

Age- and Stage-Specific Transitions Between Colorectal Cancer- Specific and Other-Cause Mortality After Resection

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Abstract

Mortality after colorectal cancer (CRC) resection reflects both cancer progression and competing health risks, but their balance may change with age, stage and time already survived. We identified 175,184 patients with stage I-III colorectal adenocarcinoma diagnosed during 2004–2018 who underwent cancer-directed resection in the Surveillance, Epidemiology, and End Results Program. Stage- and age-specific cumulative-incidence functions, Fine-Gray models and landmark analyses were used to compare CRC-specific and other-cause death. In stage I, other-cause mortality became predominant within 1–3 months in all age groups. In stage II, no crossover occurred within 10 years among patients aged < 65 years, whereas stable crossovers occurred between 2.5 and 7.3 years in older groups. No stage III age group crossed within 10 years. Age-by-stage interactions were significant for both outcomes ($P < 0.001$). Among 5-year survivors, subsequent 5-year CRC-death incidences were 4.3%, 8.6% and 13.1% in stages I–III, whereas corresponding other-cause incidences were 16.4%, 18.4% and 12.1%. Mortality composition after CRC resection is jointly associated with age, stage and survival time, supporting individualized prognostic communication, geriatric assessment and survivorship planning.

Introduction

Colorectal cancer (CRC) remains one of the most frequently diagnosed malignancies and a leading cause of cancer death worldwide, with approximately 1.9 million new cases and more than 900,000 deaths estimated in 2022 [1]. Population growth and ageing are expected to increase the absolute CRC burden substantially over coming decades [2]. In the United States, improving detection and treatment have produced a large and ageing survivor population, but prognosis remains strongly dependent on stage at diagnosis [3, 4]. Consequently, the clinical question after resection is not only whether a patient will survive, but also how the balance between CRC-related and noncancer mortality changes as the patient grows older and survives longer.

That balance is particularly important for older adults. Patients of the same chronological age vary widely in frailty, comorbidity, functional reserve, treatment tolerance, and life expectancy, while the evidence base for older and especially oldest-old patients remains limited by their underrepresentation in clinical trials [5–8]. Population-based studies show substantial age disparities after CRC surgery and demonstrate that noncancer deaths account for an increasing share of mortality with advancing age [9–12]. Yet stage may modify this association: competing mortality can become increasingly important after treatment of lower-risk disease, whereas cancer may remain the principal threat in node-positive disease even among very old patients [11–13]. A binary elderly-versus-nonelderly comparison is therefore unlikely to capture the joint clinical effects of age and tumor stage.

Conventional survival estimates are anchored at diagnosis and progressively lose relevance for patients who have already survived several years. Conditional survival updates prognosis according to time already survived and can reveal convergence between initial risk groups [14, 15]. Likewise, a single cause-specific hazard ratio or Kaplan–Meier estimate cannot directly describe absolute event

probabilities when death from another cause precludes CRC death, and time-varying effects may be obscured when proportional hazards do not hold [16]. Cumulative-incidence functions and Fine–Gray models address complementary questions in this setting: the former quantify absolute cause-specific risk in the presence of competing events, whereas the latter estimate covariate associations with the cumulative incidence of the event of interest [17, 18]. However, few population-based CRC studies have integrated granular age categories, AJCC stage, cause-specific cumulative incidence, an explicit time-to-crossover measure, and survivor-conditioned risk.

We therefore analyzed patients with stage I–III colorectal adenocarcinoma who underwent cancer-directed resection in the Surveillance, Epidemiology, and End Results Program. We aimed to (1) characterize stage-specific cumulative incidence of CRC-specific and other-cause death; (2) identify, within five age groups and each AJCC stage, whether and when other-cause mortality became stably predominant; (3) quantify age-by-stage heterogeneity using multivariable Fine–Gray regression; and (4) update the subsequent 5-year mortality composition among 1-, 3-, and 5-year survivors. We hypothesized that the dominant cause of death would shift earlier with increasing age, but that the magnitude and timing of this transition would differ substantially by stage.

Results

Cohort selection and baseline characteristics

Among 509,977 potentially eligible malignant tumor records identified from the SEER database during 2004–2018, 142,556 non-colorectal primary tumors, 29,916 non-adenocarcinoma tumors, 64,657 multiple malignant primaries, 72,497 cases with stage IV or unknown stage or documented M1 disease, 23,495 patients without qualifying cancer-directed resection, and 1,672 patients with unknown cause-of-death classification were excluded. The final analytic cohort comprised 175,184 patients (Fig. 1), including 47,553 (27.1%) with stage I, 59,657 (34.1%) with stage II, and 67,974 (38.8%) with stage III disease.

Overall, 83,433 patients (47.6%) were aged <65 years, 44,174 (25.2%) were aged 65–74 years, 34,284 (19.6%) were aged 75–84 years, 9,522 (5.4%) were aged 85–89 years, and 3,771 (2.2%) were aged ≥90 years. The cohort was 53.2% male and 79.1% White. Stage III patients were more frequently aged <65 years than stage I or II patients (53.2% vs 46.9% and 41.8%, respectively), whereas patients aged 75–84 years and those aged ≥85 years were most prevalent in stage II. Right-colon tumors were most common in stage II (36.8%), whereas rectal tumors were most common in stage III (26.6%). Poorly differentiated tumors accounted for 19.1% of stage III disease compared with 12.2% of stage II and 6.6% of stage I disease. Chemotherapy was recorded in 71.1% of stage III, 31.8% of stage II, and 8.3% of stage I patients. All baseline characteristics differed across AJCC stages ($P \leq 0.001$; Table 1).

Table 1. Baseline demographic, tumor and treatment characteristics according to AJCC stage

Stage-specific competing mortality patterns

The relative contributions of CRC-specific and other-cause mortality differed markedly by AJCC stage (Fig. 2). In stage I, the CIF for other-cause death exceeded that for CRC-specific death throughout follow-up, and the separation widened over time. In stage II, CRC-specific mortality was initially higher, but the two CIFs converged during long-term follow-up and other-cause mortality became predominant at approximately 6–7 years. In stage III, CRC-specific mortality accumulated rapidly during the first several years and remained substantially higher than other-cause mortality throughout the 10-year period.

Age-by-stage crossover in the dominant cause of death

The age-by-stage crossover matrix demonstrated a strong joint dependence of mortality composition on age and disease stage (Fig. 3). In stage I, a stable transition to other-cause-dominant mortality occurred within 1–3 months in every age group: at 3 months among patients aged <65 years and ≥90 years and at 1 month among those aged 65–74, 75–84, and 85–89 years. The corresponding $\Delta 10y$ values increased progressively with age, from +2.8 percentage points in patients aged <65 years to +52.9 percentage points in those aged ≥90 years.

In stage II, no crossover occurred within 10 years among patients aged <65 years ($\Delta 10y$, -7.1 percentage points). A stable crossover was observed at 7.3 years in patients aged 65–74 years, 3.3 years in those aged 75–84 years, 2.5 years in those aged 85–89 years, and 3.2 years in those aged ≥90 years; their respective $\Delta 10y$ values were +4.3, +19.4, +29.4, and +25.1 percentage points. By contrast, no stage III age group experienced a stable crossover within 10 years. At 10 years, CRC-specific mortality remained dominant in stage III, with $\Delta 10y$ values ranging from -23.4 percentage points in patients aged <65 years to -5.0 percentage points in those aged 85–89 years.

Multivariable Fine–Gray analyses

After multivariable adjustment, increasing age was associated with higher subdistribution hazards of both CRC-specific and other-cause death within every AJCC stage (all individual comparisons $P < 0.001$; Table 2). For CRC-specific death, compared with patients aged <65 years, sHRs for ages 65–74, 75–84, 85–89, and ≥90 years were 1.44 (95% CI, 1.33–1.54), 1.97 (1.83–2.11), 2.50 (2.23–2.79), and 3.35 (2.82–3.99), respectively, in stage I; 1.28 (1.22–1.33), 1.56 (1.49–1.63), 1.91 (1.79–2.03), and 2.45 (2.23–2.70) in stage II; and 1.23 (1.19–1.27), 1.68 (1.62–1.74), 1.99 (1.88–2.12), and 2.54 (2.31–2.80) in stage III. The age group $\times$ AJCC stage interaction was significant (Wald $\chi^2 = 44.69$; $df = 8$; $P < 0.001$).

Age-related gradients were substantially larger for other-cause death. Relative to patients aged <65 years, sHRs for ages 65–74, 75–84, 85–89, and ≥90 years were 2.96 (95% CI, 2.84–3.08), 6.12 (5.87–6.38), 9.08 (8.57–9.61), and 10.63 (9.67–11.68), respectively, in stage I; 2.54 (2.43–2.65), 4.56 (4.37–4.75), 6.10 (5.81–6.41), and 6.24 (5.76–6.76) in stage II; and 2.82 (2.70–2.95), 4.31 (4.11–4.51), 5.08

(4.77–5.41), and 4.77 (4.30–5.28) in stage III. The interaction between age group and AJCC stage was highly significant for other-cause death (Wald $\chi^2=436.64$; df=8; $P<0.001$), indicating that the magnitude of age-associated competing mortality varied by stage.

Table 2. Multivariable Fine–Gray regression analysis of age-group associations with colorectal cancer-specific and other-cause mortality within AJCC stage

AJCC stage	Age group, years	CRC-specific death		Other-cause death	
		sHR (95% CI)	<i>P</i> value	sHR (95% CI)	<i>P</i> value
Stage I	<65	1.00 (Reference)	—	1.00 (Reference)	—
	65–74	1.44 (1.33–1.54)	<0.001	2.96 (2.84–3.08)	<0.001
	75–84	1.97 (1.83–2.11)	<0.001	6.12 (5.87–6.38)	<0.001
	85–89	2.50 (2.23–2.79)	<0.001	9.08 (8.57–9.61)	<0.001
	≥90	3.35 (2.82–3.99)	<0.001	10.63 (9.67–11.68)	<0.001
Stage II	<65	1.00 (Reference)	—	1.00 (Reference)	—
	65–74	1.28 (1.22–1.33)	<0.001	2.54 (2.43–2.65)	<0.001
	75–84	1.56 (1.49–1.63)	<0.001	4.56 (4.37–4.75)	<0.001
	85–89	1.91 (1.79–2.03)	<0.001	6.10 (5.81–6.41)	<0.001
	≥90	2.45 (2.23–2.70)	<0.001	6.24 (5.76–6.76)	<0.001
Stage III	<65	1.00 (Reference)	—	1.00 (Reference)	—
	65–74	1.23 (1.19–1.27)	<0.001	2.82 (2.70–2.95)	<0.001
	75–84	1.68 (1.62–1.74)	<0.001	4.31 (4.11–4.51)	<0.001
	85–89	1.99 (1.88–2.12)	<0.001	5.08 (4.77–5.41)	<0.001
	≥90	2.54 (2.31–2.80)	<0.001	4.77 (4.30–5.28)	<0.001
Age group × AJCC stage interaction		Wald $\chi^2 = 44.69$; df = 8	<0.001	Wald $\chi^2 = 436.64$; df = 8	<0.001

Note: Values are presented as subdistribution hazard ratios with 95% confidence intervals. Within each AJCC stage, patients aged <65 years served as the reference group.

The models included the main effects of age group and AJCC stage and their interaction and were adjusted for sex, race, marital status, diagnosis period, tumor location, histologic subtype, tumor grade, and chemotherapy. *P* values for individual contrasts and interaction terms were obtained using Wald tests; reference-category *P* values are not applicable.

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CRC, colorectal cancer; sHR, subdistribution hazard ratio.

Conditional 5-year cumulative incidence among survivors

Across the separately defined landmark risk sets, the subsequent 5-year composition of mortality differed according to the survival time already attained (Fig. 4). These estimates compare conditional prognosis among eligible survivors at each landmark rather than longitudinal changes within the same fixed cohort. In stage I, the conditional 5-year CIF for CRC-specific death remained low at diagnosis and among 1-, 3-, and 5-year survivors (5.4%, 4.7%, 4.8%, and 4.3%, respectively), whereas the corresponding CIF for other-cause death was 11.7%, 12.1%, 14.3%, and 16.4%.

In stage II, the conditional 5-year CIF for CRC-specific death declined steadily from 15.1% at diagnosis to 13.3%, 11.5%, and 8.6% among 1-, 3-, and 5-year survivors. Conversely, the conditional 5-year CIF for other-cause death was 13.7% at diagnosis, remained essentially unchanged at 13.6% among 1-year survivors, and subsequently increased to 16.1% and 18.4% among 3- and 5-year survivors, respectively; other-cause mortality therefore slightly exceeded CRC-specific mortality by the 1-year landmark, and the difference widened thereafter. In stage III, the conditional 5-year CRC-specific CIF decreased from 26.6% at diagnosis to 24.9%, 19.3%, and 13.1%, whereas the other-cause CIF changed from 9.1% to 8.5%, 10.2%, and 12.1%. Thus, CRC-specific mortality remained predominant among stage III survivors, although the two causes approached near parity among patients who had already survived 5 years.

Sensitivity analyses

Cause-specific Cox regression produced the same qualitative pattern as the primary Fine–Gray analysis (Supplementary Table S2). Increasing age was associated with progressively higher cause-specific hazards of CRC-specific and other-cause death within each stage (all $P < 0.001$). For CRC-specific death, the age group $\times$ AJCC stage interaction remained significant (Wald $\chi^2 = 57.72$; $df = 8$; $P < 0.001$); the corresponding interaction for other-cause death was also significant (Wald $\chi^2 = 114.61$; $df = 8$; $P < 0.001$). The largest cause-specific hazard ratios were observed in stage I patients aged ≥ 90 years: 6.43 (95% CI, 5.43–7.63) for CRC-specific death and 23.42 (21.31–25.74) for other-cause death.

Results were also robust in the 3-month landmark Fine–Gray analysis (Supplementary Table S3). All older age groups retained significantly elevated subdistribution hazards for both outcomes within each AJCC stage (all $P < 0.001$). The age group $\times$ AJCC stage interaction remained significant for CRC-specific death (Wald $\chi^2 = 68.98$; $df = 8$; $P < 0.001$) and other-cause death (Wald $\chi^2 = 343.27$; $df = 8$; $P < 0.001$). Among patients aged ≥ 90 years, sHRs for CRC-specific death were 2.46 (95% CI, 1.98–3.06), 1.92 (1.73–2.14), and 2.43 (2.18–2.72) in stages I, II, and III, respectively; corresponding sHRs for other-cause death were 12.72 (11.51–14.06), 7.93 (7.36–8.54), and 5.66 (4.98–6.42). These findings confirmed that the principal

age- and stage-dependent patterns were not driven solely by deaths occurring during the first 3 months after diagnosis.

Discussion

In this population-based cohort of 175,184 patients with stage I–III CRC treated by cancer-directed resection, age and AJCC stage were jointly associated with both the magnitude and temporal composition of mortality. Three findings are central. First, other-cause mortality was predominant almost immediately after stage I disease across all ages, and its 10-year excess over CRC mortality widened steeply with age. Second, stage II represented a transition state: CRC mortality remained dominant for patients aged <65 years, but a stable crossover occurred progressively earlier in older groups, from 7.3 years at ages 65–74 to approximately 2.5–3.3 years at ages ≥ 75 . Third, CRC mortality remained dominant for 10 years after stage III disease in every age group, including patients aged ≥ 90 years. Comparisons across the separately defined landmark survivor cohorts reinforced the dynamic nature of these patterns: conditional 5-year CRC mortality was generally lower among patients who had already survived longer, whereas the relative contribution of other causes was generally greater. Significant age-by-stage interactions in both Fine–Gray and cause-specific models confirmed that chronological age did not have a uniform prognostic meaning across stages.

The sharp separation by stage is clinically coherent but adds information beyond conventional stage-specific survival. Contemporary guidelines appropriately intensify postoperative systemic therapy according to recurrence risk in localized colon cancer [19,20], and the duration and tolerability of oxaliplatin-based therapy remain particularly relevant in stage III disease [21]. Rectal cancer pathways additionally reflect local-recurrence risk and multimodality treatment [22]. Our results do not challenge those disease-specific recommendations; rather, they show that the competing context in which benefits and harms are experienced differs markedly. In stage I, the rapid and sustained predominance of other-cause death indicates that long-term overall survival is increasingly determined by health conditions outside CRC, particularly at advanced age. In stage III, by contrast, the absence of crossover indicates that high cancer-specific risk remains clinically consequential even in the oldest groups. Age alone should therefore not be used to infer that CRC-directed treatment or surveillance has little potential value. Stage II occupies an intermediate zone in which age, life expectancy, pathologic risk, treatment tolerance, and patient priorities warrant especially individualized discussion.

The conditional estimates have direct implications for survivorship care. Surveillance recommendations are commonly concentrated within the first 3–5 years after treatment and should be adapted to recurrence risk, functional status, and whether a patient would be eligible for treatment if disease were detected [23,24]. Conditional survival provides the appropriate conceptual framework because the prognosis of a patient who has remained event-free is not the same as the prognosis estimated on the day of diagnosis [25]. Prior CRC studies have shown marked improvement in conditional survival and attenuation of excess mortality with increasing years survived [26–28]. In our study, the subsequent 5-year CRC-death CIF fell from 15.1% at diagnosis to 8.6% among 5-year survivors with stage II disease

and from 26.6% to 13.1% in stage III disease. At the same time, other-cause risk rose to 18.4% in stage II and 12.1% in stage III. These estimates argue for a deliberate shift in survivorship priorities rather than an abrupt end to cancer care: recurrence-focused assessment remains important, but cardiovascular disease, second cancers, functional decline, nutrition, falls, and chronic-disease management account for a growing share of preventable morbidity and mortality. The crossover time should therefore be interpreted as a descriptive marker of population-level risk composition, not as a treatment threshold or a date on which surveillance should automatically stop.

Chronological age also cannot substitute for biological age. Frailty is a multidimensional state of reduced reserve and vulnerability to stressors [29], and both ASCO and NCCN recommend structured geriatric assessment to identify deficits that are not captured by routine oncology evaluation [30,31]. Randomized trials have shown that geriatric assessment–guided management can reduce serious treatment toxicity, improve communication, and support goal-concordant care without necessarily compromising cancer treatment [32–34]. Importantly for CRC, the GERICO trial found that a geriatric intervention increased completion of planned adjuvant chemotherapy among frail older patients [35]. Validated toxicity-prediction approaches and brief screening instruments can further identify patients who need comprehensive assessment [36–38]. These data provide a practical interpretation of our findings: a fit 85-year-old with stage III disease may still face CRC as the dominant threat and merit active cancer-directed management, whereas a frail patient with stage I disease may derive greater absolute benefit from rehabilitation, medication review, fall prevention, and optimization of cardiometabolic disease. The relevant decision is not whether a patient is “too old,” but which risks are modifiable and which outcomes matter most to that individual.

Several methodological features strengthen the analysis. The large, population-based cohort permitted separation of patients aged 85–89 and ≥ 90 years, groups that are usually pooled or excluded. Absolute CIFs were used because standard Kaplan–Meier methods overestimate event probability when competing deaths are treated as noninformative censoring [17]. The SEER cause-specific death classification has demonstrated reasonable utility for population-based survival analyses [39,40]. We also reported both Fine–Gray and cause-specific models because these estimands address complementary questions: subdistribution hazards relate covariates to cumulative incidence, whereas cause-specific hazards describe the instantaneous event rate among patients currently event-free [41,42]. The concordance of the primary Fine–Gray analysis, cause-specific Cox models, and 3-month landmark analysis supports the robustness of the principal age-by-stage pattern. Finally, the crossover matrix translates two continuous CIF curves into an interpretable summary while retaining the 10-year risk difference, thereby distinguishing near-equipoise from large and persistent dominance of one cause.

The findings also highlight where better evidence is needed. Contemporary population data continue to show higher perioperative vulnerability among older patients after CRC resection [43], yet carefully selected older patients can receive and benefit from modern adjuvant strategies; pooled trial data suggest that oxaliplatin-based therapy remains feasible in many patients aged ≥ 70 years, although adverse events and early discontinuation require close attention [44]. Trials designed specifically for

older or frail adults, with geriatric measures and patient-centered outcomes embedded from the outset, are therefore essential [45]. Our age-by-stage matrix could help define clinically meaningful strata for such studies and could support shared decision-making by presenting both CRC and competing mortality rather than a single overall-survival estimate. External validation using registries with comorbidity, frailty, treatment-dose, and recurrence data should be a priority before the crossover estimates are used in bedside prediction tools.

This study has limitations. First, its retrospective observational design precludes causal interpretation of treatment effects and remains vulnerable to residual confounding and selection into cancer-directed resection. Second, SEER does not capture comorbidity burden, frailty, performance status, cognition, social support, detailed chemotherapy regimens or dose intensity, treatment complications, recurrence, resection-margin status, or contemporary molecular markers such as mismatch-repair status. Recorded chemotherapy information may be incomplete, and changes in treatment across 2004–2018 may not be fully represented by diagnosis period. Third, AJCC stage required harmonization across several SEER-derived fields and editions; residual stage misclassification is possible despite restriction to stage I–III disease without documented M1 status. Fourth, cause-of-death assignment in registry data is imperfect, although SEER cause-specific classification has demonstrated reasonable utility for population survival analyses [39,40]. Fifth, landmark cohorts necessarily selected survivors and therefore describe prognosis conditional on survival rather than the original population; they should not be compared as if randomized groups. Sixth, the broad <65-year reference category may conceal heterogeneity among younger adults, whereas the oldest age groups, despite the large source cohort, still contained fewer patients. Seventh, the crossover definition depends on follow-up length, curve precision, and the requirement that other-cause CIF remain higher; it is an interpretable summary of observed risks, not a biological change point. Eighth, crossover times were descriptive point estimates without formal confidence intervals and may be sensitive to monthly time resolution and curve precision near the end of follow-up. Ninth, proportional relative-hazard effects may not remain constant throughout long-term follow-up; therefore, the Fine–Gray and cause-specific hazard ratios should be interpreted as average associations and in conjunction with the CIF and landmark estimates.

In conclusion, mortality after cancer-directed resection of stage I–III CRC is dynamic and cannot be summarized adequately by age or stage alone. Other-cause mortality dominates early after stage I disease, overtakes CRC mortality at age-dependent times after stage II disease, and does not surpass CRC mortality within 10 years after stage III disease. Across cohorts conditional on progressively longer survival, the subsequent CRC-death risk was lower and competing mortality became increasingly important. Integrating stage, granular age, time already survived, and geriatric vulnerability may improve prognostic communication, surveillance planning, and treatment decisions across the expanding population of older CRC survivors.

Methods

Data source and study design

This population-based retrospective cohort study used data from the Surveillance, Epidemiology, and End Results (SEER) 17 Registries Research Plus database (November 2025 submission). Cases were extracted using SEER*Stat version 9.0.43, with follow-up available through 2023. The analysis included patients diagnosed between 2004 and 2018, permitting harmonization of SEER-derived stage-group variables across the study period while allowing long-term follow-up. The study objective was to characterize how age and AJCC stage jointly shaped the balance between CRC-specific mortality and mortality from other causes after cancer-directed resection of the primary tumor.

This study used de-identified registry data made available to authorized users under the SEER Research Data Agreement and involved no direct contact with participants. Institutional review board approval and individual informed consent were therefore not required. All analyses were conducted in accordance with relevant guidelines and regulations. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study population

Potentially eligible malignant tumor records diagnosed during 2004–2018 were identified from the SEER extraction. Colorectal primary sites were defined by ICD-O-3 topography codes C18.0–C18.9, C19.9, and C20.9. Eligible adenocarcinoma histologies comprised conventional adenocarcinoma (8140/3, 8210/3, and 8260/3–8263/3), mucinous adenocarcinoma (8480/3 and 8481/3), and signet-ring cell carcinoma (8490/3). The cohort was restricted to a first or only malignant primary, SEER-derived stage I–III disease without documented M1 disease, qualifying cancer-directed resection of the primary tumor, and known cause-of-death classification. Cancer-directed resection was identified using RX Summ–Surg Prim Site (1998–2022) codes 30–80, encompassing segmental or more extensive colectomy/proctectomy procedures. Codes 00–29 (no surgery, tumor destruction, or local excision), 90 (surgery not otherwise specified), 99 (unknown), and missing codes were excluded. The same surgery-code range was applied to colon, rectosigmoid-junction, and rectal primaries, while its site-specific labels were interpreted according to the SEER coding manual. Detailed cohort definitions are provided in Supplementary Table S1, and the selection process is summarized in Fig. 1.

Outcomes and follow-up

Follow-up time was measured in months from diagnosis to death or last recorded follow-up, with follow-up available through 2023. Vital status, the SEER cause-specific death classification, the SEER other-cause death classification, and the cause of death to site recode were used to define a three-level competing-risk outcome: 0 for alive or censored, 1 for CRC-specific death, and 2 for death from causes other than CRC. Records coded as dead with missing or unknown cause of death were excluded. CRC-specific death and other-cause death were treated as mutually competing events. The principal outcomes were the cumulative incidence and subdistribution hazard of each cause of death.

Exposure, stage, and covariates

Age at diagnosis was categorized as <65, 65–74, 75–84, 85–89, and ≥90 years, with patients aged <65 years serving as the reference group. Stage was harmonized as AJCC stage I, II, or III using the Derived AJCC Stage Group, 6th edition, for 2004–2009; Derived AJCC Stage Group, 7th edition, for 2010–2015; SEER Combined Stage Group for 2016–2017; and Derived EOD 2018 Stage Group for 2018.

Prespecified adjustment covariates were sex; race (White, Black, Asian or Pacific Islander, American Indian/Alaska Native, or Unknown); marital status (married, unmarried, or unknown); diagnosis period (2004–2009, 2010–2014, or 2015–2018); primary tumor location (right colon, left colon, rectosigmoid junction, or rectum); histologic subtype (conventional adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma); tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown); and chemotherapy (yes vs no/unknown). Unknown categories were retained where prespecified, and no imputation was performed. Detailed variable definitions and SEER source fields are provided in Supplementary Table S1.

Stage-specific cumulative-incidence and crossover analyses

Nonparametric cumulative-incidence functions (CIFs) for CRC-specific death and other-cause death were estimated in the presence of competing risks and plotted separately for AJCC stages I, II, and III over 10 years. To quantify age-dependent changes in the dominant cause of mortality, CIFs were additionally estimated within each age-by-stage subgroup. The stable crossover time was defined as the earliest time at which the CIF for other-cause death equaled or exceeded the CIF for CRC-specific death and remained higher through the end of the 10-year observation window. Subgroups without such a transition were classified as having no crossover within 10 years. The 10-year difference ($\Delta 10y$) was calculated as the other-cause-death CIF minus the CRC-specific-death CIF and expressed in percentage points. The crossover time and $\Delta 10y$ were prespecified descriptive, exploratory summaries of the observed CIF curves; formal confidence intervals were not calculated for crossover time.

Landmark conditional 5-year cumulative incidence

Landmark analyses were performed at diagnosis and separately among patients who had survived and remained under observation for 1, 3, and 5 years. At each postdiagnosis landmark, a new risk set was defined by restricting the cohort to patients alive and under observation at that time; follow-up was then reset to the landmark, and the subsequent 5-year CIFs of CRC-specific and other-cause death were re-estimated. Accordingly, the landmark estimates describe prognosis conditional on survival to each specified time point and should not be interpreted as repeated longitudinal measurements within a fixed cohort.

Statistical analysis

Baseline characteristics were summarized as counts and percentages and compared across AJCC stages using Pearson's chi-squared tests. Multivariable Fine–Gray regression models were fitted separately for CRC-specific death and other-cause death. Each model included the five-category age-group variable, AJCC stage, and an age group $\times$ AJCC stage interaction, with adjustment for sex, race, marital status, diagnosis period, tumor location, histologic subtype, tumor grade, and chemotherapy. Stage-specific adjusted subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs) were derived using patients aged <65 years within the same AJCC stage as the reference group. The overall interaction was assessed using an 8-degree-of-freedom Wald test.

Two sensitivity analyses were undertaken. First, analogous cause-specific Cox models were fitted for each outcome; deaths from the competing cause were censored (Supplementary Table S2). Second, the Fine–Gray models were repeated in a 3-month landmark cohort restricted to patients who were alive and under observation for more than 3 months, with 3 months subtracted from the original follow-up time (Supplementary Table S3). Analyses were conducted in R version 4.4.2 using the survival, cmprsk, fastcmprsk, and ggplot2 packages. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

During manuscript preparation, the authors used ChatGPT (OpenAI) for English-language editing and formatting support. The authors reviewed and edited all output and take full responsibility for the content of the manuscript.

Abbreviations

AJCC
American Joint Committee on Cancer
CI
confidence interval
CRC
colorectal cancer
sHR
subdistribution hazard ratio.

Declarations

Competing interests

The authors declare no competing interests.

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Author Contribution

W.L., G.X. and W.S. contributed equally to this work and were responsible for study conception and design, data curation, statistical analysis, interpretation of the results, and drafting of the manuscript. M.Z., F.Y., B.R., W.M., X.D., Y.P. and N.Y. contributed to the interpretation of the findings and critically revised the manuscript. D.S. supervised the study, provided methodological and clinical guidance, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data Availability

The data analysed in this study are available from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program upon completion of the SEER Research Data Agreement and approval for access to the applicable data release.

Code availability

The R code used for data processing and statistical analyses is available from the corresponding author upon reasonable request.

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Table

Table 1 is available in the Supplementary Files section.

Figures

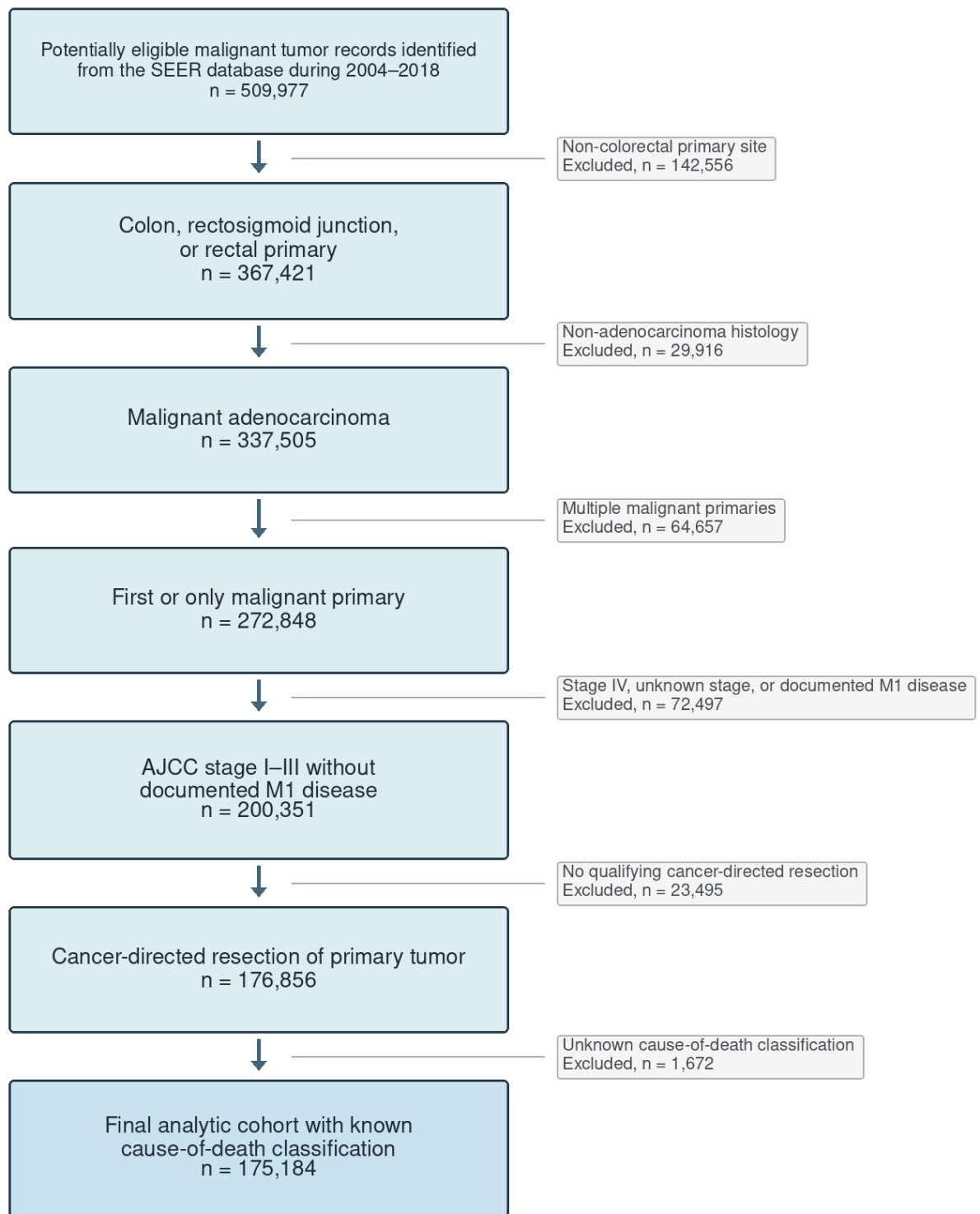


Figure 1

Flow diagram of cohort selection. Potentially eligible malignant tumor records identified from the SEER database during 2004–2018 were sequentially restricted by colorectal primary site, adenocarcinoma histology, first or only malignant primary, stage I–III disease without documented M1 disease, qualifying cancer-directed resection (RX Summ–Surg Prim Site codes 30–80), and known cause-of-death classification.

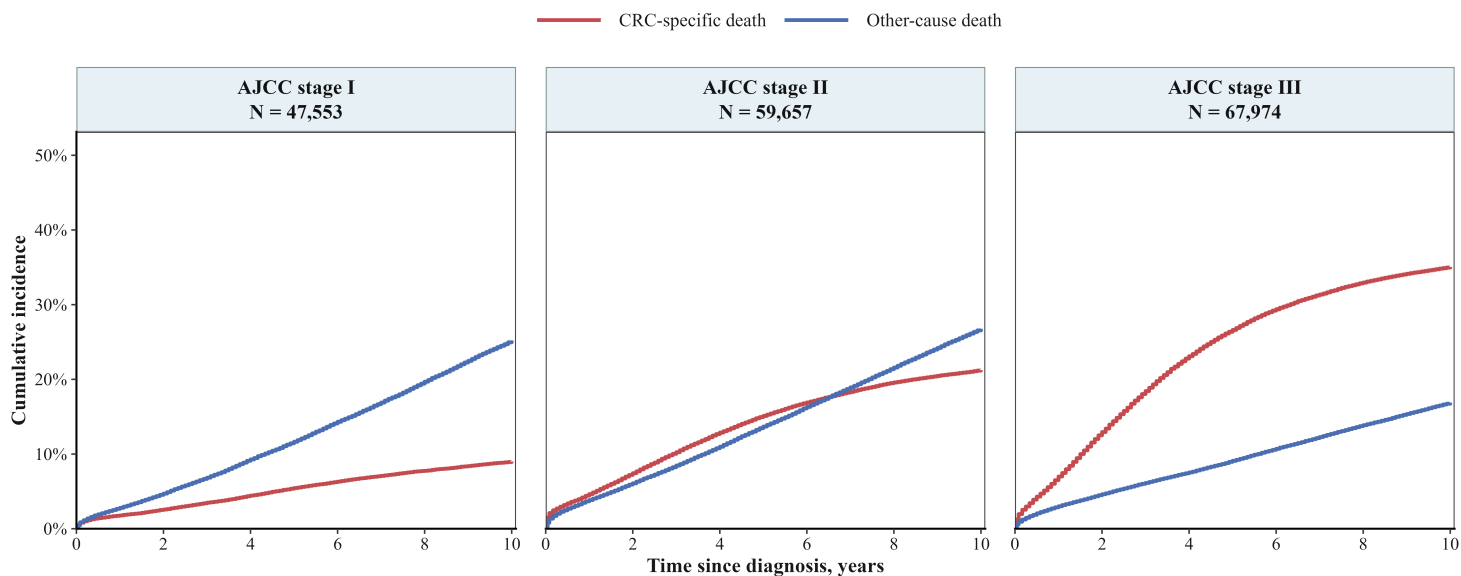


Figure 2

Stage-specific cumulative-incidence functions for colorectal cancer (CRC)-specific death and other-cause death after cancer-directed resection. Curves were estimated in the presence of mutually competing causes of death and truncated at 10 years after diagnosis.

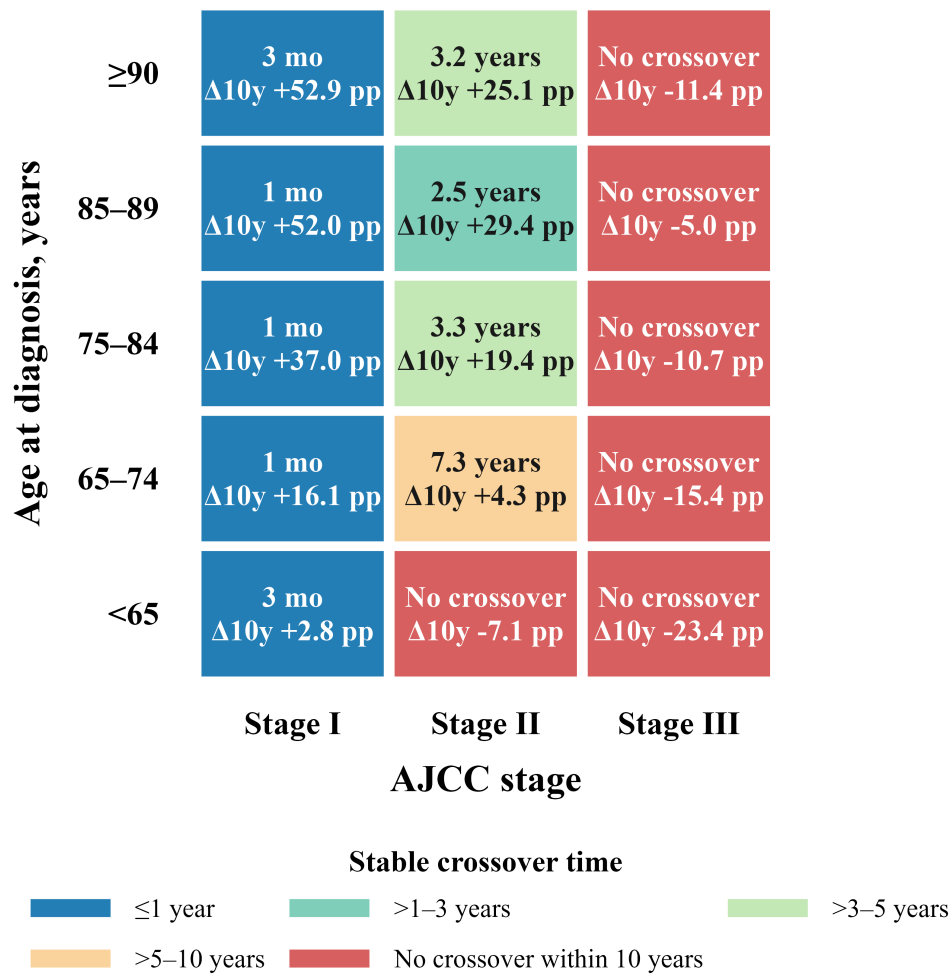


Figure 3

Age-by-stage matrix of the stable crossover between other-cause and CRC-specific cumulative incidence. Stable crossover was defined as the earliest time at which other-cause cumulative incidence equaled or exceeded CRC-specific cumulative incidence and remained higher through 10 years. Δ10y denotes the 10-year other-cause cumulative incidence minus the 10-year CRC-specific cumulative incidence, expressed in percentage points. Crossover times are descriptive exploratory estimates; formal confidence intervals were not calculated.

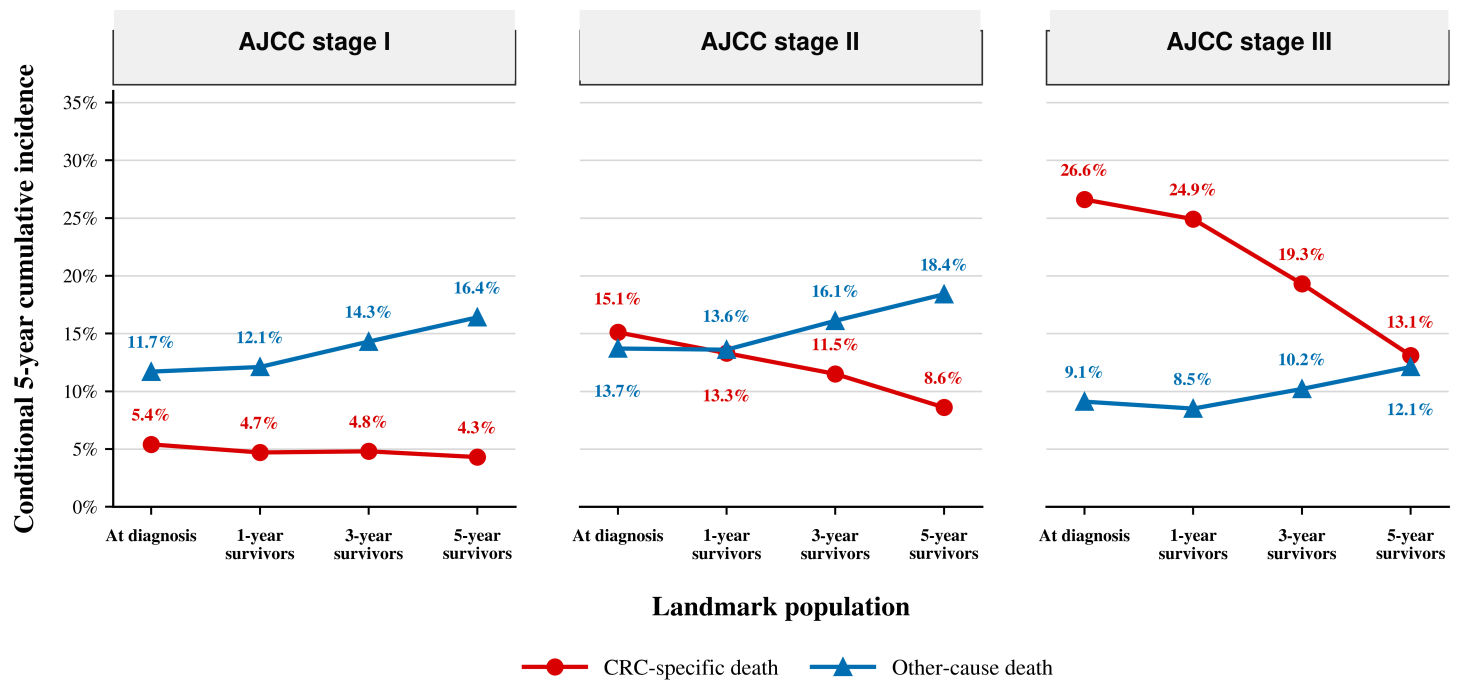


Figure 4

Subsequent 5-year cumulative incidence of CRC-specific and other-cause death at diagnosis and among patients alive and under observation at the 1-, 3-, and 5-year landmarks, according to AJCC stage. Overall landmark population sizes were 175,184 at diagnosis, 160,246 at 1 year, 121,071 at 3 years, and 88,510 at 5 years. Each point represents a separately defined landmark risk set and should not be interpreted as a longitudinal trajectory of the same fixed cohort.

Supplementary Files

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- [SupplementaryInformation.pdf](#)
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