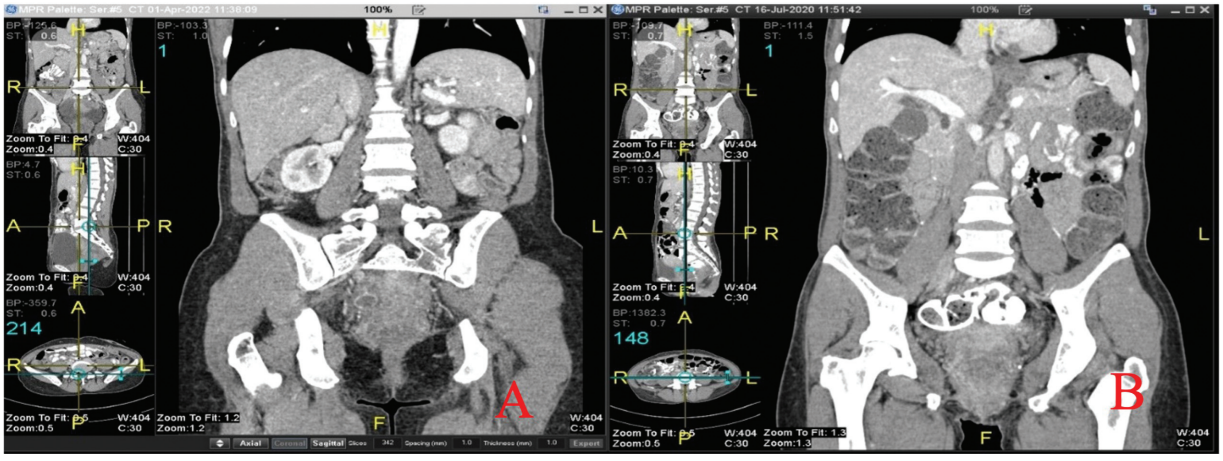

Fig. 2 Complete response to anorectal cancer (A) Does not appear to be residual mass. (B) Irregular wall thickening accompanied by narrowing of the lumen of the distal rectum to the anus.

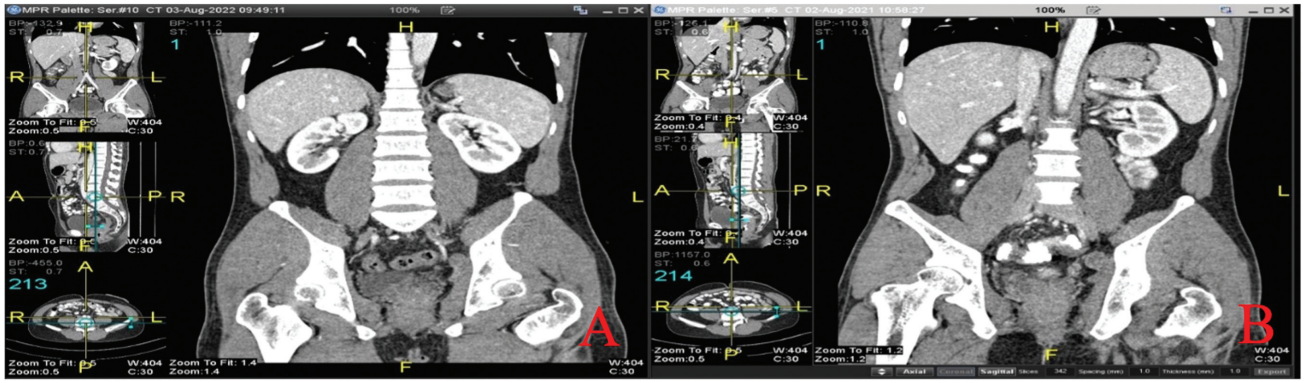

Fig. 3 Partial response to colorectal cancer (A) There are still solid lesions in the intralumen of the sigmoid colon to the proximal rectum, accompanied by thickening of the surrounding wall, slightly reduced in size. (B) Narrowing of the lumen accompanied by irregular wall thickening in the distal sigmoid colon to the anus.

collected, determine the patients who meet the inclusion criteria. Next, divide patients by age, namely less than 50 years and more than 50 years, and divide patients based on histopathological features. Then, determine chemotherapy response from the assessment of CT-Scan results seen through the web-based medical record in patients who have completed chemotherapy. The Response Evaluation Criteria in Solid Tumors (RECIST) Guideline Version 1.0 (RECIST 1.0) was used as a standard for the evaluation of the chemotherapy responses as seen in ►**Figures 1–5**. This study was approved by the hospital's Medical Research Ethics Committee.

The data were analyzed using SPSS version 26. Bivariate statistical tests were used to find the relationship between the age of colorectal cancer patients and histopathological features with chemotherapy response using Chi Square; a P value < 0.05 was considered significant. To see the closeness of the relationship, the contingency coefficient test will be used. Multivariate analysis was used to determine the relationship between age, sex, histopathological features, and stage of colorectal cancer and chemotherapy response using the ordinal logistic regression test.

Result

There were 86 subjects who met the inclusion criteria. Research data obtained includes sex, age, family history, histopathological features, levels of differentiation, and chemotherapy response (►**Table 1**).

Histopathological features and chemotherapy response to age onset are presented in ►**Table 2**. Histopathological features of adenocarcinoma were more common in late age onset, while mucinous adenocarcinoma and signet ring cell carcinoma were found in early age onset. Positive chemotherapy responses are more prevalent at late onset.

In the histopathological features of patients with stages 3 and 4, the majority of chemotherapy responses are in stable diseases (►**Table 3**).

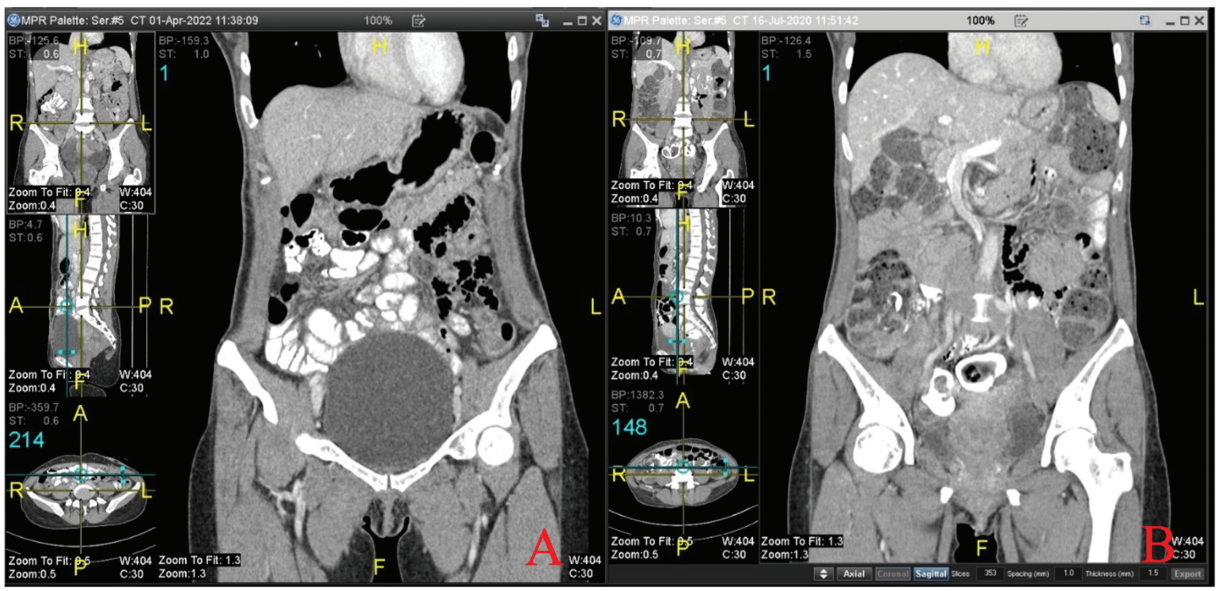

Fig. 4 Stable diseases: colorectal cancer (A) There was no improvement in size compared to image B. (B) Malignancies of the rectum that extend to the inferior part of the anus, to the superior part of the distal sigmoid, as well as to the anterior part of the prostate.

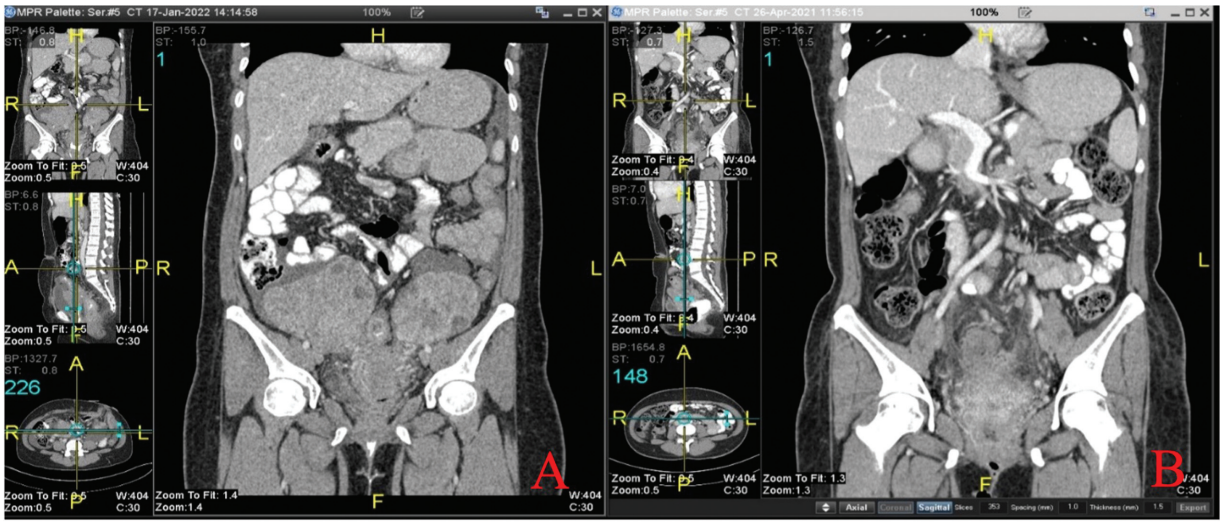

Fig. 5 Progressive diseases: colorectal cancer (A) The mass pushes the small intestine to the superior, to the right lateral, obliterating the caecum, infiltrating the ascending colon and descending colon, and to the inferior, infiltrating the rectum and posterior wall of the uterus. Residual colorectal mass (when compared to previous years, it appears to increase in terms of size; progressive disease according to RECIST guideline version 1.0) (B) Irregular wall thickening is accompanied by narrowing of the lumen in the distal region of the sigmoid colon to the medial rectum that appears to infiltrate the posterior wall of the corpus uteri.

►**Table 4** showed a significant relationship between early age onset and late age onset with histological features ($p < 0.001$).

►**Table 5** showed that there was no statistically significant relationship between age, histological features, and stage of colorectal cancer and chemotherapy response ($p > 0.05$).

Table 1 Characteristics of Research Subjects

Variable	N	%
Sex		
Male	42	48,8
Female	44	51.2
Age (years old)[a]	50.73 ± 13.37	
Early age onset	39	45,3
Late age onset	47	54.7
Family History		
With family history	11	12.7%
Without family history	75	87.3%
Histopathological feature		
Adenocarcinoma	71	82.6
Mucinous adenocarcinoma	6	7.0
Signet ring cell carcinoma	7	8.1
Other histopathology type	2	2.3
Levels of differentiation		
Well differentiated	38	59.4
Moderate differentiated	20	31.3
Poor differentiated	4	6.3
Chemotherapy response		
Complete response	14	16.3
Partial response	21	24.4
Stable diseases	37	43.0
Progressive diseases	14	16.3

[a]Mean ± SD.

►**Table 6** shows that the results of the ordinal logistic regression test showed no systematic relationship between chemotherapy response and age, histopathological features, gender, or cancer stage ($p > 0.05$). Early-stage patients and females have a greater chance of having a worse chemotherapy response. The histopathological type of mucinous adenocarcinoma has a 3.458-fold greater chance of having a worse chemotherapy response than adenocarcinoma. Adenocarcinoma has a 5.593-fold greater chance of having a worse chemotherapy response than signet ring cell carcinoma. Signet ring cell carcinoma has a 2.603-fold greater chance of having a worse chemotherapy response than other types of histopathology. Stage III cancer has a lower chance of having a worse chemotherapy response than stage IV cancer.

Disccusion

Based on the incidence data of the American Cancer Society, it shows that colorectal cancer is more common in men than women. This is also supported by several studies showing that the incidence of men is greater than that of women, although there is no statistically significant difference.[16–18] In this study, it was found that the number of women was higher than the number of men. Presumably, this is because the protective effects of the hormones estrogen and progesterone are only effective during the fertile period and begin to decrease at menopause, so the incidence of colorectal cancer in women over the age of 50 can increase.[19]

Based on age, the incidence of colorectal cancer in Indonesia has been explained before. This shows that the incidence of colorectal cancer cases is higher at late age onset, in line with this study, which found that patients at late age onset (54.7%) had a higher incidence than those at early age onset (45.3%). Age is a risk factor for colorectal cancer and increases sharply after age 50. In line with the

Table 2 Histopathological Features and Chemotherapy Response to Onset

Variable	Early Age Onset (%)	Late Age Onset (%)
Histopathological Features		
Adenocarcinoma	25 (35,2)	46 (64,8)
Mucinous adenocarcinoma	6 (100,0)	0 (0,0)
Signet ring cell carcinoma	7 (100,0)	0 0,0)
Other histopathology type	1 (50,0)	1 (50,0)
Chemotherapy response		
Complete response	6 (42,9)	8 (57,1)
Partial response	9 (42,9)	12 (57,1)
Stable diseases	17 (45,9)	20 (54,1)
Progressive diseases	7 (50,0)	7 (50,0)

Table 3 Chemotherapy Response to Histopathological Features by Cancer Stage

Variable	Chemotherapy response				Total
	Complete response	Partial response	Stable diseases	Progressive diseases	
Histopathological Features by Stage					
Adenocarcinoma					
Stage 3	6	8	11	5	30
Stage 4	5	9	21	6	41
Mucinous adenocarcinoma					
Stage 3	1	0	0	1	2
Stage 4	0	1	2	1	4
Signet ring cell carcinoma					
Stage 3	2	1	2	0	5
Stage 4	0	0	1	1	2
Other Histopathology Type					
Stage 3	0	1	0	0	1
Stage 4	0	1	0	0	1
Total					
Stage 3	9	10	13	6	38
Stage 4	5	11	24	8	48

data obtained in China,[20] Hong Kong,[21] and Japan,[22] almost 90% of patients with cancer are diagnosed after the age of 50. Based on data from the National Cancer Institute, the incidence of colorectal cancer in the United States increases with age.[21] At this time, the incidence of colorectal cancer at early age onset showed an increment, whereas a previous study found that the average age for early age onset colorectal cancer is 44 years, with the majority (75%) of colorectal cancer cases developing between the ages of 40 and 49 years compared to less than 40 years.[17,23]

In this study, it was found that colorectal cancer patients in most of the samples (87.3%) did not have a family history of

Table 4 The Relationship Between Patient Age and Histopathological Features

Variable	Histopathological Features		P Value	CC
	Adenocarcinoma	Other type		
Age				
Early Age Onset	25	14	<0,001	0,405
Late Age Onset	46	1		

Data were analyzed with the Chi Square test, and a P-value of < 0.05 was considered significant.

Table 5 The Relationship Between Patient Age, Histopathological Features, and Stage of Cancer with Chemotherapy Response

Variable	Chemotherapy Response				P Value	CC
	Complete response	Partial response	Stable diseases	Progressive diseases		
Age						
Early Age Onset	6	9	17	7	0,975	0,050
Late Age Onset	8	12	20	7		
Histopathological Features						
Adenocarcinoma	11	17	32	11	1,000	0,302
Others type	3	4	5	3		
Stage of Cancer						
III	9	7	15	7	0,313	0,201
IV	5	14	21	7		

Data were analyzed with the Chi Square test, and a P-value of < 0.05 was considered significant.

colorectal cancer (sporadic). The result was in line with the previous study on the association of risk factors, microsatellite instability, and p53 expression in the carcinogenesis of colorectal adenocarcinoma among Indonesians. That study showed that, unlike other developed countries, colorectal cancer among Indonesians in 40 years is mostly similar compared to >40 years, and both have sporadic cancer pathways.[13]

In this study, colorectal cancer is grouped into four groups based on the highest prevalence, namely adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma,

Table 6 Effect of Age, Histopathological Features, Sex, and Cancer Stage on Chemotherapy Response

	OR	P
Model Fitting Information (Chi-Square)		0.592
Goodness-of-Fit (Pearson)		0.278
Test of Parallel Lines		0.496
Partial Analysis		
Onset		
Early Age Onset	1.437	0.421
Late Age Onset	–	–
Histopathology		
Mucinous Adenocarcinoma	3.458	0.358
Adenocarcinoma	5.593	0.254
Carcinoma cell Signet Ring	2.603	0.517
Other Histopathology Type	–	–
Sex		
Female	1.892	0.123
Male	–	–
Stage		
Stage III	0.937	0.874
Stage IV	–	–

and other types are grouped into other histopathological groups. In a study conducted by Sarasqueta et al.,[18] most groups were in the adenocarcinoma type, which reached 82.6% and was followed by the signet ring cell carcinoma and mucinous adenocarcinoma types. These results are consistent with those of other researchers who have found that adenocarcinoma is the most dominant type because most colorectal cancers originate in the glandular mucosa.[18] Based on research in the North America Association Central Cancer Registry from 2004 to 2015, 87.5% were adenocarcinomas, 7.8% were mucinous adenocarcinomas, 1% were signet ring cell carcinomas, and 3.7% were other histopathologies.[24] conducted by Georgiou et al. in the United Kingdom also showed that the most common histological type was adenocarcinomas (87%), followed by mucinous adenocarcinomas (10%), signet ring cell carcinomas (2%), and other types (1%).[16]

Colorectal differentiation is divided into three categories: well, differentiated, moderately differentiated, and poorly differentiated. In this study, the highest level of differentiation was well differentiated (59.4%). This result is in line with the previous study conducted at Hasan Sadikin Hospital in 2018, in which 19 patients were well differentiated, 15 patients were moderately differentiated, and two patients were poorly differentiated.[6] This result was opposite in Georgious et al. and Cercek et al., where the highest level of differentiation was moderately differentiated at 73% and 76%, respectively, followed by poor differentiation at 19%.[16,17]

In this study, the other histopathological types besides adenocarcinoma were more common at a young age (93.3%). These results are in accordance with the results of Siegel et al. and Sarasqueta's study, in which mucinous adenocarcinoma has a higher young age ratio than adenocarcinoma.[2,18] The age of onset of patients also has a significant relationship with histopathological features, with a P value of < 0.001. This study is in line with Chao Li's study, which found a significant association between young age and histopathological features.[25]

After therapy in colorectal tumors, either by surgery, chemotherapy, or radiotherapy. Evaluation of tumor response to therapy is very important. Chemotherapy response can be assessed based on radiological examination and laboratory examination. Chemotherapy response based on radiological examination using CT scan is based on RECIST criteria, which are categorized into complete response, partial response, stable disease, and progressive disease, as conducted in this study, and is the gold standard for assessment of therapeutic response in solid tumors.[26]

In this study, both early age onset and late age onset showed the same chemotherapy response, and there was no relationship between age and chemotherapy response ($p > 0.05$). In line with the study conducted by Janna Manjelievskasia et al., which states that there is no difference in survival between young and middle age groups even though they have been given multi-regimen adjuvant chemotherapy in the young age group,[27] and the results of Peter J. Kneuertz's study on young age groups in stages 3 and 4, even with multiagent regimens, there are minimal differences in survival rates.[28] The absence of a significant relationship between age and chemotherapy response in this study could be caused by the histopathological type between early age onset and late age onset, which mostly showed adenocarcinoma type, while the other studies showed that early age patients have mucinous adenocarcinoma and signet ring cell carcinoma, poorly differentiated invasion to the perineural and vein, all of which were thought to lead to worse outcomes in early age onset patients.[29]

Mucinous adenocarcinoma and signet ring cell carcinoma are often diagnosed at an advanced stage and respond worse to chemotherapy due to aggressive tumor infiltration growth that invades lymphovascular tissues.[2,16] In this study, there was no statistically significant association between histopathological type and chemotherapy response. In line with research conducted by Benjamin et al., after a multivariate analysis, there was no difference in survival rate between the mucinous and non-mucinous groups after adjuvant chemotherapy.[30] A Korean study found no difference between mucinous adenocarcinoma and adenocarcinoma in adjuvant chemotherapy response in stages I and II.[31] In another study, mucinous adenocarcinomas are more commonly associated with the CpG island methylator phenotype (CIMP), microsatellite instability (MSI), and KRAS mutations, as well as molecular characteristics that support tumor growth and invasion, resulting in aggressive behavior and lymphovascular invasion leading to higher stages.[32–35]

Patients with stage III (node-positive) disease should be treated with surgery and adjuvant chemotherapy. Approved regimens include FOLFOX or XELOX for six months.[7] Patients with stage IV metastases are treated with chemotherapy alone; surgery is performed in cases of uncontrolled GI bleeding, obstruction, or perforation. A small percentage of patients with pulmonary or liver metastases can be treated with a combination of systemic therapy and resection. For decades, the standard first-line therapy was FOLFOX, but the introduction of irinotecan, oxaliplatin, and biological agents targeting angiogenesis and the epidermal growth factor receptor (EGFR) significantly improved survival. First-line options include FOLFOX, XELOX, and FOLFIRI. FOLFIRI is generally used in healthy patients with the potential for resectable tumors. In this study, the relationship between cancer stage and chemotherapy response was tested, but the results obtained were not statistically significant. In line with the research of O'Sullivan et al., who conducted research on chemotherapy response in colorectal cancer patients with early age-onset stages III and IV, there was no difference in survival advantage even with multi-therapy.[36]

In a partial analysis of ordinal logistic regression assays, it was seen that young patients had a greater chance of having a worse chemotherapy response than older patients. Although therapy is carried out to optimal standards, patients with colorectal cancer with early onset and metastases have worse outcomes than expected. with metastases have worse outcomes than expected.[12] Stage III cancer has a better chance of having a chemotherapy response than stage IV cancer. The management of the study sample is different from the maximum standard management in the National Comprehensive Cancer Network (NCCN) guidelines for 2022,[37,38] namely, no targeting therapy is carried out in stage 4 colorectal cancer. In this study sample, 54.6% is stage 4, so it can be one of the factors that affect the results of the study.

Although statistically there was no significant association, there was still a benefit to giving chemotherapy at an early age of onset, even though some literature showed a less significant association. There are several limitations in this study, including the fact that the number of research samples tends to be small and that the condition of the sample is too homogeneous because it tends to be saturated in patients of one sub-group in several groups, so that certain subgroups cannot be analyzed and must be combined with other subgroups because of insufficient data.

The results of this study are expected to be used as a reference in the follow-up research process to conduct research with a larger population and sample on the relationship between age onset, histopathological features, degree of differentiation, and chemotherapy response. Further research needs to be done on a more specific analysis of factors that influence chemotherapy response, including pathway oncogenesis with complete biomolecular examination and selection of stages in accordance with therapeutic standards.

Conclusion

There was no relationship between the patient's age onset and histopathological features with chemotherapy response, which was assessed based on response evaluation criteria in the solid tumors in colorectal cancer population.

Highlights

- Age is a risk factor for colorectal cancer and increases sharply after age 50.
- Adenoma carcinoma is the most prevalent type of colorectal cancer.

- Increasing prevalence of patients with early age-onset colorectal cancer.

Statements and Declarations
The preparation of this study was supported by internal funding from a Research Grant from Riset Kompetensi Dosen Unpad (RKDU) Faculty of Medicine, Universitas Padjadjaran, with registered number 2203/UN6.3.1/PT.00/2022.

Ethical Declaration
The Dr. Hasan Sadikin Hospital ethics committee approved the study with No. Ethical Approval LB.02.01/X.6.5/351/2022. The Dr. Hasan Sadikin Hospital ethics committee approved the study. Every research participant signed an informed consent form before participating in the study.

Author's Contribution
All authors participated in the conception and design of the study, drafting, and finalizing the manuscript. Kiki Lukman, Gun Gun Gunawan, and Prapanca Nugraha participated in collecting the patient's information. Birgitta M. Dewayani and Etis Primastari participated in the histologic examination of the colorectal diagnosis. Reno Rudiman, Yunia Sribudiani, and Lisa Y. Hasibuan analyzed and interpreted the data.

Data Availability
All data and tables used to support the findings of this study are included within the article and available upon request to the corresponding author.

Conflict of Interest
All authors reported the preparation of this study was supported by internal funding from a Research Grant from Riset Kompetensi Dosen Unpad (RKDU) Faculty of Medicine, Universitas Padjadjaran, with registered number 2203/UN6.3.1/PT.00/2022.
The authors have no conflicts of interest to declare.

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