Impact of old age on resectable colorectal cancer outcomes

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Objective: This study was performed to identify a reasonable cutoff age for defining older patients with colorectal cancer (CRC) and to examine whether old age was related with increased colorectal cancer-specific death (CSD) and poor colorectal cancer-specific survival (CSS).

Methods: 76,858 eligible patients from the Surveillance, Epidemiology and End Results (SEER) database were included in this study. The Cox proportional hazards regression model and the Chow test were used to determine a suitable cutoff age for defining the older group. Furthermore, a propensity score matching analysis was performed to adjust for heterogeneity between groups. A competing risk regression model was used to explore the impact of age on CSD and non-colorectal cancer-specific death (non-CSD). Kaplan–Meier survival curves were plotted to compare CSS between groups. And a Cox regression model was used to validate the results. External validation was performed on data from 1998 to 2003 retrieved from the SEER database.

Results: Based on a cutoff age of 70 years, the examined cohort of patients was classified into a younger group (n =51,915, <70 years of old) and an older group (n =24,943, ≥70 years of old). Compared with younger patients, older patients were more likely to have fewer lymph nodes sampled and were less likely to receive chemotherapy and radiotherapy. When adjusted for other covariates, age-dependent differences of 5-year CSD and 5-year non-CSD were significant in the younger and older groups (15.84% and 22.42%, P < 0.001; 5.21% and 14.21%, P < 0.001). And an age of ≥70 years remained associated with worse CSS comparing with younger group (subdistribution hazard ratio [SHR], 1.51 [95% confidence interval [CI], 1.45-1.57], P < 0.001). The Cox regression model as a sensitivity analysis had a similar result. External validation also supported an age of 70 years as a suitable cutoff, and this older group was associated with having reduced CSS and increased CSD.

Conclusions: Seventy is a suitable cutoff age to define those considered as having elderly CRC. Elderly CRC was associated with not only increased non-CSD but also with increased CSD. Further research is needed to provide evidence of whether cases of elderly CRC should receive stronger treatment if possible.

1 **Impact of old age on resectable colorectal cancer outcomes**

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19   **ABSTRACT**

20   **Objective:** This study was performed to identify a reasonable cutoff age for defining older

21   patients with colorectal cancer (CRC) and to examine whether old age was related with increased

22   colorectal cancer-specific death (CSD) and poor colorectal cancer-specific survival (CSS).

23   **Methods:** 76,858 eligible patients from the Surveillance, Epidemiology and End Results (SEER)

24   database were included in this study. The Cox proportional hazards regression model and the

25   Chow test were used to determine a suitable cutoff age for defining the older group. Furthermore,

26   a propensity score matching analysis was performed to adjust for heterogeneity between groups.

27   A competing risk regression model was used to explore the impact of age on CSD and non-

28   colorectal cancer-specific death (non-CSD). Kaplan–Meier survival curves were plotted to

29   compare CSS between groups. And a Cox regression model was used to validate the results.

30   External validation was performed on data from 1998 to 2003 retrieved from the SEER database.

31   **Results:** Based on a cutoff age of 70 years, the examined cohort of patients was classified into a

32   younger group (n =51,915, <70 years of old) and an older group (n =24,943, ≥70 years of old).

33   Compared with younger patients, older patients were more likely to have fewer lymph nodes

34   sampled and were less likely to receive chemotherapy and radiotherapy. When adjusted for other

35   covariates, age-dependent differences of 5-year CSD and 5-year non-CSD were significant in the

36   younger and older groups (15.84% and 22.42%, P < 0.001; 5.21% and 14.21%, P < 0.001). And

37   an age of ≥70 years remained associated with worse CSS comparing with younger group

38   (subdistribution hazard ratio [SHR], 1.51 [95% confidence interval [CI], 1.45-1.57], P < 0.001).

39   The Cox regression model as a sensitivity analysis had a similar result. External validation also

40   supported an age of 70 years as a suitable cutoff, and this older group was associated with having

41   reduced CSS and increased CSD.

42   **Conclusions:** Seventy is a suitable cutoff age to define those considered as having elderly CRC.

43   Elderly CRC was associated with not only increased non-CSD but also with increased CSD.

44   Further research is needed to provide evidence of whether cases of elderly CRC should receive

45   stronger treatment if possible.

46   **Keywords:** Colorectal cancer; old; age; cancer specific death; SEER; competing risk regression

47

48   **INTRODUCTION**

49   Age-specific risk rises markedly in old age, and as mortality from heart disease and other non-

50   cancer causes decrease, this leaves the elderly population at high risk for developing bowel

51   cancer(Papamichael et al. 2009). The increasing incidence of colorectal cancer (CRC) in the

52   segment of the population > 70 years of age necessitates an examination of what type of

53   treatment is most appropriate for these patients with colorectal cancer. Approximately 60% of

54   CRC patients are > 70 years of age at the time of diagnosis, and 43% are > 75 years of

55   age(Papamichael et al. 2009). It remains controversial whether so-called "elderly CRC" exhibits

56   a differential prognosis compared to younger CRC and whether age (i.e., old) is an independent

57   prognostic factor. There is now a general consensus that those in the old population possess a

58   high frequency of frailty and comorbidities, exhibiting increased mortality from other causes

59   among those with CRC. However, it remains unknown whether old patients have an increased

60   incidence of colorectal cancer specific death (CSD). A previous report demonstrated that older

61   patients with CRC who survived the first year after surgery exhibited the same overall cancer-

62   related survival as did younger patients(Dekker et al. 2011). Of note, chronological age is

63   distinct from biological age(Odden et al. 2012; Robinson et al. 2009). The definition of 'elderly'

64   differs, being given as anything between >65 years and >80 years in different studies(Seymour

65   2004; Twelves et al. 2005). As such, it is difficult to know whether 70 years is a reasonable

66   cutoff age to safely extrapolate these results or whether the decision should depend on the

67   physical and functional status of the patient rather than just on chronological age.

68   Unlike younger patients with CRC, wherein more reliable evidence-based guideline based on

69   clinical trials are available, older patients are still in need of increased evidence to guide clinical

70   practices due to most trials excluding older patients with CRC. We used big data to explore the

71   impact of old age on CRC prognoses to help guide clinical practice in the treatment of elderly

72   CRC patients.

73

74   **MATERIALS & METHODS**

75   **Data**

76   Data on colon cancer records from 18 cancer registries in the National Cancer Institute's

77   Surveillance, Epidemiology and End Results (SEER) Cancer database based on the November

78   2015 submission were collected. SEER.Stat software was utilized to identify patients with

79   resectable stage I-III CRC, and information regarding chemotherapy was obtained by submitting

80   a special data request to the SEER program.

81   Cohort inclusion criteria were as follows: (1) Years of diagnosis from 2004 to 2011. (2) Patients

82   diagnosed with stage I-III CRC. (3) Patients received surgery (Surgery code 30-80). (4)

83   Histological type ICD-O-3 was limited to 8140/3, 8480/3, 8481/3 and 8490/3. Exclusion criteria

84   were as follows: (1) Patients lacking documentation of age at diagnosis, gender, race, marital

85   status, differentiated grade, and classification T. (2) Patients younger than 20 years or older than

86   80 years. (3) Patients with multiple primary tumors. (4) Patients who survived less than one

87   month from diagnosis. (5) Cause of death was unknown. (6) Number of lymph nodes sampled

88   was unknown. (7) The number of positive lymph nodes was unknown.

89

90   **Variables declaration**

91   Patients were classified into younger (<70 years old) and older (≥70 years old) groups based on

92   the defined cutoff age of 70 years. Race was divided into white, black and other. Marital status

93   was categorized as married, single (never married, unmarried or domestic partner) or divorced

94   (separated, widowed and divorced). Tumor location was grouped into left CRC or right CRC.

95   Left colorectal cancer includes the rectum, rectosigmoid junction, sigmoid colon, descending

96   colon and splenic flexure. Right colorectal cancer includes the transverse colon, hepatic flexure,

97   ascending colon, cecum, and appendix. Histological type was categorized as adenocarcinoma,

98   mucinous adenocarcinoma, or ring signet cell cancer. All cases were regrouped according to the

99   7th American Joint Committee on Cancer (AJCC) TNM staging system. Number of lymph nodes

100 (nLN) sampled was regrouped as 0, 1-3, 4-6, 7-11, and ≥12. The variable chemotherapy was

101 classified as chemotherapy "yes" or "no/unknown" according to the SEER program(Noone et al.

102 2016).

103

Statistical analysis

105 The restrict cubic spline function, "RCS", with three knots was used to transform the continuous

106 variable of age. The "rcspline.plot" function provided plots of the estimated restricted cubic

107 spline function relating a single predictor (age) to the response for a Cox model. The Chow test

108 method (Fstats and breakpoints in strucchange package) was used to explore a suitable cutoff

109 value for age to define elderly CRC. Differential distribution of clinicopathological

110 characteristics between younger and older subgroups was indicated by standardized difference

111 (SD)(Austin 2009). Propensity scores were used to balance the difference of distribution between

112 younger and older groups on sociodemographic and clinical characteristics. Matchit package in

113 R software was used as the nearest method with ratio 1:1. Cancer-specific death (CSD) and non-

114 cancer-specific death (non-CSD) were considered the primary endpoint and were calculated by

115 the Gray test(Howlader et al. 2014). The secondary endpoint was CSS. The non-CSD referred to

116 the dead due to other causes. When CSDs were calculated, follow up time was calculated from

117 the date of diagnosis to the date of death from colorectal cancer. Alive were defined as censored,

118 and the non-CSD was considered a competing event. The subdistribution hazard ratio (SHR) of

119 variables for cause-specific death was estimated using the Fine and Gray proportional hazard

120 model(Fine & Gray 1999). As a comparison, the hazard ratio (HR) of variables was also

121 estimated with a Cox proportional hazards model.

122 The cutoff of age and prognostic value of old were validated externally using a cohort from

123 1998 to 2003. A standard difference that was less than 0.1 indicated a negligible difference in the

124 mean or prevalence of a covariate between groups(Normand et al. 2001). When a two-sided *P*

125 value was less than 0.05, the difference was considered statistically significant. All statistical

126 analyses were performed using R software (version 3.3.2).

127

128 **RESULTS**

129 **1. Baseline characteristics and identification of the old age cutoff value**

130 76,858 eligible patients were included in this cohort. The endpoint date for follow up was

131 November 2013, and the median follow-up time was 55.0 months (range 1.0-119.0 months).

132   The median age of patients was 64 years (IQR 20-80 years). With age as a continuous

133 variable, the hazard ratio (HR) of CSS was 1.54 (95% CI 1.39- 1.69, *P* < 0.001). The HR of CSS

134 slowly increased before 70 years of age, and then increased significantly after 70 years according

135 to the Cox model (**Fig. 1**).

136

137 **2. Clinicopathological features of old colorectal cancer patients**

138 Based on the cutoff age of 70 years, the test cohort of patients was classified into the following

139 two groups: younger group (n =51,915, <70 years of old) or older group (n =24,943, ≥70 years of

140 old). Older patients exhibited a high frequency of male, Caucasians, right CRC, mucinous

141 carcinoma, more poorly differentiated grade and earlier stage. Detailed clinicopathological

142 characteristics of the chemotherapy subgroups are presented in **Table 1**. Compared with younger

143 patients, older patients were more likely to have fewer lymph nodes sampled and were less likely

144   to receive chemotherapy and radiotherapy.

145   The sample size of patients in the older group was obviously fewer than in the younger

146   group, and these groups had different clinical characteristics, so a method for propensity score

147   matching (PSM) was used to balance differences in baseline characteristics and generate a

148   corrected test cohort. Most covariates were well balanced between younger and older groups in

149   the corrected test cohort (**Table 1**).

150

151   **3. Competing risk regression model was used to explore the impact of age on CSD and non-**

152   **CSD**

153   14,425 (18.77%) and 6,982 (9.08%) patients died of CSD and non-CSD, respectively. The

154   corrected test cohort after PSM, a total of 47,616 patients analyzed, showed that 9,273 (19.47%)

155   and 5,514 (11.58%) patients died of CSD and non-CSD, respectively. The 5-year CSD in the

156   younger and older groups were 15.84% and 22.42%, respectively, and were significantly

157   different ($P < 0.001$). The 5-year non-CSD in the younger and older groups were 5.21% and

158   14.21%, respectively, and were also significantly different ($P < 0.001$) (**Fig. 2**). Univariate and

159   multivariate analyses demonstrated that old age was associated with CSD (**Table 2**)).

160

161   **4.Subgroup analysis by characteristics in raw data**

162   Subgroup analyses were performed based on gender, race, differentiated type, pathological type,

163   T and N classification, nLN, TNM stage, chemotherapy and radiotherapy in the raw data. In all

164   subsets (except for ring signet cell cancer), patients in the older group exhibited poorer prognosis

165 compared with those in the younger group. (**Fig. 3**). Furthermore, we performed an interaction

166 analysis using Cox model between the therapy and age in stage III patients in raw data (**Fig. S2**).

167 The results showed that the older group benefited more from chemotherapy than younger group

168 (*P* value = 0.001). However, the interaction between radiotherapy and old was not significant (*P*

169 value = 0.328).

170

171 **5. Univariate and Multivariate Cox regression analysis**

172 A Kaplan-Meier survival curve for CSS is presented in **Fig. 4**. Univariate analysis showed a

173 HR for CSS of older patients of 1.57 (95% CI 1.51-1.64, *P* < 0.001, reference to younger group)

174 in the corrected cohort. Multivariate analysis showed that the HR for CSS in older patients was

175 1.64 (95% CI 1.57-1.70, *P* < 0.001, reference to younger group) (for detailed data see **Table 3**)

176 (raw data are shown in **Table S1**).

177

178 **6. External validation**

179 In the validated cohort, 66,946 patients from 1998 to 2003 were retrieved from the SEER dataset.

180 The corrected validated cohort after PSM was used to validate the above results. The relationship

181 between age and colorectal cancer-specific death for Cox model presented a single arm "U"

182 shape (**Fig. S1**). Seventy was still the cutoff age in the validated cohort. Detailed

183 clinicopathological characteristics are presented in **Table S2**. In the corrected validated cohort,

184 there were few differences in the distribution of different clinicopathological factors between

185 older and younger groups (see **Table S2**). Univariate and multivariate analysis showed that old

186 age is related with poor CSS (based on the Cox model) and increased CSD (based on the

187 competing risk model) (see **Table S3**).

188

189 **DISCUSSION**

190 The statistical methods "RCS" and "Chow test" were used to determine that 70 years is a

191 reasonable cutoff age to define elderly CRC. Elderly CRC included a high frequency of male

192 patients, right site CRC, mucinous carcinoma, more poorly differentiated grades and earlier

193 stages. There were fewer than 12 lymph nodes sampled and earlier stages in the older group.

194 After eliminating the distribution difference between older and younger groups by PSM, elderly

195 CRC had worse outcomes (CSS), and age was shown to be an independent prognostic factor,

196 while elderly CRC was related with increased non-CSD as well as CSD. In almost all subgroups,

197 elderly CRC exhibited worse outcomes. The external cohort validated the reasonability of 70

198 years as a cutoff age to define elderly CRC and further confirmed that elderly CRC exhibited

199 worse outcomes (CSS or CSD).

200   In clinical practice, the optimal cutoff age is anticipated to define elderly CRC. The

201 screening program for CRC defined 65 years as a cutoff age(Papamichael et al. 2009). In other

202 previously published studies(McCleary et al. 2013a; Merchant et al. 2017; Tournigand et al.

203 2012; Twelves et al. 2005), 70 years was adopted as a cutoff age. Updated SEER-Medicare

204 analysis data and three population-based data sets conducted by Sanoff et al(Sanoff et al. 2012)

205 showed that only 44% of the 5941 patients evaluated received adjuvant chemotherapy within 3

206 months of surgical resection for stage III CRC. In their study, 65 years was used to define elderly

207   CRC. In clinical trials, 75 years was more frequently set as the upper limit; therefore, a more

208   real-world data analysis adopted 75 years as their cutoff age(van Erning et al. 2013). We

209   concluded that 70 years should be adopted as a suitable cutoff age.

210   Once the cutoff age was defined, we found that elderly CRC exhibited a significantly

211   different outcome than young CRC. Several studies have shown that elderly CRC has

212   comparable outcomes compared with younger CRC. Dekker et al.'s(Dekker et al. 2011) study

213   showed that if one excluded death due to operation comorbidities (mostly death occurring one

214   year after an operation), there were rather similar outcomes between the younger and older

215   groups. Late period survival was similar between older and younger subgroups for resectable

216   CRC(Dekker et al. 2011). One Canadian study(Merchant et al. 2017) showed that elderly CRC

217   did exhibit worse prognosis and was associated with a high Charlson index. In their study, they

218   did not differentiate between CSD and non-CSD; therefore, their study did not conclude that

219   elderly CRC was related with increased CSD. In our study, we used a competing risk model to

220   distinguish non-CSD and CSD. Furthermore, we report that elderly CRC is associated with

221   increased CSD. In late period follow up, the Gray's cumulative events curve on CSD separated

222   more clearly, indicating that elderly CRC is associated with worse CSD, which might be due to

223   different register periods. Therefore, we included patients from different periods as a validation

224   cohort. The validation cohort also confirmed that elderly CRC was not only related with

225   increased CSD but also with increased non-CSD. Our study confirmed that elderly CRC exhibits

226   poorer prognosis from several aspects. Except for external validation and competing risk mode,

227   we also confirm that elderly CRC is associated with worse outcomes using PSM to balance the

228   differential distribution.

229   Worse outcome of elderly CRC is multi-faceted. Fewer numbers of lymph nodes were

230   removed from those with elderly CRC, contributing to residual tumor matter in the anticipated

231   dissection region (mean to R1 resection) and underestimated tumor stages. Moreover, elderly

232   CRC exhibited less capacity to endure stronger treatments, resulting in lower intensity adjuvant

233   chemotherapy and radiotherapy. Our correlation analysis indicated that elderly CRC was related

234   with lower incidence of chemotherapy. The outcome of less frequent chemotherapy was similar

235   to findings in previous studies(Abraham et al. 2013; Kahn et al. 2010; van Erning et al. 2014;

236   van Erning et al. 2013). Finally, a CRC screening program resulted in the increased detection of

237   precancerous lesions (such as polyps) that were treated in the old population. If the CRC

238   diagnosis escaped screening, there was typically increased short-term carcinogenesis and more

239   aggressive tumor behavior. Another study showed that elderly CRC had a greater index of

240   genetic mutations and that the incidence of BRAF mutations was higher. Berg et al. indicated

241   that CIMP tumors are more common in the older population, who also have a higher rate of

242   KRAS and BRAF mutations(Berg et al. 2010).

243   Elderly CRC with worse outcomes might require stronger treatments; however, a previous

244   study suggested that elderly CRC does not require enhanced treatment. Many elderly patients

245   will benefit from radical treatment approaches, but others will not, and in some cases, non-

246   operative "palliative" management should be offered, even though the cancer is "curable".

247   Guidelines from the International Society of Geriatric Oncology (SIOG) did not recommend that

248   elderly CRC patients regularly receive adjuvant chemotherapy with limited evidence to support

249 the benefit from such strategy(Papamichael et al. 2009). MOSAIC: lyses showed there to be no

250 statistically significant benefit conferred by addition of oxaliplatin in terms of disease-free

251 survival (DFS) or OS for older patients (70–75years), although female patients 70–75 years of

252 age exhibited the same oxaliplatin benefit as did younger patients(Tournigand et al. 2012).

253 Interestingly, the DFS and OS benefits in patients 70–75 years were similar to those of younger

254 patients for the first 3 years of follow-up but were lost later on due to deaths from other

255 causes(Andre et al. 2009; Tournigand et al. 2012). NSABP-C-07:Patients ≥70 years failed to

256 derive a statistically significant DFS or OS benefit from addition of oxaliplatin(Tournigand et al.

257 2012). Indeed, those patients receiving FLOX had poorer survival, which was attributed to

258 toxicity. XELOXA (NO16968): the benefits observed for XELOX were maintained, although to

259 a lesser degree in patients ≥65 and ≥70 years of age, in contrast to the results from MOSAIC and

260 NSABP-C-07 trials(Twelves et al. 2012). Meta-analysis of ACCENT did not support that

261 patients ≥70 years receive additional oxaliplatin chemotherapy(McCleary et al. 2013a; McCleary

262 et al. 2013b). In contrast, from an analysis using real-world data, almost all showed that elderly

263 CRC can benefit from adjuvant chemotherapy with acceptable toxicity(Abraham et al. 2013;

264 Kahn et al. 2010; Sanoff et al. 2012; Sanoff & Goldberg 2007; Schrag et al. 2001; van Erning et

265 al. 2014; van Erning et al. 2013). One study using SEER-Medicare data indicated that elderly

266 CRC tolerated chemotherapy well, exhibiting worse prognosis due to reduced treatment(Sanoff

267 et al. 2012). More recent studies showed that with the technological development of laparoscopic

268 surgery and enhanced recovery programs after surgery (ERAS), elderly CRC could tolerate

269 operation well. The literature suggests that elderly patients benefit from multimodal

270   rehabilitation programs or ERAS in the same way as younger patients(van Steenbergen et al.

271   2013). Our interaction analysis between the therapy and age in stage III patients showed that the

272   older group benefited more from chemotherapy than younger group (*P* value = 0.001). And

273   compared with younger patients, older patients were more likely to have fewer lymph nodes

274   sampled and were less likely to receive chemotherapy and radiotherapy. Therefore, current

275   treatment paradigms in the older group may be insufficient. As life expectancy increases, more

276   effective treatments are necessary for the old population.

277   To reduce bias as much as possible, we used PSM to balance clinicopathological

278   characteristics and used a competing risk model to exclude impact from non-CSD. Finally, we

279   confirmed that elderly CRC was related with more CSD and non-CSD. Age(old) is an

280   independent factor to predict increased CSD. And the Cox model as a sensitivity analysis also

281   had a similar result. Our analysis provides more evidence for elderly CRC receiving stronger

282   adjuvant chemotherapy. The above conclusions can only be acquired from real world data

283   analysis rather than from clinical trials alone.

284   As a retrospective study, it is impossible to avoid all bias for patient selection. There are

285   several limitations inherent to the database used in the current study. The Charlson index is not

286   available in SEER data. Though the SEER-Medicare can retrieve Charlson index, only patients

287   older than 60 years are registered in their dataset. The Charlson index is strongly related with

288   non-CSD in the old population. Competing risk models can effectively eliminate the impact from

289   unavailable Charlson index. BMI is also an important influence factor in the colorectal cancer

290   specific mortality(Kroenke et al. 2016). However, the information about BMI in the SEER data

291 is not available. Furthermore, insurance status is an independent risk factor both for advanced

292 disease in their cancer diagnosis and for cancer mortality(Rosenberg et al. 2015), and uninsured

293 patients more often have higher T, N and M stage(Amini et al. 2016). But the insurance recode

294 variable is only available from 2007 in the SEER database. Additionally, comorbidities and

295 detailed information about driver gene mutations (KRAS or BRAF) is not available. The variable

296 chemotherapy is only classified as chemotherapy "yes" or "no/unknown" since SEER treatment

297 information cannot accurately distinguish between "no treatment" and "unknown"(Noone et al.

298 2016). Furthermore, the sensitivity of SEER chemotherapy data is only 72.1%(Noone et al.

299 2016), as the detailed regime and duration of chemotherapy is not available in the SEER dataset.

300

301 **CONCLUSIONS**

302 In summary, 70 years is a suitable cutoff age to define elderly CRC. Elderly CRC is associated

303 with not only increased non-CSD but also increased CSD. This SEER-based analysis provides

304 further evidence that current chemotherapy in the elderly may be insufficient. Additional

305 research is required to investigate whether elderly CRC will receive stronger treatment if

306 possible.

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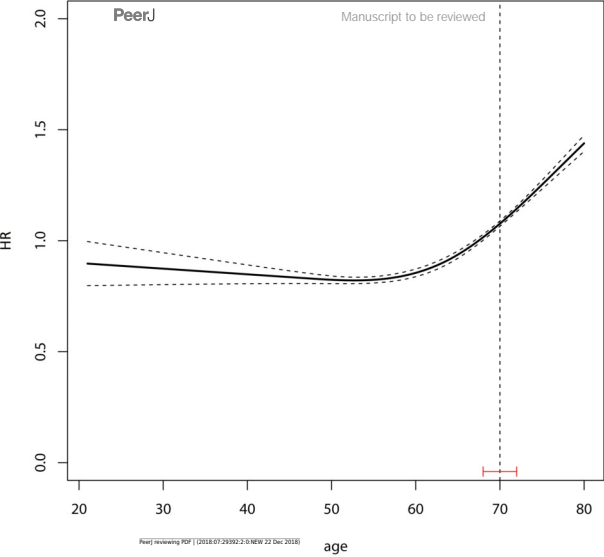
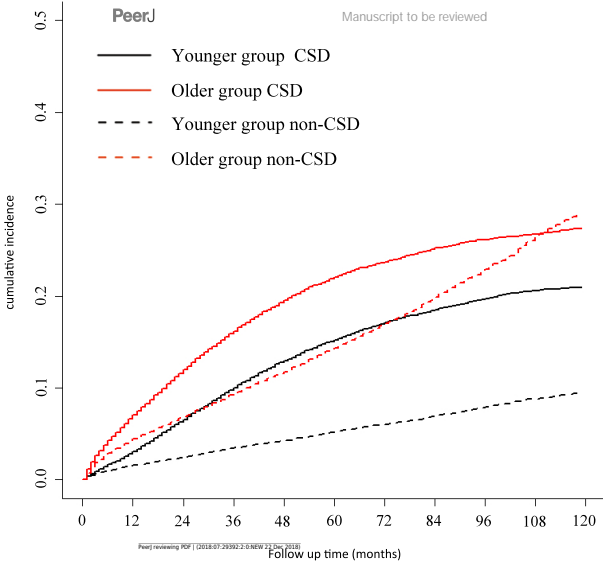
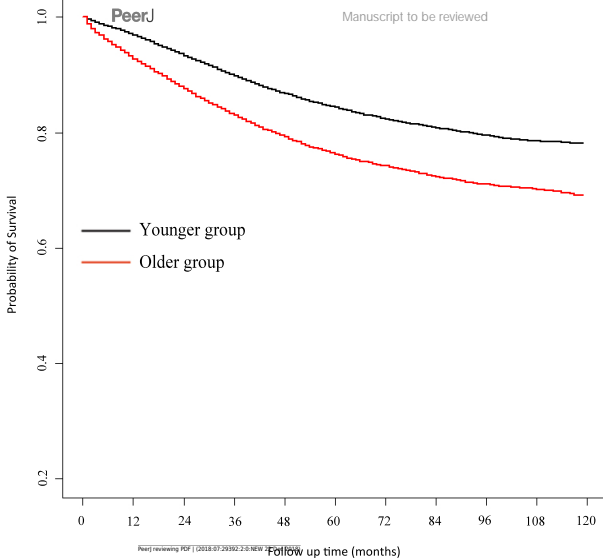
415

70 was identified as a suitable cutoff age to define elderly CRC with 95% CI 68-72.

Cox proportional hazard model with continued variable of age after transformation with restrict cubic spline method was plotted to examine the relationship between age and HR of colorectal cancer-specific death 76,858 eligible patients were included in the test cohort with dummy variables for each age to attain the HR of every age. Chow test was used to determine a suitable cutoff age.

Gray method showed cumulative incidence curves of CSD and non-CSD in younger and older groups.

CSD: cancer-specific death. non-CSD: non-cancer-specific death.

Forest plot of cancer-specific survival by patient subgroup in raw data.

HR: hazard ratio.

Kaplan-Meier estimate of cancer-specific survival.

The characteristics of 76,858 colorectal cancer patients in the younger and older groups.

Characteristics	Younger(<70yrs) Before PSM	Older(≥70yrs) Before PSM	SD	Younger(≤70yrs) After PSM	Older(≥70yrs) After PSM	SD
	N (%)	N (%)		N (%)	N (%)	
Gender						
Male	22748(43.82)	12925(51.82)	0.57	11648(49.41)	11924(50.59)	0.02
Female	29167(56.18)	12018(48.18)	0.92	12160(50.57)	11884(49.43)	0.02
Marital status						
Married	33210(63.97)	14227(57.04)	0.87	14646(50.78)	14197(49.22)	0.03
Single	9416(18.14)	2314(9.28)	1.52	2370(50.60)	2314(49.40)	0.02
Divorced	9289(17.89)	8402(33.68)	0.10	6792(48.21)	7297(51.79)	0.07
Race						
White	39981(77.01)	20482(82.12)	0.68	19317(49.92)	19379(50.08)	<0.01
Black	6768(13.04)	2289(9.18)	1.14	2339(50.55)	2288(49.45)	0.02
Others	5166(9.95)	2172(8.71)	0.89	2152(50.13)	2141(49.87)	0.01
Location						
Left	33719(64.95)	12307(49.34)	1.05	12470(50.69)	12131(49.31)	0.03
Right	18196(35.05)	12636(50.66)	0.37	11338(49.26)	11677(50.74)	0.03
Histological type						
Adenocarcinoma	46246(89.08)	21952(88.01)	0.76	21056(50.23)	20862(49.77)	0.01
Mucinous adenocarcinoma	5181(9.98)	2778(11.14)	0.63	2538(48.14)	2734(51.86)	0.07
Signet ring cell cancer	488(0.94)	213(0.85)	0.85	214(50.23)	212(49.77)	0.01
Differentiated grade						
Well	4225(8.14)	1983(7.95)	0.77	1952(50.03)	1950(49.97)	<0.01
Moderate	39154(75.42)	18409(73.80)	0.77	17677(50.41)	17391(49.59)	0.02
Poor	8536(16.44)	4551(18.25)	0.64	4179(48.33)	4467(51.67)	0.07
T-classification [a]						
T1	4594(8.85)	2179(8.74)	0.76	2178(50.09)	2170(49.91)	<0.01
T2	8546(16.46)	4580(18.36)	0.63	4429(49.92)	4443(50.08)	<0.01
T3	32608(62.81)	15320(61.42)	0.77	14518(50.25)	14376(49.75)	0.01
T4	6167(11.88)	2864(11.48)	0.79	2683(48.76)	2819(51.24)	0.05
N-classification [a]						
N0	29285(56.41)	15866(63.61)	0.62	15072(50.35)	14863(49.65)	0.01
N1	14542(28.01)	6083(24.39)	0.90	5764(49.11)	5972(50.89)	0.04
N2	8088(15.58)	2994(12.00)	1.04	2972(49.99)	2973(50.01)	<0.01
nLN						
0	2733(5.26)	1343(5.38)	0.73	1324(50.06)	1321(49.94)	<0.01
1-2	872(1.68)	456(1.83)	0.66	407(47.22)	455(52.78)	0.11
3-5	2518(4.85)	1422(5.70)	0.58	1314(50.00)	1314(50.00)	<0.01
6-11	9808(18.89)	5494(22.03)	0.59	5013(49.18)	5180(50.82)	0.03

≥12	35984(69.31)	16228(65.06)	0.82	15750(50.34)	15538(49.66)	0.01
Stage [a]						
I	10334(19.91)	5741(23.02)	0.60	5647(50.23)	5596(49.77)	0.01
II	18951(36.50)	10125(40.59)	0.64	9425(50.42)	9267(49.58)	0.02
III	22630(43.59)	9077(36.39)	0.95	8736(49.41)	8945(50.59)	0.02
CT						
No	24094(46.41)	16990(68.12)	0.35	15580(49.56)	15856(50.44)	0.02
Yes	27821(53.59)	7953(31.88)	1.34	8228(50.85)	7952(49.15)	0.03
RT						
No	40769(78.53)	22233(89.14)	0.62	20949(49.82)	21098(50.18)	0.01
Yes	11146(21.47)	2710(10.86)	1.53	2859(51.34)	2710(48.66)	0.05

1 [a] Stage TNM, T, N-classification to 7th edition of AJCC staging system.

2 All statistical tests were two-sided.

3 Abbreviations: PSM: propensity score matching; SD: standardized difference; nLN: number of lymph nodes;

4 CT: chemotherapy treatment; RT: radiotherapy treatment.

5 Left includes rectum, rectosigmoid junction, sigmoid colon, descending colon and splenic flexure.

6 Right includes transverse colon, hepatic flexure, ascending colon, cecum, and appendix.

Univariate and Multivariate Analysis of Colorectal Cancer-Specific Death of 47,616 patients after PSM.

Risk Factors	Univariate analysis		Multivariate analysis	
	SHR (95%CI)	P [b]	SHR (95%CI)	P [b]
Age				
<70	1		1	
≥70	1.47(1.41-1.53)	<0.001	1.50(1.44-1.56)	<0.001
Gender				
Female	1		1	
Male	1.06(1.02-1.10)	0.005	1.11(1.06-1.16)	<0.001
Marital status				
Married	1		1	
Unmarried	1.48(1.39-1.58)	<0.001	1.27(1.19-1.36)	<0.001
Divorced	1.35(1.30-1.42)	<0.001	1.25(1.19-1.31)	<0.001
Race				
White	1		1	
Black	1.31(1.23-1.40)	<0.001	1.26(1.18-1.35)	<0.001
Other	0.95(0.88-1.02)	0.176	0.90(0.84-0.97)	0.008
Location				
Left	1		1	
Right	0.93(0.89-0.97)	<0.001	1.01(0.96-1.06)	0.759
Histology				
Adenocarcinoma	1		1	
Mucinous adenocarcinoma	1.14(1.07-1.21)	<0.001	1.08(1.01-1.15)	0.018
Signet ring cell carcinoma	3.05(2.62-3.54)	<0.001	1.48(1.26-1.74)	<0.001
Differentiated grade				
Grade I	1		1	
Grade II	1.43(1.31-1.56)	<0.001	1.27(1.16-1.39)	<0.001
Grade III	2.45(2.23-2.69)	<0.001	1.59(1.45-1.76)	<0.001
T-classification [a]				
T1	1		1	
T2	0.73(0.65-0.83)	<0.001	0.96(0.85-1.08)	0.472
T3	2.15(1.95-2.37)	<0.001	2.19(1.98-2.43)	<0.001
T4	5.46(4.92-6.05)	<0.001	4.77(4.27-5.33)	<0.001
N- classification [a]				
N0	1		1	
N1	2.33(2.22-2.44)	<0.001	2.16(2.05-2.28)	<0.001
N2	4.48(4.26-4.71)	<0.001	4.05(3.81-4.30)	<0.001
nLN				
0	1		1	
0-2	0.49(0.42-0.58)	<0.001	0.39(0.33-0.46)	<0.001

3-5	0.61(0.55-0.68)	<0.001	0.43(0.39-0.48)	<0.001
6-11	0.56(0.52-0.61)	<0.001	0.33(0.30-0.36)	<0.001
≥12	0.47(0.44-0.51)	<0.001	0.24(0.22-0.26)	<0.001
CT				
No	1		1	
Yes	1.70(1.64-1.77)	<0.001	0.84(0.80-0.89)	<0.001
RT				
No	1		1	
Yes	1.35(1.28-1.43)	<0.001	1.15(1.08-1.23)	<0.001

1   [a] T classification according to 7th AJCC staging system.

2   [b] P values obtained from the χ^2 test. All statistical tests were two-sided.

3   Abbreviations: PSM: propensity score matching; CSD: cancer specific death; nLN: number of lymph nodes;

4   CT: chemotherapy treatment; RT: radiotherapy treatment; SHR: subdistribution hazard ratio.

5   Left includes rectum, rectosigmoid junction, sigmoid colon, descending colon and splenic flexure.

6   Right includes transverse colon, hepatic flexure, ascending colon, cecum, and appendix.

Univariate and Multivariate Analysis of Colorectal Cancer-Specific Survival of 47,616 patients after PSM.

Risk Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P [b]	HR (95%CI)	P [b]
Age				
<70	1		1	
≥70	1.57(1.51-1.64)	<0.001	1.64(1.57-1.70)	<0.001
Gender				
Female	1		1	
Male	1.08(1.04-1.13)	<0.001	1.14(1.10-1.19)	<0.001
Marital status				
Married	1		1	
Unmarried	1.54(1.44-1.64)	<0.001	1.33(1.25-1.42)	<0.001
Divorced	1.39(1.33-1.46)	<0.001	1.29(1.23-1.35)	<0.001
Race				
White	1		1	
Black	1.34(1.26-1.43)	<0.001	1.29(1.21-1.38)	<0.001
Other	0.93(0.86-1.00)	0.06	0.87(0.81-0.94)	<0.001
Location				
Left	1		1	
Right	0.93(0.89-0.97)	0.001	1.01(0.96-1.06)	0.697
Histology				
Adenocarcinoma	1		1	
Mucinous adenocarcinoma	1.13(1.07-1.21)	<0.001	1.07(1.01-1.14)	0.033
Signet ring cell carcinoma	3.10(2.69-3.58)	<0.001	1.55(1.34-1.79)	<0.001
Differentiated grade				
Grade I	1		1	
Grade II	1.43(1.31-1.57)	<0.001	1.30(1.19-1.42)	<0.001
Grade III	2.47(2.25-2.72)	<0.001	1.64(1.49-1.81)	<0.001
T-classification [a]				
T1	1		1	
T2	0.73(0.64-0.82)	<0.001	0.96(0.85-1.08)	0.488
T3	2.15(1.95-2.37)	<0.001	2.24(2.02-2.49)	<0.001
T4	5.57(5.02-6.17)	<0.001	5.01(4.49-5.59)	<0.001
N- classification [a]				
N0	1		1	
N1	2.33(2.23-2.45)	<0.001	2.22(2.10-2.34)	<0.001
N2	4.53(4.31-4.77)	<0.001	4.24(4.00-4.49)	<0.001
nLN				
0	1		1	
0-2	0.48(0.40-0.56)	<0.001	0.37(0.31-0.43)	<0.001

3-5	0.58(0.53-0.65)	<0.001	0.41(0.37-0.46)	<0.001
6-11	0.54(0.49-0.58)	<0.001	0.30(0.28-0.33)	<0.001
≥12	0.44(0.41-0.48)	<0.001	0.22(0.20-0.23)	<0.001
CT				
No	1		1	
Yes	1.65(1.59-1.72)	<0.001	0.78(0.75-0.82)	<0.001
RT				
No	1		1	
Yes	1.32(1.25-1.40)	<0.001	1.14(1.07-1.22)	<0.001

1   [a] T classification according to 7th AJCC staging system.

2   [b] P values obtained from the χ2 test. All statistical tests were two-sided.

3   Abbreviations: PSM: propensity score matching; CSD: cancer specific death; nLN: number of lymph nodes;

4   CT: chemotherapy treatment; RT: radiotherapy treatment; HR: hazard ratio.

5   Left includes rectum, rectosigmoid junction, sigmoid colon, descending colon and splenic flexure.

6   Right includes transverse colon, hepatic flexure, ascending colon, cecum, and appendix.