Supplementary Online Content

Boyne DJ, Cuthbert CA, O'Sullivan DE, et al. Association between adjuvant chemotherapy duration and survival among patients with stage II and III colon cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(5):e194154. doi:10.1001/jamanetworkopen.2019.4154

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Search Strategy

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 09, 2018
Search Strategy:

#	Searches
1	(Colo* adj2 (cancer or tumour* or tumor* or neoplasm* or carcinoma* or adenocarcinoma*)).tw,kf.
2	exp Colorectal Neoplasms/
3	((Adjuvant or postoperative or post-operative or postsurgical or post-surgical or "after surger*") adj2 (therap* or treatment* or chemotherap*)).tw,kf.
4	FOLFOX.tw,kf.
5	XELOX.tw,kf.
6	CAPOX.tw,kf.
7	5-FU.tw,kf.
8	Oxaliplatin.tw,kf.
9	Fluorouracil.tw,kf.
10	Capecitabine.tw,kf.
11	Leucovorin.tw,kf.
12	exp Chemotherapy, Adjuvant/
13	Duration.tw,kf.
14	Discontinu*.tw,kf.
15	(Cycles adj3 (completed or received or omission or receipt or enough or number*)).tw,kf.
16	Withdrawal.tw,kf.
17	Complian*.tw,kf.
18	Adherence.tw,kf.
19	Terminat*.tw,kf.
20	((Completed or completion or complete) adj3 (chemotherapy or therapy or treatment)).tw,kf.
21	1 or 2
22	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
24	21 and 22 and 23
25	limit 24 to (english language and yr="2003 -Current")

Database(s): **Embase** 1974 to 2018 August 09
Search Strategy:

#	Searches
1	(Colo* adj2 (cancer or tumour* or tumor* or neoplasm* or carcinoma* or adenocarcinoma*)).tw,kw.
2	exp colorectal cancer/
3	((Adjuvant or postoperative or post-operative or postsurgical or post-surgical or "after surger*") adj2 (therap* or treatment* or chemotherap*)).tw,kw.
4	FOLFOX.tw,kw.
5	XELOX.tw,kw.
6	XELOX.tw,kw.
7	CAPOX.tw,kw.
8	5-FU.tw,kw.
9	Oxaliplatin.tw,kw.
10	Fluorouracil.tw,kw.
11	Capecitabine.tw,kw.
12	Leucovorin.tw,kw.
13	exp adjuvant chemotherapy/
14	Duration.tw,kw.
15	Discontinu*.tw,kw.
16	(Cycles adj3 (completed or received or omission or receipt or enough or number*)).tw,kw.
17	Withdrawal.tw,kw.
18	Complian*.tw,kw.
19	Adherence.tw,kw.
20	Terminat*.tw,kw.
21	((Completed or completion or complete) adj3 (chemotherapy or therapy or treatment)).tw,kw.
22	exp treatment duration/
23	1 or 2
24	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
25	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
26	23 and 24 and 25
27	limit 26 to (english language and yr="2003 -Current")
28	limit 27 to (conference abstract or conference paper or "conference review")
29	27 not 28

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2018
Search Strategy:

#	Searches
1	(Colo* adj2 (cancer or tumour* or tumor* or neoplasm* or carcinoma* or adenocarcinoma*)).tw,kf.
2	exp Colorectal Neoplasms/
3	((Adjuvant or postoperative or post-operative or postsurgical or post-surgical or "after surger*") adj2 (therap* or treatment* or chemotherap*)).tw,kf.
4	FOLFOX.tw,kf.
5	XELOX.tw,kf.
6	CAPOX.tw,kf.
7	5-FU.tw,kf.
8	Oxaliplatin.tw,kf.
9	Fluorouracil.tw,kf.
10	Capecitabine.tw,kf.
11	Leucovorin.tw,kf.
12	exp Chemotherapy, Adjuvant/
13	Duration.tw,kf.
14	Discontinu*.tw,kf.
15	(Cycles adj3 (completed or received or omission or receipt or enough or number*)).tw,kf.
16	Withdrawal.tw,kf.
17	Complian*.tw,kf.
18	Adherence.tw,kf.
19	Terminat*.tw,kf.
20	((Completed or completion or complete) adj3 (chemotherapy or therapy or treatment)).tw,kf.
21	1 or 2
22	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
24	21 and 22 and 23
25	limit 24 to (english language and yr="2003 -Current")

Database(s): **CINAHL**
Search Strategy:

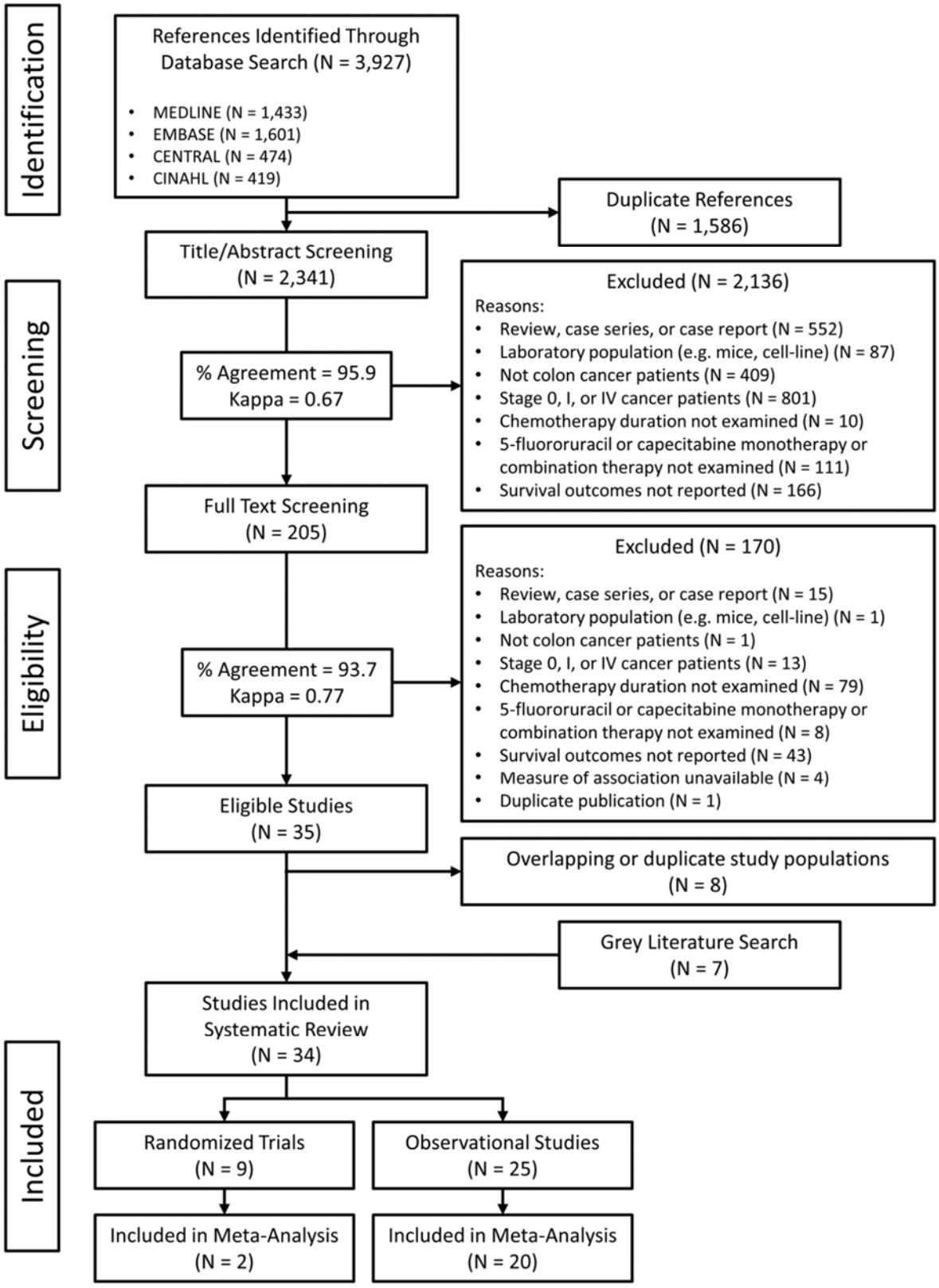
#	Searches
1	TI ((Colo* W2 (cancer or tumour* or tumor* or neoplasm* or carcinoma* or adenocarcinoma*))) OR AB ((Colo* W2 (cancer or tumour* or tumor* or neoplasm* or carcinoma* or adenocarcinoma*)))
2	(MH "Colorectal Neoplasms+")
3	TI (((Adjuvant or postoperative or post-operative or postsurgical or post-surgical or "after surger*") W2 (therap* or treatment* or chemotherap*))) OR AB (((Adjuvant or postoperative or post-operative or postsurgical or post-surgical or "after surger*") W2 (therap* or treatment* or chemotherap*)))
4	TI FOLFOX OR AB FOLFOX
5	TI XELOX OR AB XELOX
6	TI CAPOX OR AB CAPOX
7	TI 5-FU OR AB 5-FU
8	TI Oxaliplatin OR AB Oxaliplatin
9	TI Fluorouracil OR AB Fluorouracil
10	TI Capecitabine OR AB Capecitabine
11	TI Leucovorin OR AB Leucovorin
12	(MH "Chemotherapy, Adjuvant+")
13	TI Duration OR AB Duration
14	TI Discontinu* OR AB Discontinu*
15	TI ((Cycles W3 (completed or received or omission or receipt or enough or number*))) OR AB ((Cycles W3 (completed or received or omission or receipt or enough or number*)))
16	TI Withdrawal OR AB Withdrawal
17	TI Complian* OR AB Complian*
18	TI Adherence OR AB Adherence
19	TI Terminat* OR AB Terminat*
20	TI (((Completed or completion or complete) W3 (chemotherapy or therapy or treatment))) OR AB (((Completed or completion or complete) W3 (chemotherapy or therapy or treatment)))
21	(MH "Treatment Duration+")
22	1 or 2
23	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
24	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
25	22 and 23 and 24 (**Limiters** - Published Date: 20030101-20181231)

eAppendix 2. Additional Information Regarding the Derivation of Effect Estimates

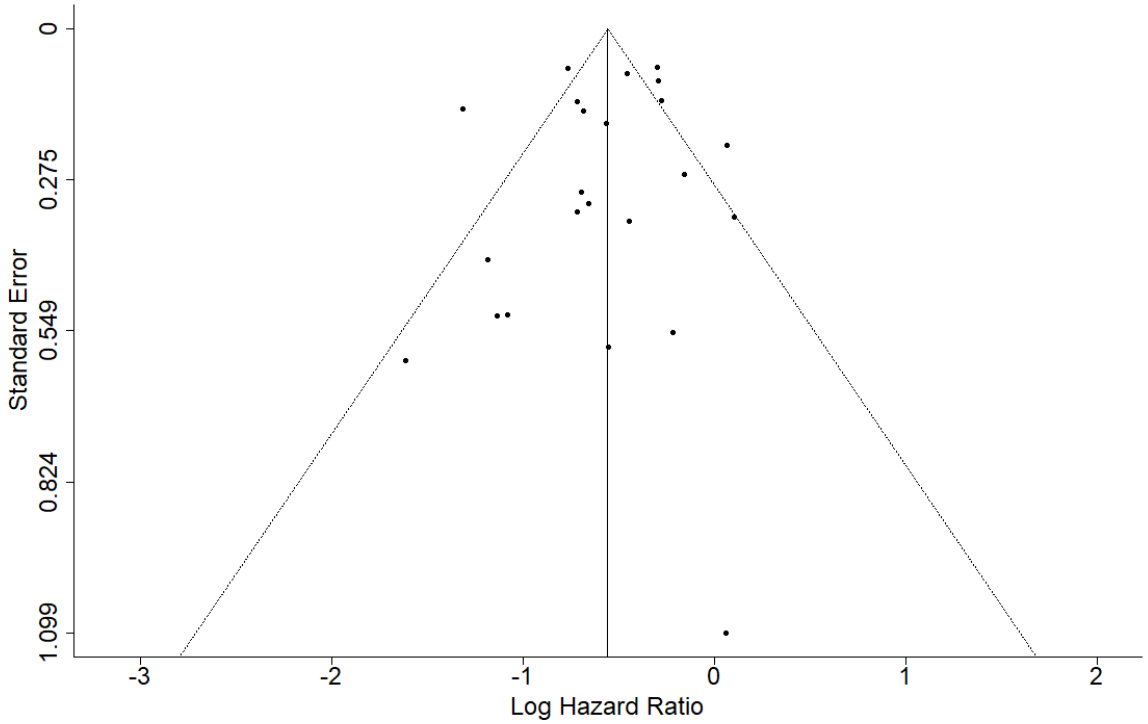
In situations where the hazard ratio and corresponding variance estimates were unavailable, we derived an estimate using the number of individuals within each exposure group, the total number of events, and the p-value from the log-rank test using the method described by Tierney et al. (2007).[1] If the authors provided effect estimates comparing different chemotherapy durations relative to a referent group not of interest to this publication (i.e. individuals who received no chemotherapy), we derived an effect estimate using the following formula: $HR_{A\ vs.\ B} = HR_{A\ vs.\ C} / HR_{B\ vs.\ C}$. We used the following formula to estimate the variance of the foregoing effect estimate: $var(\ln(HR_{A\ vs.\ B}) = var(\ln(HR_{A\ vs.\ C}) - \ln(HR_{B\ vs.\ C})) = var(\ln(HR_{A\ vs.\ C}) + var(\ln(HR_{B\ vs.\ C})) - 2*cov(var(\ln(HR_{A\ vs.\ C})), var(\ln(HR_{B\ vs.\ C}))$. When applying this formula, we assumed a covariance of zero since the covariance was not directly estimable using the reported data. Assuming a positive covariance, this approach will bias the variance estimate in the conservative direction by inflating the variance and reducing the precision in the effect estimate.

The former method was used for one study (Moris et al. (2007))[2] and the method described by Tierney et al. (2007) was used for six studies.[3-8]

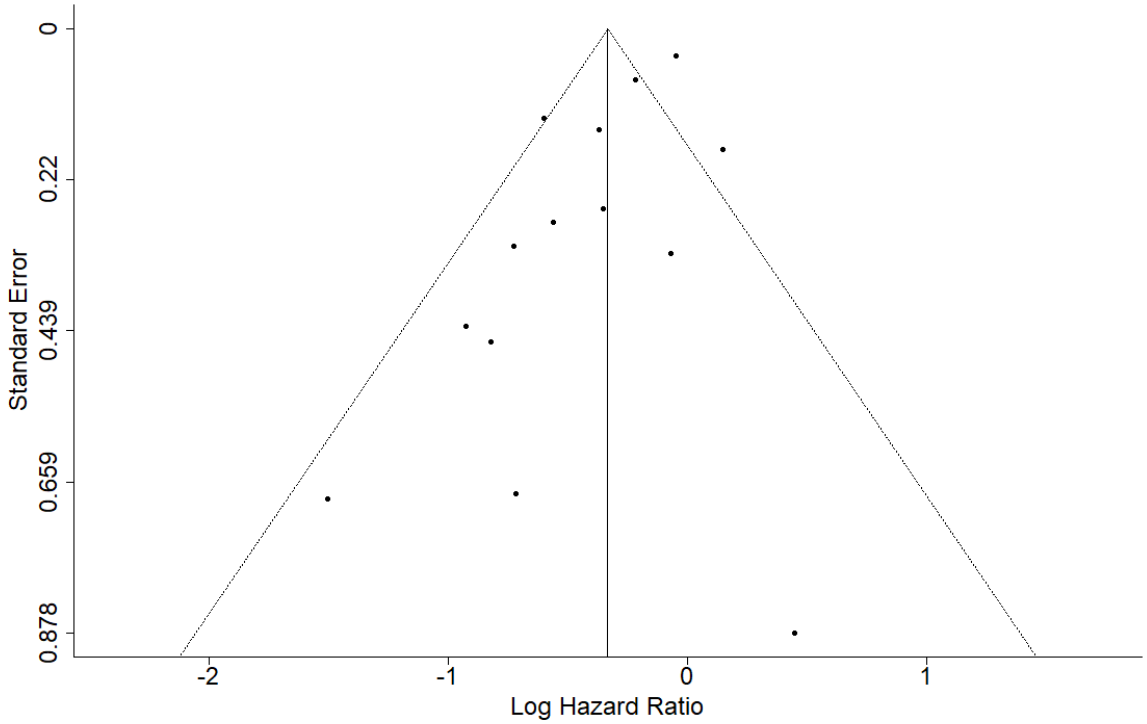
eFigure 1. PRISMA Flow Diagram



eFigure 2. Funnel Plot Assessing Publication Bias Among Studies of Overall Survival



eFigure 3. Funnel Plot Assessing Publication Bias Among Studies of Disease-Free Survival



eTable 1. Raw Data Extracted From the Studies Included in the Meta-analysis (n = 22)

Study	Chemotherapy Regime	Chemotherapy Duration	Overall Survival	Disease-Free Survival
Randomized Clinical Trials				
IDEA (2018)[9]	FOLFOX/CAPOX	6 months	-	Ref.
		3 months	-	HR: 1.05 (95% CI: 0.97-1.13)
Ito (2000)[10]	Carmofur	12 months	n = 50 5-year OS = 87%	n = 50 5-year DFS = 77%
		3 months	n = 94 5-year OS = 72% g-Wilcoxon test = 0.0361 total events = 29	n = 94 5-year DFS = 63% g-Wilcoxon test = 0.0487 total events = 39
Observational Studies				
Ahmed (2010)[11]	5-flourouracil	6 months	HR: 0.49 (95% CI: 0.38-0.64)	HR: 0.55 (95% CI: 0.42-0.70)
		1-5 months	Ref.	Ref.
Cespedes Feliciano (2017)[3]	FOLFOX	6-12 cycles	n = 491 OS higher in 6-12 month arm	Cespedes Feliciano (2017)
		1-5 cycles	n = 42 log-rank p-value = 0.04 Total events = 51	
Chapuis (2009)[4]	5-flourouracil	6 months	n = 68 3-year OS = 82%	-
		1-5 months	n = 36 3-year OS =72% log-rank p-value = 0.030 total events = 40	-
Figer (2011)[5]	5-flourouracil	7-12 months	n = 305 greater OS relative to 1-6 month arm	-
		1-6 months	n = 93 log=rank p-value = 0.002 total events = 156	-

Hassan (2015)[12]	5-flourouracil / capecitabine / FOLFOX / CAPOX	6 months	HR: 0.2 (95% CI: 0.06-0.64)	-
		1-5 months	Ref.	-
Hwang (2017)[13]	5-flourouracil / capecitabine	4-6 months	Ref.	-
		1-3 months	HR: 3.72 (95% CI: 2.80-4.94)	-
	FOLFOX / CAPOX	4-6 months	Ref.	-
		1-3 months	HR: 2.15 (95% CI: 1.87-2.47)	-
	tegafur	4-6 months	Ref.	-
		1-3 months	HR: 1.74 (95% CI: 0.56-5.41)	-
Ji (2018)[14]	FOLFOX	6 months	Ref.	Ref.
		4 months	HR: 0.958 (95% CI: 0.229-4.044)	HR: 0.743 (95% CI: 0.236-2.344)
Kim (2014)[6]	5-flourouracil / capecitabine / FOLFOX / CAPOX	75%+ cycles	n = 210 5-year OS = 80%	-
		< 75% cycles	n = 58 5-year OS = 64% log-rank p-value = 0.0054 total events = 57	-
Kornmann (2008)[15]	5-flourouracil	14-39 weeks	HR: 0.4 (95% CI: 0.2-0.6)	-
		1-13 weeks	Ref.	-
Kumar (2015)[16]	FOLFOX	10-12 cycles	HR: 1.07 (95% CI: 0.70-1.61)	HR: 1.16 (95% CI: 0.82-1.63)
		1-9 cycles	Ref.	Ref.
Laurent (2018)[17]	FOLFOX	12 cycles	Ref.	-
		1-11 cycles	HR: 3.1 (95% CI: 1.1-8.5)	-
Morris (2007)[2]	5-flourouracil	4-6 cycles	HR: 0.55 (0.45-0.67) vs. no chemotherapy	-
		1-3 cycles	HR: 1.09 (0.88 – 1.35) vs. no chemotherapy	-
Neugut (2006)[18]	5-flourouracil	5-7 months	HR: 0.59 (0.49-0.71)	-
		1-4 months	Ref.	-
Qiu (2009)[19]	FOLFOX/ CAPOX/Capecitabine/5-flourouracil/tegafur	Slope	-	beta for ln(HR) per two month increase in chemotherapy duration = -0.618; se = 0.288

Sgouros (2015)[7,a]	5-flourouracil / FOLFOX	6 month (stage II)	n = 61 3-year OS = 92.7	n = 61 3-year DFS = 96.3
		1-5 months (stage II)	n = 29 3-year OS = 88.2 log-rank p-value = 0.2179 total events = 15	n = 29 3-year DFS = 81.6 log-rank p-value = 0.0166 total events = 10
		6 month (stage III)	n = 78 3-year OS = 75.5	n = 78 3-year DFS = 61.9
		1-5 months (stage III)	n = 31 3-year OS = 83.2 log-rank p-value = 0.7313 total events = 42	n = 31 3-year DFS = 58.7 log-rank p-value = 0.6606 total events = 46
Sun (2015)[20]	Capecitabine	8 cycles	Ref.	Ref.
		1-7 cycles	HR: 3.27 (95% CI:1.44-7.45)	HR: 2.27 (0.93-5.53)
Tsai (2013)[21]	5-fluorouracil / tegafur	5-12 months	HR: 0.55 (95% CI: 0.42-0.73)	HR: 0.65 (95% CI: 0.49-0.87)
		1-4 months	Ref.	Ref.
Tsai (2016)[22]	FOLFOX	8-12 cycles	HR: 0.52 (95% CI: 0.28-0.97)	-
		1-7 cycles	Ref.	-
		7-12 cycles	-	HR: 0.57 (95% CI: 0.33-0.996)
		1-6 cycles	-	Ref.
van Erning (2017)[23]	Capecitabine	6-8 cycles	Ref.	Ref.
		1-5 cycles	HR: 2.00 (95% CI: 1.12-3.59)	HR: 2.07 (95% CI: 1.11-3.84)
	CAPOX	6-8 cycles	Ref.	Ref.
		1-5 cycles	HR: 1.17 (95% CI: 0.70-1.97)	HR: 1.42 (95% CI: 0.85-2.37)
Yun (2010)[8]	Capecitabine	8 cycles	-	n = 155; 3-year DFS = 90.7%

		1-7 cycles	-	n = 18;
				3-year DFS = 70.9%;
				log-rank test p-value = 0.028;
				total events = 23

[a] The log-rank p-value and the total number of events were not reported in the original manuscript but were obtained directly from the authors

Abbreviation: HR = Hazard Ratio; OS = Overall Survival; DFS = Disease-free survival

eTable 2. Reason for Risk of Bias Assignment in the Confounding and Selection Into the Study Domains

Study	Reason for assigning a Serious Risk of Bias due to Confounding	Moderate or Serious Risk of Bias due to Selection into the Study
Ahmed (2010)[11]	-	Serious risk of bias: the authors excluded patients lost to follow-up as well as "…patients who had inconclusive information about the number of treatment cycles…" and did not provide the number of patients excluded for these reasons. In addition, survival time was estimated starting from the time of surgery as opposed to the time of chemotherapy initiation.
Cespedes Feliciano (2017)[3]	No adjustment for age, sex, or stage	Moderate risk of bias: survival time was estimated starting from the time of diagnosis as opposed to the time of chemotherapy initiation.
Chapuis (2009)[4]	No adjustment for age or sex	Moderate risk of bias: survival time was estimated from the time of chemotherapy completion rather than the time of chemotherapy initiation.
Figer (2011)[5]	No adjustment for age, sex, stage, or site	Moderate risk of bias: survival time was estimated starting from the time of surgery as opposed to the time of chemotherapy initiation.
Hassan (2015)[12]	No adjustment for stage or chemotherapy regimen	Moderate risk of bias: survival time was estimated starting from the time of surgery as opposed to the time of chemotherapy initiation
Ji (2018)[14]	No adjustment for age, sex, or stage	-
Kim (2014)[6]	No adjustment for age or sex, or chemotherapy regimen	-
Morris (2007)[2]	-	Moderate risk of bias: survival time was estimated starting from the time of diagnosis as opposed to the time of chemotherapy initiation.
Neugut (2006)[18]	-	Serious risk of bias: excluded participants who, "were enrolled in a health maintenance organization (HMO) at any point from 12 months before to 8 months after initiation of FU chemotherapy… and/or were not covered by Medicare Parts A and B at any point during that period." Also excluded patients, "… who received

		more than 7 months of treatment because they could not be distinguished from patients intended to receive longer (e.g., 12 month) regimens." In addition, survival time was also estimated from the time of diagnosis as opposed to the time of chemotherapy initiation.
Sgouros (2015)[7]	No adjustment for age, sex, site, or chemotherapy regimen	-
Sun (2015)[20]	No adjustment for age, sex, or stage	Moderate risk of bias: They excluded patients who had, "… less than 3 cycles of therapy for reasons other than toxicity…". In addition, survival time was also estimated from the time of diagnosis as opposed to the time of chemotherapy initiation.
Tsai (2016)[22]	-	Serious risk of bias: The authors excluded patients lost to follow-up without providing the number excluded. In addition, survival time was estimated starting from the time of surgery as opposed to the time of chemotherapy initiation.
Yun (2010)[8]	No adjustment age, sex, or stage	Moderate risk of bias: Survival time was estimated from the time of surgery as opposed to the time of chemotherapy initiation.

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