Original Article

Colorectal Cancer Before 45 Years Old: Same Disease, Different Behavior – A Retrospective Cohort Study from Taiwan

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Key Words
Colon cancer;
Colorectal cancer screening;
Rectal cancer;
Young-onset;
Risk factor

Background. Early-onset colorectal cancer (EOCRC) is increasing worldwide and is increasingly recognized as a distinct clinical entity. This study evaluated clinicopathological characteristics and survival outcomes of colorectal cancer (CRC) patients aged £ 45 years compared with those aged > 45 years in Taiwan.

Methods. We retrospectively analyzed 6,909 patients with stage 0-IV CRC who underwent curative-intent surgery between 2011 and 2017 using the Chang Gung Research Database. Patients were stratified into two age groups (≤ 45 vs. > 45 years). Clinicopathological features, laboratory parameters, treatment patterns, overall survival (OS), and disease-free survival (DFS) were compared. Survival analyses were performed using the Kaplan-Meier method.

Results. Of the included patients, 526 (7.6%) were aged ≤ 45 years. Younger patients more frequently presented with aggressive histological subtypes, including mucinous adenocarcinoma and signet-ring cell carcinoma, as well as larger tumors, distal tumor location, and advanced-stage disease. Chemotherapy and neoadjuvant treatment were administered more frequently in younger patients. Elevated inflammatory markers, including white blood cell count, platelet count, and neutrophil-to-lymphocyte ratio, were also observed in the younger cohort. Despite presenting with more advanced disease, younger patients demonstrated significantly better 5-year OS and DFS in stage II and III disease. However, patients with stage IV EOCRC showed inferior DFS and poorer long-term survival compared with older patients.

Conclusion. EOCRC demonstrates distinct clinicopathological characteristics and survival patterns compared with later-onset CRC. Although younger patients often present with aggressive pathological features, survival outcomes in non-metastatic disease remain favorable, likely due to better treatment tolerance. Earlier screening and individualized treatment strategies are warranted for this growing patient population.

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Colorectal cancer (CRC) remains a significant public health concern, with incidence and mortality rates increasing globally. In Taiwan, CRC is the second most common malignancy and third leading cause of cancer-related mortality. Recognizing the increasing trend in CRC diagnoses in younger popula-

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tions, the Ministry of Health and Welfare adjusted its screening guidelines in 2024, lowering the recommended age for fecal occult blood testing to 45-74 years for the general population and 40-44 years for individuals with a family history of CRC.[1]

According to the cancer registry data from the Ministry of Health and Welfare, the age-standardized incidence rate of CRC increased from 22.9 per 100,000 individuals in 1995 to 42.9 per 100,000 in 2019, representing an 87.3% increase. The number of newly diagnosed cases has surpassed 17,000 annually. Concurrently, the age-standardized mortality rate increased from 13.3 per 100,000 in 1995 to 14.6 per 100,000 in 2020, reflecting a 9.8% increase. These data highlight the growing burden of CRC and need for improved early detection strategies.

Emerging evidence suggests that younger CRC patients are more likely to present with lymph node-positive disease than older CRC patients.[2,3] Population-based studies have demonstrated a higher prevalence of lymph node involvement in younger colorectal cancer patients. Similarly, a recent study on rectal cancer found that patients aged under 50 years had a higher likelihood of lymph node positivity and a greater number of positive lymph nodes even after adjusting for the number of lymph nodes examined and other confounding factors.[4] These findings suggest that younger CRC patients may have distinct tumor biology, warranting further investigation.

This study aimed to evaluate the association between age at diagnosis and clinicopathological characteristics, use of adjuvant chemotherapy, disease-free survival (DFS), and overall survival (OS) in patients with stage 0-IV CRC who underwent curative resection at Chang Gung Memorial Hospital. By analyzing these factors, we sought to improve the understanding of age-related differences in CRC.

Methods

Data source

We conducted a retrospective analysis from the data retrieved from the Chang Gung Research Database (CGRD), a dataset derived from the electronic medical records of Chang Gung Memorial Hospital (CGMH). The CGMH system consists of two medical centers, two regional hospitals, and three district hospitals, and is the largest hospital system in Taiwan. According to a cancer registry report from the Taiwan Ministry of Health and Welfare, CGMH provides approximately 14% of the healthcare services for Taiwan's cancer population.[5] The CGRD is de-identified and is systematically updated annually with new data generated by CGMH. It contains clinical epidemiological, laboratory test, inpatient and outpatient, emergency healthcare, pathological report, disease category, surgery, and cancer registry data.[6]

Study population

Patients diagnosed with stage 0-IV CRC who were treated surgically with curative attempt from January 2011 to October 2017 were enrolled in this study. Patients who lacked complete blood cell count data within 1 week prior to the operation were excluded.

Covariates

The baseline variables considered in the analyses included patient age, sex, tumor location, white blood cell (WBC) count, lymphocyte count, neutrophil count, hemoglobin level, neutrophil-to-lymphocyte ratio (NLR), platelet count, serum albumin level, and serum carcinoembryonic antigen (CEA) level.

Patients with International Classification of Diseases for Oncology morphology codes mostly commonly consistent with colorectal cancer (adenocarcinoma NOS (8140), papillary adenocarcinoma (8260), adenocarcinoma in adenomatous polyp (8261), mucinous adenocarcinoma (8480), carcinoid tumor (8240), and signet-ring cell adenocarcinoma (8490)) were included in the analysis.

We also collected data on health-related behaviors, including alcohol consumption, betel nut chewing, and cigarette smoking. The American Joint Committee on Cancer (AJCC) stages were originally coded in the database according to the 6th, 7th, or 8th AJCC edition, depending on the date of diagnosis. Related

data were all transformed to staging according to the 8th AJCC edition to maintain consistency for the purpose of this study.

Outcomes

Our primary outcomes were DFS and OS of patients diagnosed with all stages of CRC who had undergone curative surgical resection of the primary tumor.

Statistics

Descriptive statistics were calculated for patient demographics, tumor characteristics, and outcomes using the chi-squared test, Wilcoxon rank-sum test, or ANOVA as appropriate, based on age grouping. Continuous variables were reported as medians with interquartile ranges. OS and DFS were calculated at 5 years using the Kaplan-Meier method. SPSS Statistics version 26.0 (IBM) and MedCalc 23 were used for the statistical analyses. Statistical significance was set at $p < 0.05$.

Results

A total of 6909 patients with colorectal cancer (including colon, rectal, and anal cancers) identified from 2011 to 2017 were included in the analysis. Fig. 1 illustrates the age distribution of colorectal cancer patients during the study period. Of the included patients, 526 were 45 years and younger of age and 6383 were above 45 years of age. Table 1 compares patient demographics and tumor characteristics between patients aged ≤ 45 years and those aged > 45 years. There was a significantly higher proportion of female patients in the younger group cohort than those > 45 years old (54.0% vs. 41.9%, $p < 0.001$). Patients who were ≤ 45 years of age had higher incidence of mucinous adenocarcinoma (8.4% vs. 4.9%), carcinoid tumor (3.2% vs. 0.4%), and signet ring cell carcinoma

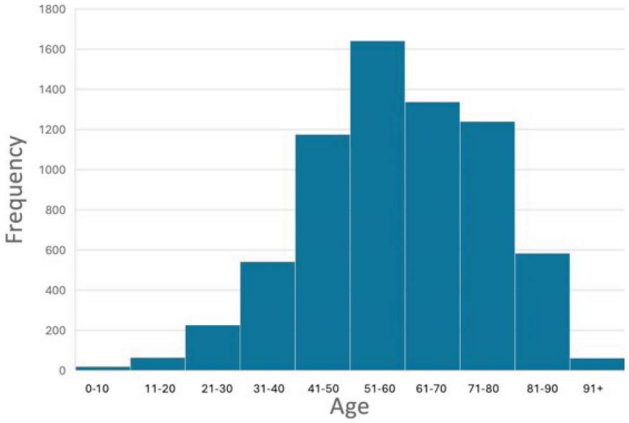

Fig. 1. Age distribution of colorectal cancer patients.

Table 1. Demographics and tumor characteristics of patients ≤ 45 years and > 45 years of age

	age ≤ 45	n = 526	age > 45	n = 6383	*p* value
Age	38.74		66.51		.000
Sex					.000
Male	242	46.0%	3707	58.1%	
Female	284	54.0%	2676	41.9%	
BMI					.034
< 18.5	41	7.8%	349	5.5%	
≥ 18.5	462	87.8%	5654	88.6%	
Unknown	23	4.4%	380	6.0%	
BMI	23.84		24.19		.000
Smoking					.486
Yes	148	71.3%	1891	69.4%	
No	375	28.1%	4430	29.6%	
Unknown	3	0.6%	62	1.0%	
Alcohol					.230
Yes	106	20.2%	1443	22.6%	
No	418	79.5%	4889	76.6%	
Unknown	2	0.4%	51	0.8%	

Table 1. Continued

	age ≤ 45	n = 526		age > 45	n = 6383		*p* value
Betel nuts							.401
Yes	47	8.9%		533	8.4%		
No	477	90.7%		5791	90.7%		
Unknown	2	0.4%		59	0.9%		
Tumor histology							.000
Adenocarcinoma	413	78.5%		5123	80.3%		
Papillary adenocarcinoma	18	3.4%		610	9.6%		
Mucinous adenocarcinoma	44	8.4%		310	4.9%		
Adenocarcinoma in adenomatous polyp	6	1.1%		205	3.2%		
Carcinoid tumor	17	3.2%		24	0.4%		
Signet ring cell carcinoma	11	2.1%		28	0.4%		
Others	17	3.2%		83	1.3%		
Tumor size							.000
< 5 cm	245	46.6%		3571	55.9%		
≥ 5 cm	220	41.8%		2101	32.9%		
Other	61	11.6%		711	11.1%		
Tumor							.000
Right side	118	22.4%		1796	28.1%		
Left side	189	35.9%		2283	35.8%		
Rectum and anus	213	40.5%		2294	35.9%		
Unknown	6	1.1%		10	0.2%		
Obstruction							.000
Yes	179	34.0%		1731	27.1%		
No	316	60.1%		4442	69.6%		
Unknown	31	5.9%		210	3.3%		
Perforation							.001
Yes	31	5.9%		270	4.2%		
No	464	88.2%		5903	92.5%		
Unknown	31	5.9%		210	3.3%		
KRAS gene mutation							.000
Yes	39	7.4%		354	5.5%		
No	70	13.3%		477	7.5%		
Unknown	417	79.3%		5552	87.0%		
Chemotherapy							.000
Yes	308	58.6%		2815	44.1%		
No	159	30.2%		3237	50.7%		
Neoadjuvent	59	11.2%		331	5.2%		
Stage							.000
0	22	4.2%		564	8.8%		
I	80	15.2%		1363	21.4%		
II	117	22.2%		1638	25.7%		
III	178	33.8%		1957	30.7%		
IV	129	24.5%		861	13.5%		
WBC (10^3/μL)	7.81	7.5096	8.1019	7.37	7.2912	7.4392	.000
Neutrophile (10^3/μL)	66.13	65.1742	67.0855	66.01	64.7428	65.2862	.000
Lymphcyte (10^3/μL)	24.62	23.7630	25.4868	25.54	25.2944	25.785	.000
NLR	3.91	3.4999	4.3154	3.83	3.6806	3.98797	.000
Hb (g/dL)	12.29	12.1014	12.4880	12.27	12.2146	12.3162	.000
Platelet (10^3/μL)	305.88	297.1748	314.5931	250.12	247.9134	252.328	.000
Albumin (g/dL)	4.21	4.1559	4.2556	3.98	3.9848	3.9947	.000
CEA (ng/mL)	33.60	18.5866	48.6122	34.03	20.6217	47.2833	.000

(2.1% vs. 0.4%); higher incidence of tumor size above 5 cm (41.8% vs. 32.9%); more rectal and anal tumors (40.5% vs. 35.9%); more tumor obstruction (34.0% vs. 27.1%); more advanced disease (stage III 33.8% vs. 30.7%, stage IV 24.5% vs. 13.5%); and higher proportion receiving chemotherapy (58.6% vs. 44.1%) and neoadjuvant chemotherapy (11.2% vs. 5.2%), than those > 45 years of age. In our analysis comparing laboratory parameters between CRC patients aged ≤ 45 and > 45 years, younger patients exhibited significantly higher levels of WBCs, neutrophils, platelet counts, albumin, and CEA (all $p < 0.001$). The NLR was slightly elevated in the younger patients, reflecting a distinct inflammatory profile.

Figs. 2a-2f presents the Kaplan-Meier survival curves stratified by stage. At 5 years, patients ≤ 45 years of age exhibited significantly better survival than those over 45 years old in stages 0-III, with the differences reaching statistical significance in stages II and III. By contrast, younger patients with stage IV disease had poorer survival. Moreover, the two age groups showed comparable long-term OS when all stages were considered together.

Patients over 45 years old had higher DFS than those under 45 years old at 5 years follow-up. Patients under 45 years old had a higher DFS rate than those over 45 years old when stratified into stages 0 to III, and there was a statistically significant difference at stage II and III (Figs. 3a-3d). However, there was a magnificent decrease in the DFS rate of patients under 45 years old at stage IV, which was even lower than that of patients over 45 years old (Figs. 3e, 3f).

Discussion

CRC in young adults has emerged as a distinct clinical and biological entity, with an increasing number of studies underscoring the need to re-evaluate current diagnostic, therapeutic, and screening paradigms. Our analysis of 6,909 patients who underwent curative surgery for CRC from 2011 to 2017 provides significant insights into age-related disparities in clinical presentation, pathological features, treatment response, and survival outcomes. Particularly, we focused on patients aged ≤ 45 versus > 45 years, revealing nuanced and important differences that align with growing global concerns about early-onset CRC (EOCRC).

Young patients (≤ 45 years) comprised 7.6% of our cohort, a proportion consistent with both Taiwanese and international epidemiological data, which has documented an increasing incidence in this subgroup. This age group had a significantly higher proportion of female patients (54.0% vs. 41.9%, $p < 0.001$), suggesting potential sex-related differences in susceptibility or disease biology.

Biological markers were further distinguished between the two age groups. Younger patients had higher NLRs, platelet counts, and albumin levels, suggesting a distinct inflammatory and nutritional profile at the time of diagnosis. The NLR, a known prognostic biomarker in several malignancies, including CRC, reflects systemic inflammation and is associated with tumor aggressiveness and poor outcomes when elevated.[7] However, in our cohort, the slightly higher NLR in younger patients (3.91 vs. 3.83, $p < 0.001$) did not translate into inferior early-stage outcomes, potentially because of their robust response to therapy.

Anatomical tumor distribution demonstrated notable age-related differences in our cohort. Younger patients more frequently exhibited tumors in distal locations, particularly the rectum and anus (40.5% vs. 35.9%, $p < 0.001$), compared to their older counterparts. This observation suggests a possible etiologic heterogeneity in tumor development across age groups. Supporting this hypothesis, Stoffel et al. reviewed the distinct clinical, pathological, and molecular features of early-onset colorectal cancer (CRC), highlighting a predominance of distal lesions and unique tumor biology in younger patients, including variations in Wnt signaling and lower prevalence of BRAF mutations.[8] These differences not only underscore potential disparities in carcinogenic pathways between age groups but also have practical implications for screening strategies. Specifically, the anatomical predilection for distal tumors in younger patients may affect the diagnostic yield of screening modalities, such as colonoscopy versus sigmoidoscopy, and warrants further consideration in the design of age-appropriate CRC detection programs.

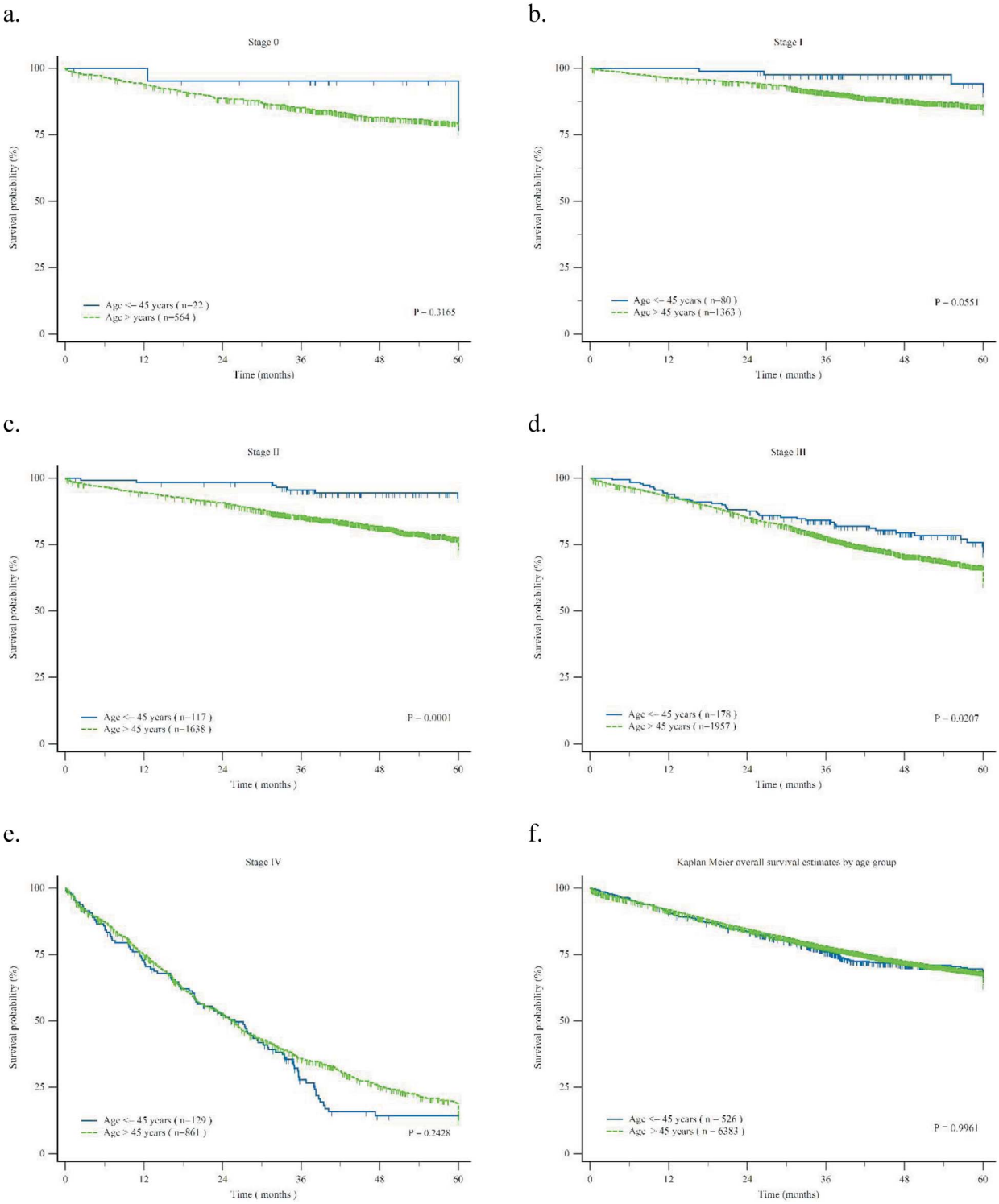

Fig. 2. Kaplan Meier overall survival analysis by stage.

From a histopathological standpoint, younger CRC patients demonstrated more aggressive tumor profiles, as evidenced by the increased prevalence of mucinous adenocarcinoma (8.4% vs. 4.9%), signet ring cell carcinoma (2.1% vs. 0.4%), and carcinoid tumors (3.2% vs. 0.4%). These subtypes are generally associated

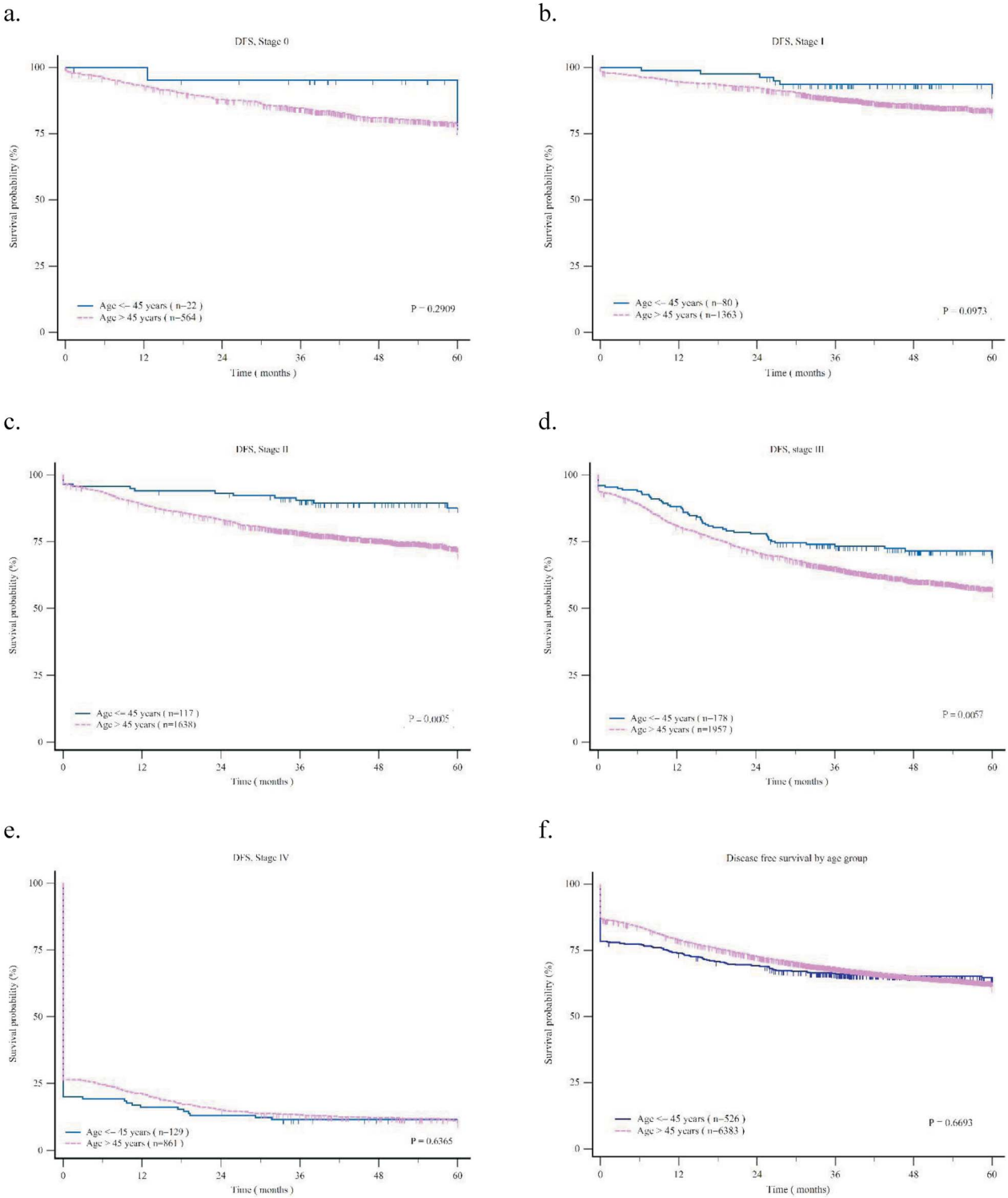

Fig. 3. Kaplan Meier disease free survival analysis by stage, between patients 45 and > 45 years of age, with colorectal cancer.

with poor differentiation, lymphovascular invasion, and a higher likelihood of metastasis. Such tumor biology may explain the significantly greater proportion of younger patients with stage IV disease (24.5% vs.

13.5%, $p < 0.001$), despite their overall better physiological baseline. Wang et al. and Meyer et al. confirmed that young patients were more likely to present with lymph node positivity, peritoneal spread, and unfavorable histology, even after adjusting for other clinical factors.[9,10]

Although younger patients were more likely to present with advanced and symptomatic disease, their OS in the stage-stratified analysis revealed superior outcomes in stages II ($p < 0.001$) and III ($p = 0.021$) and a favorable trend in stage I ($p = 0.055$) compared with that of patients aged over 45 years.[2] This survival advantage may be attributed to multiple factors, including better baseline performance status, fewer comorbidities, and a higher likelihood of receiving multimodal therapy.[11] Notably, chemotherapy and neoadjuvant therapy were significantly more common in the younger cohort (58.6% vs. 44.1% and 11.2% vs. 5.2%, respectively, $p < 0.001$).

In stage IV patients, the OS curves between the two age cohorts began to diverge significantly around the 33-month mark (Fig. 2e), whereas the DFS curves did not show a comparable inflection (Fig. 3e). This discrepancy suggests potential differences in disease course or post-progression survival between younger and older patients. Despite their generally better performance status and tolerance to therapy, younger patients may harbor tumors with more aggressive molecular characteristics, leading to poorer long-term outcomes once treatment resistance develops. In contrast, older patients may experience a more indolent disease course, resulting in relatively stable survival despite advanced disease. Interestingly, the DFS patterns revealed a more nuanced scenario: although no overall DFS difference was observed ($p = 0.669$), younger patients had significantly better DFS in stage II ($p < 0.001$) and stage III ($p = 0.006$), suggesting more effective disease control in intermediate stages. Paradoxically, younger patients with stage IV disease showed worse DFS outcomes, reinforcing the hypothesis of more aggressive tumor biology or therapeutic resistance in advanced disease. These findings are consistent with those of Akinkuotu et al., who reported inferior survival in younger patients with metastatic CRC despite intensive treatment,[12] highlighting the importance of a biology-driven, individualized approach in managing early-onset metastatic CRC.

At the molecular level, young-onset CRC is increasingly being recognized as a genomically distinct disease. A higher prevalence of KRAS mutations was observed among younger patients (7.4% vs. 5.5%, $p < 0.001$), although much of the molecular data remain incomplete owing to limitations in the available genomic profiling. EOCRCs are less likely to harbor BRAF mutations and more likely to exhibit Wnt pathway activation and COMP overexpression, with the latter being associated with epithelial-mesenchymal transition and metastatic potential.[13] These features suggest alternative carcinogenic pathways and the need for targeted therapy development specific for EOCRC.

These findings have significant clinical implications. They support the decision of the American Cancer Society and Taiwan's Ministry of Health to lower the CRC screening age to 45 years for average-risk individuals.[8] However, considering that a considerable number of EOCRC cases occur before the age of 45 years, reliance solely on age-based screening may miss a subset of at-risk individuals. There is an urgent need to develop risk prediction models that incorporate genetic, molecular, behavioral, and environmental factors to better stratify patients for early detection.[8,14]

Therefore, treatment protocols should be revisited. Although younger patients tend to tolerate chemotherapy better, the risk of overtreatment in early-stage disease is non-negligible. For example, Quah et al. demonstrated that young patients receive more aggressive treatment regimens but derive limited incremental survival benefits compared with older patients with similar stage disease.[11] Therefore, age-specific treatment algorithms that possibly integrate molecular profiling and inflammatory markers could help optimize therapeutic outcomes and avoid unnecessary toxicity.

This study has several limitations, including its retrospective nature, potential selection bias, and incomplete molecular profiling (e.g., KRAS, BRAF, and MSI status). Data on treatment-related toxicity and quality of life were also unavailable. Moreover, information on neoadjuvant CCRT for rectal cancer

was not consistently recorded, which may have introduced confounding, especially when comparing colon and rectal cancer outcomes. Despite these limitations, our study remains one of the largest real-world analyses of EOCRC in an Asian population and offers meaningful insights for clinical care and future research.

Conclusion

In conclusion, CRC in patients aged ≤ 45 years is characterized by distinct clinicopathological features, more aggressive tumor biology, and differing treatment responses compared with that in older adults. While younger patients often present with advanced disease and poor prognostic histology, their overall and disease-free survival, particularly in stages II and III, are favorable, likely because of aggressive treatment approaches. However, the inferior DFS observed in metastatic EOCRC and the potential for overtreatment in the early stages underscore the need for age-specific management strategies, including earlier screening, comprehensive molecular profiling, and individualized therapy. Future prospective studies are warranted to delineate the biological mechanisms and optimize treatment algorithms for this growing patient population.

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原　著

45 歲以下大腸直腸癌患者之臨床異質性：來自台灣的回溯性世代研究

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背景　早發性大腸直腸癌 (early-onset colorectal cancer, EOCRC) 之發生率近年於全球持續上升，並逐漸被認為具有獨特的臨床特性與生物學行為。本研究旨在比較台灣 45 歲以下與 45 歲以上大腸直腸癌患者之臨床病理特徵及存活結果差異。

方法　本研究回溯性分析長庚研究資料庫中 2011 年至 2017 年間接受根治性手術之第 0 至 IV 期大腸直腸癌患者，共納入 6,909 位病人，並依診斷年齡分為 ≤ 45 歲與 > 45 歲兩組。比較兩組之臨床病理特徵、實驗室數據、治療方式，以及整體存活率 (overall survival, OS) 與無病存活率 (disease-free survival, DFS)。存活分析採 Kaplan-Meier 方法進行。

結果　共 526 位 (7.6%) 患者年齡 ≤ 45 歲。年輕患者較常出現侵襲性病理亞型，包括黏液性腺癌與印戒細胞癌，並具有較大腫瘤、遠端腫瘤位置及較高比例之晚期疾病。年輕族群接受化學治療與術前治療之比例亦較高。此外，年輕患者具有較高之白血球數、血小板數及嗜中性球與淋巴球比值，顯示其具有不同之發炎反應特徵。儘管年輕患者診斷時多為晚期疾病，但在第二期與第三期中，其 5 年整體存活率與無病存活率均優於高齡患者。然而，在第四期疾病中，年輕患者則呈現較差之無病存活表現與較不良之長期存活結果。

結論　早發性大腸直腸癌具有不同於高齡發病族群之臨床病理特徵與存活模式。雖然年輕患者常伴隨較具侵襲性的病理表現，但在非轉移性疾病中仍具有較佳存活結果，可能與較佳之治療耐受性有關。針對此逐漸增加之族群，應考慮更早期之篩檢策略與個別化治療模式。

關鍵詞　結腸癌、大腸直腸癌篩檢、直腸癌、早期發病、危險因子。