

Supplementary

Stage-Specific Characterization of “Early-Onset Colorectal Cancer”: Localized and Synchronous Metastatic Disease

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Supplementary Tables

Table S1. Multivariable binary logistic analysis for localized EOCRC*

Variable ⁺	OR (95% CI)	P
Gender (Female vs male)	2.17 (1.24-3.77)	0.006
PNI (Yes vs No)	2.28 (1.30-4.02)	0.004

* a significant model (chi-square=14.950, df=2, p=0.001), constant p=0.000

+ variables that were statistically significant in univariable analysis were included.

Table S2. Multivariable binary logistic analysis for localized EOCRC *

Variable ⁺	OR (95% CI)	P
Gender (Female vs male)	2.26 (1.28-4.01)	0.005
PNI (Yes vs No)	2.15 (1.20-3.85)	0.010
Diabetes (Yes vs No)	0.64 (0.23-1.77)	0.393
Hypertension (Yes vs No)	0.17 (0.05-0.61)	0.007
CAD (Yes vs No)	0.27 (0.03-2.23)	0.229

* a significant model (chi-square=39.940, df=5, p=0.000), constant p=0.001

+ variables that were statistically significant in univariable analysis were included.

Table S3. Univariable Cox regression analysis for recurrence-free survival (RFS) in localized EOCRC patients

Variable	HR (95% CI)	P
Gender, (Male vs. female)	1.07 (0.37-3.02)	0.896
Diabetes (Present vs absent)	0.04 (0.00-48.36)	0.377
Hypertension, (Present vs absent)	1.03 (0.13-7.89)	0.973
CAD (Present vs absent)	0.04 (0.00-864.81)	0.722
Primary tumor location, Transverse vs right	0.66 (0.07-5.97)	0.715
Left vs right	0.55 (0.13-2.24)	0.411
Rectum vs right	1.29 (0.36-4.60)	0.689
Urgent surgery (Obstruction vs. no)	2.57 (0.57-11.52)	0.517
T stage 3 vs 2	NC	0.935
4 vs 2	NC	0.931
N stage 1a-b vs 0	2.08 (0.56-7.78)	0.272
1c vs 0	3.60 (0.80-16.18)	0.094
2 vs 0	3.72 (0.82-16.729)	0.086
Tumor deposit (Present vs absent)	1.34 (0.30-5.98)	0.695
Tumor grade, n (%) 2 vs 1	0.71 (0.08-5.73) <i>S*: 0.79 (0.10-5.90)</i>	0.752 <i>0.825</i>
3 vs 1	1.64 (0.14-18.31) <i>S: 2.01 (0.20-19.49)</i>	0.687 <i>0.545</i>
Mucinous component (Present vs absent)	1.14 (0.36-3.58)	0.822
LVI (Present vs absent)	1.62 (0.57-4.58)	0.358
PNI (Present vs absent)	1.16 (0.42-3.22)	0.769
Budding (Present vs absent)	1.24 (0.34-4.44)	0.735
MSI-H (Yes vs No)	1.19 (0.26-5.36) <i>S: 1.28 (0.29-5.58)</i>	0.814 <i>0.741</i>
RAS (Mutant vs WT)	7.09 (1.87-26.76) / <i>S: 15.06 (3.35-67.73)</i>	<0.001 <i>0.001</i>
RAF, n (%) Mutant vs WT	0.04 (0.00-3977) <i>S: 2.60 (0.63-10.71)</i>	0.592 <i>0.180</i>
ABO group A vs AB	0.91 (0.19-4.30) <i>S: 0.91 (0.19-4.45)</i>	0.906 <i>0.916</i>
B vs AB	NC <i>S: 0.80 (0.07-9.23)</i>	0.985 <i>0.862</i>
O vs AB	0.83 (0.15-4.55) <i>S: 0.85 (0.15-4.77)</i>	0.830 <i>0.856</i>
Rh (Negative vs positive)	0.24 (0.03-1.84) <i>S: 0.22 (0.02-1.69)</i>	0.170 <i>0.146</i>
Perioperative treatment (Yes vs No)	0.04 (0.00-55.20)	0.38
Adjuvant chemotherapy, XELOX vs No	NC	0.928
FOLFOX vs No	NC	0.925
Capecitabine vs No	NC	1
Neoadjuvant radiotherapy Short course (5x5) vs No	1.60 (0.20-12.78)	0.654
Long Course (CRT) vs No	2.38 (0.79-7.17)	0.122
Neoadjuvant chemotherapy XELOX vs No	NC	0.438
FOLFOX vs No	NC	0.737

Abbreviations: EOCRC: early-onset colorectal cancer, CRC: colorectal cancer, CAD: coronary artery disease, LVI: lymphovascular invasion, PNI: perineural invasion, MSI-H: microsatellite instability-high, WT: wild type, NC: not calculated, CRT: chemoradiotherapy, FOLFOX: Folinic acid, 5-fluorouracil and oxaliplatin, XELOX: Oxaliplatin and capecitabine [**S: sensitivity analysis*: Sensitivity analyses were performed for the variables that had missing data. Pooled results of multiple imputations were presented.]

Table S4. Multivariable Cox regression analysis for recurrence-free survival (RFS) in localized EOCRC patients

Variable	HR (95% CI)	P
N stage		
1a-b vs 0	1.62 (0.27-9.52) <i>S: 1.90 (0.45-7.94)</i>	0.59 <i>0.377</i>
1c vs 0	51.92 (4.36-618.08) <i>S: 3.32 (0.68-16.18)</i>	0.002 <i>0.136</i>
2 vs 0	2.54 (0.30-20.95) <i>S: 4.47 (0.93-21.46)</i>	0.38 <i>0.061</i>
RAS (Mutant vs WT)	14.25 (2.61-77.61) <i>S: 14.83 (3.00-73.15)</i>	0.002 <i>0.001</i>
Neoadjuvant radiotherapy		
Short course (5x5) vs No	NC <i>S: 1.06 (0.08-12.60)</i>	<i>S: 0.963</i>
Long Course (CRT) vs No	2.39 (0.50-11.33) <i>S: 1.78 (0.52-6.05)</i>	0.27 <i>0.351</i>

Abbreviations: EOCRC: early-onset colorectal cancer, WT: wild type, NC: not calculated, CRT: chemoradiotherapy, [**S: sensitivity analysis*: Sensitivity analyses were performed for the variables that had missing data. Pooled results of multiple imputations were presented.]

Table S5. Multivariable Cox regression analysis for recurrence-free survival (RFS) in localized EOCRC patients (additionally adjusted by basic characteristics)

Variable	HR (95% CI)	P
Age (continuous variable)	0.95 (0.87-1.04)	0.321
Gender, (Male vs. female)	0.29 (0.02-4.31)	0.372
Hypertension, (Present vs absent)	37.70 (0.89-145.68)	0.059
Diabetes (Present vs absent)	0.00 (0.00-NC)	0.866
CAD (Present vs absent)	0.00 (0.00-NC)	0.975
Primary tumor location		
Transverse vs right	NC	NC
Left vs right	1.40 (0.03-53.87)	0.855
Rectum vs right	0.02 (0.00-NC)	0.962
N stage		
1a-b vs 0	3.70 (0.26-52.47)	0.333
1c vs 0	249.55 (3.11-2000.18)	0.014
2 vs 0	6.58 (0.15-272.11)	0.321
RAS (Mutant vs WT)	32.92 (2.32-467.05)	0.010
Neoadjuvant radiotherapy		
Short course (5x5) vs No	NC	0.980
Long Course (CRT) vs No	NC	0.946

Abbreviations: EOCRC: early-onset colorectal cancer, CAD: coronary artery disease WT: wild type, NC: not calculated, CRT: chemoradiotherapy

Table S6. Univariable Cox regression analyses for PFS and OS in synchronous metastatic EOCRC patients

Variable	PFS		OS	
	OR (95% CI)	P	OR (95% CI)	P
Gender (Female vs male)	0.77 (0.34-1.76)	0.542	1.16 (0.45-3.00)	0.748
Diabetes (Absent vs present)	0.91 (0.12-6.93)	0.932	25.94 (0.02-277.87)	0.360
Hypertension (Absent vs present)	1.12 (0.33-3.82)	0.851	2.36 (0.50-11.02)	0.272
CAD (Absent vs present)	NC	NC	NC	NC
Smoking history (Absent vs present)	1.12 (0.54-2.76)	0.623	1.32 (0.51-3.41)	0.554
Location (Rectum vs colon)	2.72 (1.15-6.45)	0.023	2.65 (1.02-6.86)	0.044
MSI (High vs. stable)	0.44 (0.05-3.43) <i>S: 0.38 (0.07-1.94)</i>	0.436 <i>0.247</i>	0.58 (0.07-4.58) <i>S: 0.31 (0.04-2.06)</i>	0.611 <i>0.223</i>
<i>RAS</i> (Mutant vs wild type)	1.07 (0.43-2.61) <i>S: 1.02 (0.42-2.42)</i>	0.879 <i>0.963</i>	0.94 (0.32-2.73) <i>S: 0.80 (0.29-2.20)</i>	0.920 <i>0.672</i>
<i>RAF</i> (Mutant vs wild type)	NC	NC	NC	NC
Liver metastasis (Absent vs present)	3.29 (0.69-15.60)	0.133	2.85 (0.60-13.52)	0.186
Peritoneal metastasis (Absent vs present)	0.73 (0.09-5.57)	0.763	0.16 (0.01-1.51)	0.112
Lung metastasis (Absent vs present)	0.54 (0.26-1.28)	0.164	0.47 (0.18-1.24)	0.130
Bone metastasis (Absent vs present)	NC	NC	NC	NC
CEA (continuous variable)	1.001 (1.000-1.002)	0.056	1.001 (1.000-1.002)	0.079
Ca19-9 (continuous variable)	1.00 (1.00-1.00)	0.344	1.00 (1.00-1.00)	0.531
Urgent surgery (Absent vs present)	1.94 (0.80-4.74)	0.141	3.39 (0.97-11.79)	0.055
First-line treatment (all treatments compared to 5FU-OX doublet)	All 1.000 with varying 95% CI	All p is 1.000	All 1.000 with varying 95% CI	All p is 1.000
Local treatment (Absent vs present)	0.99 (0.44-2.25)	0.997	1.71 (0.68-4.31)	0.250
Surgery as a local treatment (Absent vs present)	1.19 (0.27-5.26)	0.811	29.87 (0.16-545,359)	0.201
TARE-TACE-RF as local treatments (Absent vs present)	1.05 (0.46-2.40)	0.895	1.26 (0.50-3.16)	0.617
ABO				
A vs AB	0.32 (0.06-1.64) <i>S: 0.29 (0.06-1.45)</i>	0.176 <i>0.133</i>	0.44 (0.08-2.35) <i>S: 0.68 (0.08-5.61)</i>	0.339 <i>0.717</i>
B vs AB	0.20 (0.03-1.36) <i>S: 0.22 (0.03-1.43)</i>	0.102 <i>0.115</i>	0.48 (0.07-3.21) <i>S: 0.78 (0.08-7.06)</i>	0.449 <i>0.828</i>
O vs AB	0.36 (0.07-1.84) <i>S: 0.36 (0.047-1.80)</i>	0.225 <i>0.217</i>	0.87 (0.17-4.29) <i>S: 1.14 (0.17-7.51)</i>	0.872 <i>0.885</i>
Rh (negative vs positive)	1.04 (0.24-4.54) <i>S: 1.12 (0.26-4.85)</i>	0.951 <i>0.876</i>	0.79 (0.10-6.10) <i>S: 0.53 (0.05-5.36)</i>	0.825 <i>0.580</i>

EOCRC: Early onset colorectal cancer, CRC: colorectal cancer, CAD: coronary artery disease, LVI: lymphovascular invasion, PNI: perineural invasion, MSI-H: microsatellite instability-high, WT: wild type, UK: unknown, 5FU: 5-fluorouracil, OX: oxaliplatin, IRI: irinotecan, EGFR: epidermal growth factor receptor, TARE: Transarterial radioembolization, TACE: Transarterial chemoembolization, RFA: Radiofrequency ablation, NC: Not calculated. [**S: sensitivity analysis*: Sensitivity analyses were performed for the variables that had missing data. Pooled results of multiple imputations were presented.]