

The association of comorbidities with administration of adjuvant chemotherapy in stage III colon cancer patients: a systematic review and meta-analysis

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Abstract

Background: Chemotherapy is an established treatment for stage III colon cancer cases. Older age is known to be associated with less chemotherapy use in these patients, but there might be other relevant factors besides age that influence treatment administration. We summarized evidence on associations between comorbidity and adjuvant chemotherapy administration in stage III colon cancer patients in a systematic review and meta-analysis.

Methods: We searched the PubMed and Web of Science databases up to 2 June 2020 for studies on comorbidities and chemotherapy use in patients with stage III colon cancer. Summary odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using random-effects models. Subgroup analyses according to year of colon cancer diagnosis, timing of comorbidity assessment, and geographical region were also conducted.

Results: Thirty-three studies were included in this review, including 219,406 stage III colon cancer patients overall. Chemotherapy administration was 60.9% (95% CI: 56.9% to 64.9%), increasing from 57.1% before 2001 to 66.3% after 2010. There were inverse associations between comorbidities and chemotherapy administration. Compared with patients with Charlson comorbidity score 0, those with scores 1 (OR=0.79, 95% CI=0.72–0.87) and 2+ (OR=0.49, 95% CI=0.42–0.56) received chemotherapy less often. Among comorbidities, the strongest predictors of chemotherapy non-use were dementia (OR=0.37, 95% CI=0.33–0.54), followed by heart failure (OR=0.44, 95% CI=0.28–0.70) and stroke (OR=0.56, 95% CI=0.38–0.81).

Conclusions: Merely 60% of stage III colon cancer patients receive chemotherapy. Comorbidities are strong predictors of chemotherapy non-use, but the association differs by comorbid condition and is strongest with dementia. Given the survival disadvantage of colon cancer patients with comorbidities, further evidence on the risk–benefit ratio of chemotherapy according to the type and severity of comorbidity and on the extent to which the survival disadvantage of comorbidity is explained by less use or lower tolerability of chemotherapy is needed to foster personalized medical care in these patients.

Keywords: chemotherapy, chronic disease, colonic neoplasm, comorbidity, meta-analysis

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Background

Colorectal cancer is the third most commonly diagnosed malignancy and the second major cause of cancer death worldwide.¹ Approximately two-thirds of colorectal cancers occur in the colon.¹ In recent decades, surgical resection of

colon cancer tumors has been complemented by postoperative chemotherapy mainly for stage III patients.² Although stage II patients with high-risk features (e.g. presence of lymphovascular and perineural invasion) appear to benefit from chemotherapy,³ application of chemotherapy in this

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patient group is controversial. In stage III patients, clinical trials have suggested that chemotherapy use is associated with about 25% reduction in all-cause mortality.^{4,5}

Despite the benefits of chemotherapy for stage III colon cancer, between one-third and nearly half of the patients still do not receive this effective treatment.^{6,7} Older age is the main determinant of chemotherapy non-use,^{6,8,9} but about one-fifth of patients younger than 75 years do not receive chemotherapy,^{9,10} suggesting that there might be other relevant factors that affect treatment administration aside from age. Colon cancer is mainly diagnosed at older age, when comorbidities (e.g. diabetes) are common^{11,12} and they might impact treatment decisions. It is well documented that comorbidities are strongly associated with poorer colon cancer prognosis,¹³ and mediation by less chemotherapy utilization by patients with comorbidities has been suggested as one of the possible mechanisms underlying this association.¹⁴

In recent years, several studies have evaluated associations between comorbidities and chemotherapy use in patients with stage III colon cancer. However, no study has summarized results from such studies in a systematic review or a meta-analysis. Quantification of this association is important, as it may have clinical relevance and may confound the association between chemotherapy and patient survival in observational studies. Herein, we conducted a systematic review and meta-analysis to summarize evidence on associations between comorbidity and administration of adjuvant chemotherapy in stage III colon cancer patients, paying particular attention to whether the associations also differ by specific comorbidities, age, year of diagnosis, timing of comorbidity assessment, or geographical region.

Methods

Search strategy

We systematically searched PubMed and Web of Science (Core Collection) from inception (1978 and 1995, respectively) to 2 June 2020 for relevant studies. For the PubMed search, the following search strategy was used, incorporating Medical Subject Headings (MeSH) terms: (comorbidity OR comorbidities OR multimorbidity OR “chronic diseases”[Title/Abstract] OR “chronic conditions”[Title/Abstract] OR “chronic illnesses”[Title/Abstract] OR comorbidity[MeSH]) AND ((chemotherapy OR “adjuvant treatment” OR

treatment[Title/Abstract] OR “adjuvant therapy” OR chemotherapy[MeSH]) AND (use OR uptake OR receipt OR nonuse OR underuse OR initiation OR administration OR utilization OR adherence OR patterns)) AND (“colon cancer” OR “bowel cancer” OR “colonic cancer” OR “colonic neoplasms”[MeSH]). Further details of the search strategy have been summarized in Supplemental Table S1. We also hand-searched the reference lists of articles for additional relevant studies. This review was conducted in accordance with the PRISMA¹⁵ and MOOSE guidelines,¹⁶ and its protocol was registered with PROSPERO (registration number CRD42020187250).

Eligibility criteria

Studies were eligible for inclusion in this review if they: (i) were published observational studies that assessed comorbidity [summary measures or specific diseases such as diabetes, myocardial infarction, heart failure, renal disease, stroke, chronic obstructive pulmonary disease (COPD), or dementia] and their associations with adjuvant chemotherapy use in stage III colon cancer patients; and (ii) reported risk estimates of these associations [e.g. odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (95% CIs)] or provided sufficient information to calculate them. We defined chemotherapy use as receipt of any chemotherapy regimen after colon cancer surgery.

We did not consider clinical trials because participants of such studies are often younger¹⁷ and have lower comorbidity compared with cancer patients in the real-life setting.^{18,19} Studies on colorectal or colon cancer patients in general that did not provide results specific for stage III colon cancer patients were excluded, except for those that analyzed stage III together with high-risk stage II patients because high-risk stage II patients represented a small fraction of the study populations (<15%). In case multiple studies used the same study population, the less informative articles were excluded (Figure 1). Studies published as abstracts or posters only were excluded because their information was not sufficient for quality assessment.

Data extraction and quality assessment

Two authors (DB and KG) used pre-designed data extraction forms to abstract data from the eligible studies independently. One of the forms

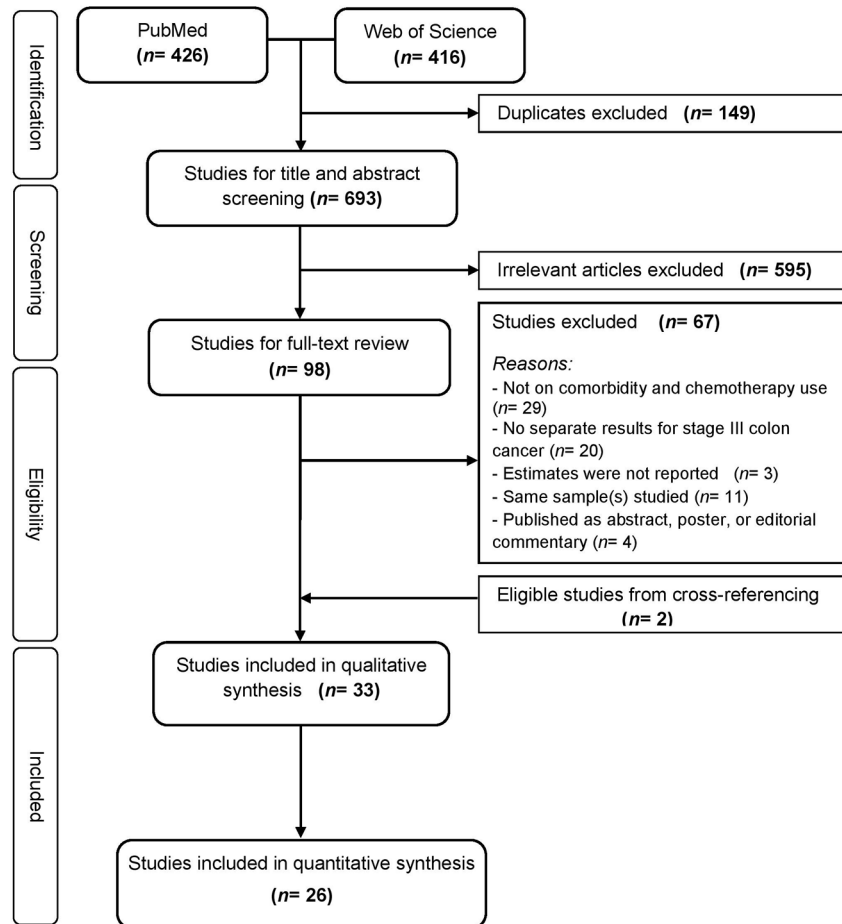


Figure 1. PRISMA flow diagram showing selection of eligible studies.

Seven (7) studies used different comorbidity groupings and reference groups and hence could not be included in the quantitative analysis.

summarized basic characteristics of the studies (e.g. first author, country, period of colon cancer diagnosis, sample size), as reported in Table 1. The second form summarized the results of each of the studies as well as the covariates that were adjusted for, as shown in Supplemental Tables S2–S3. We used the Newcastle–Ottawa Scale²⁰ to assess the quality and risk of bias of the included studies. In brief, the included studies were assessed against the following criteria: (i) representativeness of the study sample, (ii) valid assessment of comorbidities, (iii) appropriate ascertainment of chemotherapy use, and (iv) adjustment for at least age and year of colon cancer diagnosis in the multivariable analysis. Further details of the assessment criteria and corresponding scores are shown in Supplemental Table S4. The highest achievable score was nine: higher scores indicate high quality and low risk of bias. In case of initial disparity in the data extraction or quality assessment between

the two authors, consensus was achieved through additional review and comprehensive discussion.

Statistical analysis

Studies that used the same summary measure [e.g. Charlson comorbidity index (CCI)⁵⁰ and Adult comorbidity evaluation (ACE-27)⁵¹] or assessed similar comorbid conditions were selected for meta-analysis, if their reference groups allowed for combination of risk estimates. We treated RRs and ORs as equivalent estimates because they were all derived from cohort studies. In brief, we log-transformed the extracted estimates and calculated their standard errors indirectly.⁵² We then used both the fixed-effect and random-effects models to estimate summary ORs. Results from the random-effects models are reported as the main results because they take into consideration both within- and

Table 1. Characteristics of the included studies on comorbidities and chemotherapy administration.

Author	Country	Study design	Sample characteristics			Comorbidity assessment			Chemo use			Quality scores					
			Source (registry)	Period of diagnosis	Size	Age (years)	% women	Time	Summary measure	Prop.		RE	EX	0	AD	Total(9)	
Gupta and Lamont ²¹	USA	Retro. cohort	Yes	1993–1996	3386	67+	NR	NR	Before diagnosis	CCI	NR	NR	2	2	1	0	5
Lemmens <i>et al.</i> ²²	Netherlands	Retro. cohort	Yes	1995–2001	NR	50+	NR	NR	Up to diagnosis	Count	NR	NR	2	4	2	0	8
McGory <i>et al.</i> ²³	USA	Retro. cohort	Yes	1994–2001	13231	All adults	NR	28%	Before surgery	CCI	28%	48%	2	2	2	1	7
Gross <i>et al.</i> ²⁴	USA	Retro. cohort	Yes	1993–1999	5330	67+	60%	53%	Up to 1 month after diagnosis	Individual	53%	60%	2	3	2	1	8
Cress <i>et al.</i> ²⁵	USA	Retro. cohort	Yes	1997	915	All adults	53%	25%	NR	CCI	25%	67%	2	3	2	1	8
Sarfati <i>et al.</i> ²⁶	NZ	Retro. cohort	Yes	1996–2003	189	25+	46%	49%	Up to diagnosis	CCI	49%	68%	1	4	2	0	7
Kahn <i>et al.</i> ²⁷	USA	Pros. cohort	No	2003–2005	675	18+	44%	74%	Before surgery	ACE-27	74%	76%	1	4	2	0	7
van Steenberg <i>et al.</i> ²⁸	Netherlands	Retro. cohort	Yes	2001–2007	1637	<65–75+	52%	58%	Up to diagnosis	Count	58%	NR	2	2	1	1	6
Winget <i>et al.</i> ²⁹	Canada	Retro. cohort	Yes	2002–2005	618	69.3 ^b	48%	32%	Before diagnosis	CCI	32%	63%	2	3	2	0	7
Baillargeon <i>et al.</i> ³⁰	USA	Retro. cohort	Yes	1993–2005	15319	67+	NR	NR	Before diagnosis	Individual	NR	NR	2	3	1	1	7
Foley <i>et al.</i> ³¹	USA	Retro. cohort	Yes	1992–2002	692	18+	66%	57%	Before diagnosis	CCI	57%	42%	2	3	2	0	7
Hu <i>et al.</i> ³²	USA	Retro. cohort	Yes	1991–2005	12265	65+	59%	48%	Up to 1 month after diagnosis	CCI	48%	64%	2	3	2	1	8
Quipourt <i>et al.</i> ³³	France	Retro. cohort	Yes	2004–2007	302	<75–85+	NR	NR	Up to diagnosis	CCI	NR	NR	2	3	1	0	6
Carpenter <i>et al.</i> ³⁴	USA	Retro. cohort	Yes	2003–2005	3926	65+	57%	NR	NR	Individual	NR	62%	2	2	2	1	7
van der Geest <i>et al.</i> ³⁵	Netherlands	Retro. cohort	Yes	2006–2008	565	<60–75+	55%	62%	NR	CCI	62%	60%	2	2	2	0	6
Hoeben <i>et al.</i> ³⁶	Netherlands	Case control	Yes	1997–2004	557	75+	42%	73%	NR	ACE-27	73%	NA	1	3	2	0	6
Hermosillo-Rodriguez <i>et al.</i> ³⁷	USA	Retro. cohort	Yes	2002–2011	126 ^a	50+	0%	NR	NR	Individual	NR	66%	0	2	2	0	4
Zanders <i>et al.</i> ³⁸	Netherlands	Retro. cohort	Yes	2006–2008	3100	All adults	NR	NR	Up to diagnosis	Individual	NR	NR	2	3	1	1	7
Fleming <i>et al.</i> ³⁹	USA	Retro. cohort	Yes	2006–2008	561	66–79	53%	87%	NR	ACE-27	87%	63%	1	2	1	0	4
Jorgensen <i>et al.</i> ⁴⁰	Australia	Retro. cohort	Yes	2007–2008	580	65+	NR	NR	NR	CCI	NR	65%	1	2	2	1	6

(Continued)

Table 1. (Continued)

Author	Country	Study design	Sample characteristics			Comorbidity assessment			Chemo use		Quality scores ^a					
			Source (registry)	Period of diagnosis	Size	Age (years)	% women	Time	Summary measure	Prop.	RE	EX	0	AD	Total(9)	
Kranup <i>et al.</i> ⁴¹	Denmark	Pros. cohort	No	2001–2008	2841	18+	54%	Before surgery	CCI	79%	61%	2	3	2	0	7
Becerra <i>et al.</i> ⁴²	USA	Retro. cohort	Yes	2007–2008	124008	All adults	53%	NR	CCI	30%	34%	2	2	2	1	7
Murphy <i>et al.</i> ⁴³	USA	Retro. cohort	Yes	Multiple years ^d	1849	20+	NR	Up to surgery	CCI	NR	65%	2	4	2	1	9
Booth <i>et al.</i> ⁴⁴	Canada	Retro. cohort	Yes	2002–2008	2801	20+	48%	Before surgery	CCI	19%	66%	1	3	2	0	6
Hsieh <i>et al.</i> ⁴⁵	USA	Retro. cohort	Yes	2011	3180	18+	49%	Up to chemo ^e	CCI	70%	64%	2	2	1	1	6
Chen <i>et al.</i> ¹⁴	USA	Retro. cohort	Yes	2007–2009	3903	65+	61%	Before diagnosis	CCI ^f	59%	35%	2	2	1	0	5
Guerrero <i>et al.</i> ⁴⁶	USA	Retro. cohort	Yes	2005–2014	438	63 ^b	53%	NR	CCI	44%	63%	2	2	2	0	6
van den Broek <i>et al.</i> ⁴⁷	Netherlands	Retro. cohort	Yes	2000–2009	348	<60–80+	51%	Up to diagnosis	CCI	56%	51%	2	4	2	0	8
Yamano <i>et al.</i> ¹⁰	Japan	Retro. cohort	No	2004–2006	1120	<65–75+	NR	NR	CCI	25%	67%	2	2	2	0	6
Boakye <i>et al.</i> ⁴⁸	Germany	Pros. cohort	No	2003–2014	523 ^a	30–92	42%	Up to diagnosis	CCI	48%	68%	1	4	2	1	8
Sarasqueta <i>et al.</i> ⁴⁹	Spain	Pros. cohort	No	2010–2012	654	<65–80+	36%	NR	CCI	45%	75%	2	2	2	0	6
Boyle <i>et al.</i> ⁹	UK	Retro. cohort	Yes	2014–2017	11932	18+	48%	Before diagnosis	RCS CCI	43%	61%	2	3	2	0	7
Minicozzi <i>et al.</i> ⁷	European Countries ^c	Retro. cohort	Yes	2010–2013	1835	15+	44%	Up to diagnosis	CCI	NR	65%	2	2	2	0	6

^aIncluded high-risk stage II colon cancer patients.^bMean age.^cEight European cancer registries (Belgium, Estonia, Germany, Italy, Poland, Portugal, Slovenia, and Spain).^d1990–1991, 1995, 2000–2005, and 2010.^eUp to the time of administration of chemotherapy.^fFor estimate of prevalence only (assessed the association between dementia and chemotherapy use).^gQuality assessment was conducted using the Newcastle–Ottawa scale [RE, Representativeness of sample; EX, Exposure assessment; O, Outcome (chemotherapy) assessment; AD, Adjustment for at least age and year of diagnosis]—higher scores indicate high quality and low risk of bias.

ACE-27, Adult comorbidity evaluation-27; CCI, Charlson comorbidity index; Chemo, Adjuvant chemotherapy; NR, Not reported; NZ, New Zealand; Prop, Proportion of patients with comorbidity; Pros, Prospective; RCS, Royal College of Surgeons; Retro, Retrospective; UK, United Kingdom; USA, United States of America.

between-study heterogeneity.⁵³ When studies reported risk estimates for CCI scores >2 separately, the estimates were first pooled using a fixed-effect model before including them in the main analysis (e.g. ORs for CCI 2 and 3+ were combined to get an estimate for category CCI 2+).^{23,40,41,48} Some studies also reported results stratified by sources of comorbidity information (in-patient and outpatient records)²¹ and age at diagnosis only (<75 and 75+ years),^{10,27} which we combined in a similar way to derive estimates for all comorbidity sources and for all ages, respectively.

We assessed heterogeneity between studies using the I^2 statistic, where $I^2 > 50\%$ indicated substantial heterogeneity.⁵⁴ We also used the Egger's test to assess potential publication bias aside from visualization with the funnel plot.⁵⁵ The Trim-and-Fill funnel plot method was moreover used to investigate and correct for potential publication bias.⁵⁶ We also conducted subgroup analyses by combining studies according to specific comorbidities, timing of comorbidity assessments, year of colon cancer diagnosis, geographical region, and quality score. Variations (heterogeneity) in the associations between comorbidity and chemotherapy use according to these factors were evaluated using a random-effects meta-regression.

Two-sided statistical testing was employed, with a significance level of 5%. All analyses were performed with the SAS software, version 9.4 (SAS Institute, Cary, NC) and the "meta" package (version 4.12-0)⁵⁷ in R, version 3.6.3 (R Development Core Team).

Results

Literature search and characteristics of the included studies

The literature search yielded 842 records: 426 from PubMed and 416 from Web of Science (Figure 1). After removal of duplicates and full-text review, 33 studies were included in this review. Of the 33 studies, 26 using similar comorbidity scores and groupings or analyzing similar specific comorbid conditions were included in the quantitative synthesis. Of studies included in this review, the majority (91%) were from North America (18/33) and Europe (12/33, Table 1). Nearly all the studies from North America originated in the USA (16/18), and half the studies from Europe

were from the Netherlands (6/12). Almost all the included studies were cohort studies (32/33), the vast majority using data from population-based cancer registries linked to hospital data (28/33). A majority of the studies referred to patients diagnosed before 2010 (26/33). Over half of the studies included patients of all ages (21/33), whereas nearly half of the studies from the USA (7/16) included only patients aged 65+ years. The sample sizes ranged from 126 to 124,008 patients, with a total of over 219,406 colon cancer patients. Two smaller studies additionally included high-risk stage II colon cancer patients.^{37,48} The majority of the studies adjusted for at least age in the analyses, with the exception of six studies reporting crude results only.^{10,14,27,36,37,47} The median quality assessment score of the studies was 7/9 (interquartile range, 6–7).

Assessment of comorbidity

About one-third of the studies (13/33) determined comorbidities before or up to colon cancer diagnosis (Table 1), whereas approximately one-fifth (7/33) determined comorbidities before colon cancer surgery or during hospitalization for colon cancer surgery. The majority of the studies evaluated comorbidities from administrative data (25/33), whereas one-fourth assessed them from medical records (8/33). A majority of the studies used summary measures of comorbidity (27/33), mostly the CCI or its adaptation (22/27), with few using the ACE-27 ($n = 3$) or numeric count ($n = 3$).

Our meta-analysis of 23 studies providing data on the prevalence of comorbidity showed that over half of the patients had at least one comorbid condition (51.3%, 95% CI: 42.8% to 59.6%; Table 2), but they differed by summary score. For example, while the prevalence of comorbidities in patients assessed with ACE-27 was 78.8%, it was 45.0% in patients assessed with CCI ($p < 0.001$). The prevalence of comorbidities also differed by geographical region even among studies that used the CCI. For example, CCI score >0 was higher in Europe than in North America (56.2% versus 40.3%), even though almost all the studies from Europe included patients of all ages, whereas nearly half of the North American studies included only patients aged 65+ years. The prevalence of comorbidities increased from 38.8% in the studies including patients diagnosed before 2001 to 53.1% in those including patients diagnosed after 2010.

Chemotherapy administration

Of 26 studies providing data on chemotherapy use (Table 2), the proportion of patients receiving chemotherapy was 60.9% (95% CI, 56.9% to 64.9%). Chemotherapy use increased steadily over time; it increased from 57.1% in the studies whose patients were diagnosed before 2001 to 66.3% in those whose patients were diagnosed after 2010 ($p=0.04$). Chemotherapy administration was 63.3% in Europe and 58.8% in North America ($p=0.25$).

Associations of overall comorbidity with chemotherapy administration

Twenty-seven studies evaluated the associations of summary measures [quantified by CCI ($n=22$),^{7,9,10,21,23,25,26,29,31–33,35,40–49} by ACE-27 ($n=3$),^{27,36,39} or by numeric count ($n=3$)^{22,28,47}—one study reported results for both CCI and numeric count⁴⁷] with chemotherapy use (Supplemental Table S2). Regardless of how overall comorbidity was quantified, comorbidity was inversely associated with chemotherapy administration, but the associations were not statistically significant in some of the smaller studies.^{31,39,46,49} In one study, associations of comorbidities with chemotherapy non-use were only seen for comorbidities obtained from inpatient records, but not for those obtained from outpatient records.²¹

Results from 15 out of the 22 studies using the CCI and with similar comorbidity groupings were combined in a meta-analysis (Figure 2).^{9,10,21,23,25,32,35,40–44,47–49} Compared with patients with CCI score 0, those with scores 1 (OR=0.79, 95% CI=0.72–0.87) and 2+ (OR=0.49, 95% CI=0.42–0.56) received chemotherapy less often. There was a high degree of heterogeneity in the results ($I^2=88%$, $p_{\text{heterogeneity}} < 0.01$ and $I^2=85%$, $p_{\text{heterogeneity}} < 0.01$ for CCI scores 1 and 2+, respectively). The funnel plot suggested mild publication bias in the results for CCI 1 (Egger's test $p=0.06$) but not for CCI 2+ (Egger's test $p=0.33$, Supplemental Figure S1). Correction with the Trim-and-Fill method led to an attenuation of the OR of chemotherapy use to 0.89 (95% CI=0.81–0.97, for CCI 1 *versus* 0).

Our meta-analysis of studies on the associations of overall comorbidity quantified by ACE-27 score^{27,36,39} and numeric count^{22,28,47} with

Table 2. Prevalence of comorbidity and administration of adjuvant chemotherapy, overall and by year of cancer diagnosis and geographical region.

Variable	<i>n</i>	Est. (95% CI)	<i>p</i>
Prevalence of comorbidities			
Overall	23	51.3 (42.8–59.6)	
By summary score			<0.001
CCI	18	45.0 (37.1–53.3)	
ACE-27	3	78.8 (70.0–85.5)	
Count	2	58.7 (56.5–60.8)	
CCI by year of cancer diagnosis			0.38
Before 2001	4	38.8 (26.3–53.0)	
2001–2010	8	44.6 (30.2–59.9)	
2011–2017	3	53.1 (38.7–67.0)	
CCI by geographical region			0.04 ^a
North America	10	40.3 (30.4–51.1)	
Europe	6	56.2 (45.2–66.7)	
Oceania	1	49.2 (42.1–56.3)	
Asia	1	25.0 (22.6–27.6)	
Administration of adjuvant chemotherapy			
Overall	26	60.9 (56.9–64.9)	
By year of diagnosis			0.12
Before 2001	5	57.1 (47.8–65.9)	
2001–2010	13	59.3 (52.6–65.7)	
2011–2017	4	66.3 (60.8–71.2)	
By geographical region			0.12 ^a
North America	16	58.8 (52.9–64.5)	
Europe	7	63.3 (58.1–68.3)	
Oceania	2	65.8 (62.4–69.1)	
Asia	1	67.0 (64.2–69.7)	

Prevalence estimates were calculated from the random-effects model, using the random intercept logistic regression model based on the logit transformation.
^aFor differences between regions with two or more studies only.
 ACE-27, Adult comorbidity evaluation-27; CCI, Charlson comorbidity index; CI, Confidence interval; Est, Estimate (in percentage); *n*, Number of studies included in the analysis.

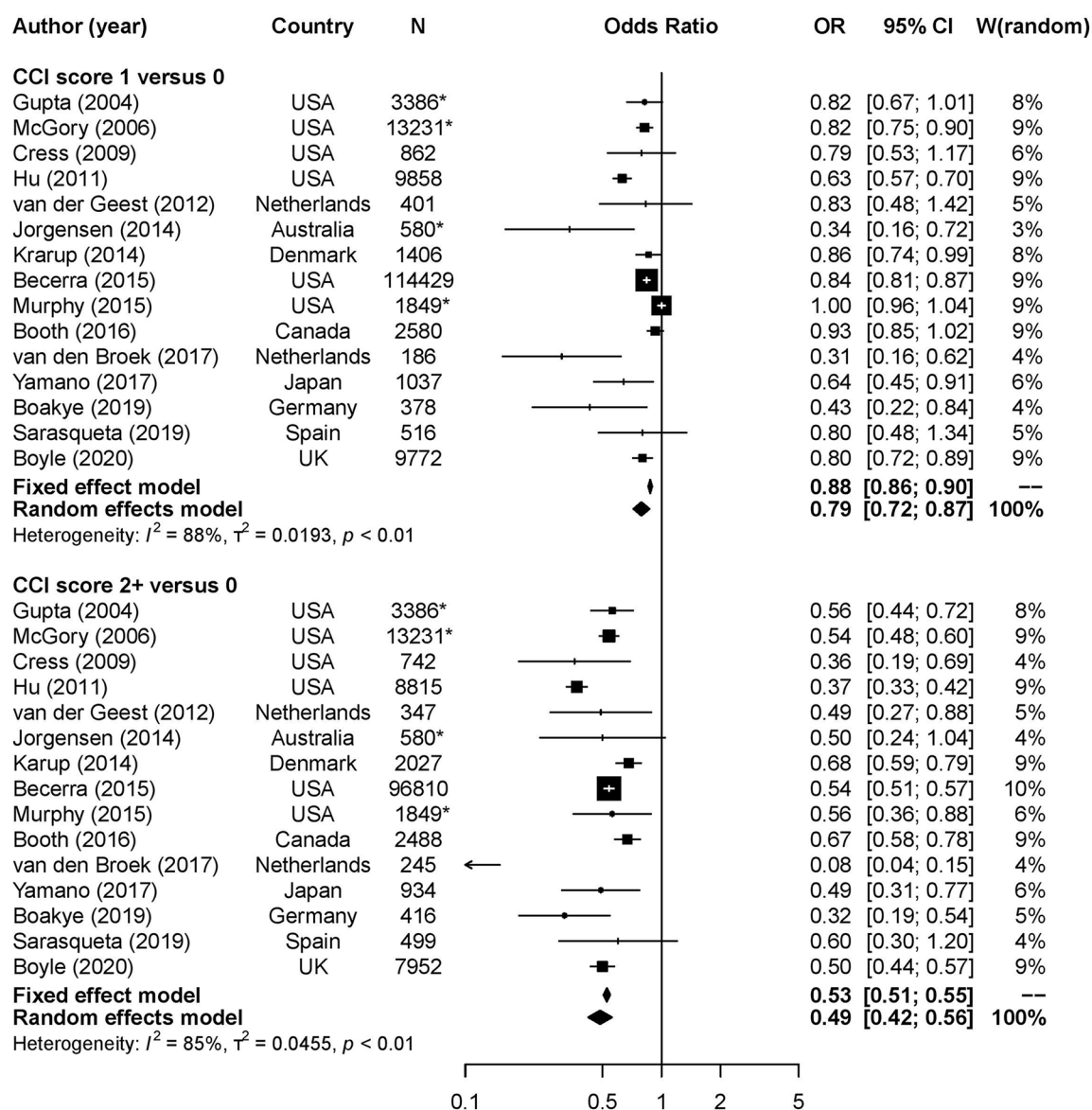


Figure 2. Meta-analysis of overall comorbidity quantified by CCI and chemotherapy administration.

*Total sample size.

Seven (7) studies used different comorbidity groupings and reference groups and hence could not be included in the quantitative analysis. ORs and 95% CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of receiving chemotherapy).

Size of data markers indicates the weight of each study in the analysis.

CCI, Charlson comorbidity index; CI, Confidence interval; N, Sample size; OR, Odds ratio; UK, United Kingdom; USA, United States of America; W, Weight.

chemotherapy administration is illustrated in Figure 3. The associations of ACE-27 with chemotherapy administration were modest, with only the severe *versus* no comorbidity difference reaching statistical significance (OR=0.52, 95% CI=0.31–0.86). There was no evidence of heterogeneity in the results, and the funnel plot did not suggest any publication bias (data not

shown). For the numeric count, we observed an inverse association between number of comorbidities and chemotherapy use. Compared with patients with no comorbidity, those with one and 2+ comorbidities had 44% (OR=0.56, 95% CI=0.33–0.94) and 75% (OR=0.25, 95% CI=0.09–0.69) lower odds of receiving chemotherapy, respectively. There was a high degree of

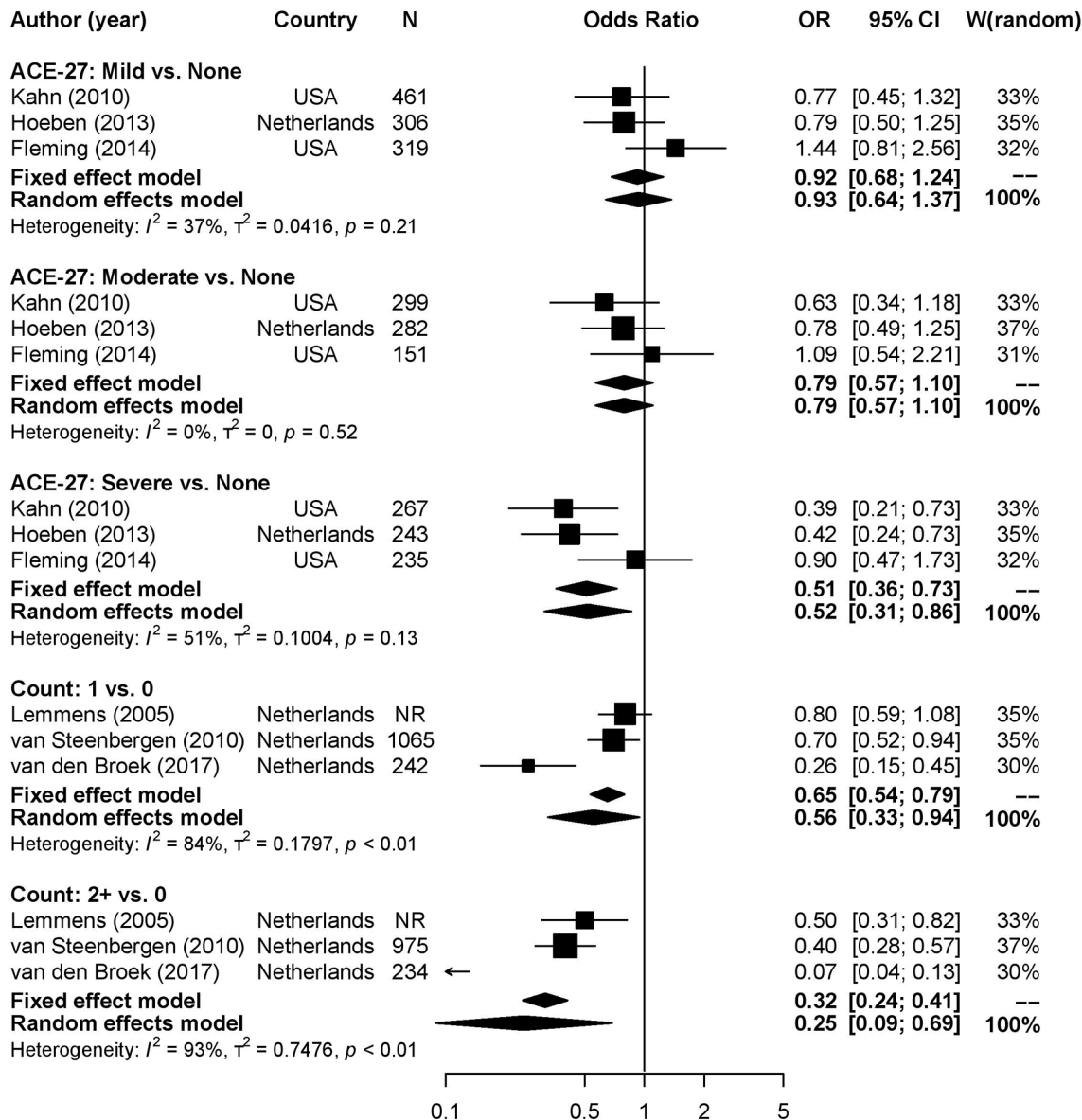


Figure 3. Meta-analysis of overall comorbidity quantified by ACE-27 score and numeric count and chemotherapy administration. ORs and 95% CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of receiving chemotherapy). Size of data markers indicates the weight of each study in the analysis. ACE-27, Adult comorbidity evaluation-27; CI, Confidence interval; N, Sample size; NR, Not reported; OR, Odds ratio; USA, United States of America; W, Weight.

heterogeneity ($I^2 = 84%$, $p_{\text{heterogeneity}} < 0.01$ and $I^2 = 93%$, $p_{\text{heterogeneity}} < 0.01$ for one and 2+ comorbidities, respectively) due to one small study that reported crude results only.⁴⁷ Removal of that study yielded an I^2 of 0% ($p_{\text{heterogeneity}} = 0.15$) and the associations were attenuated (data not shown). However, patients with one and 2+ comorbidities still had significantly lower odds of chemotherapy use, 25% and 57%, respectively.

Associations of individual comorbidities with chemotherapy administration

Our meta-analysis of studies on the associations of diabetes ($n = 5$),^{24,34,37,38,48} myocardial infarction ($n = 2$),^{39,48} heart failure ($n = 4$),^{24,37,39,48} stroke ($n = 2$),^{38,48} renal disease ($n = 2$),^{34,48} COPD ($n = 6$),^{22,24,37-39,48} and dementia ($n = 5$)^{14,21,30,34,39} with chemotherapy administration is shown in Figure 4. Patients having any of these diseases

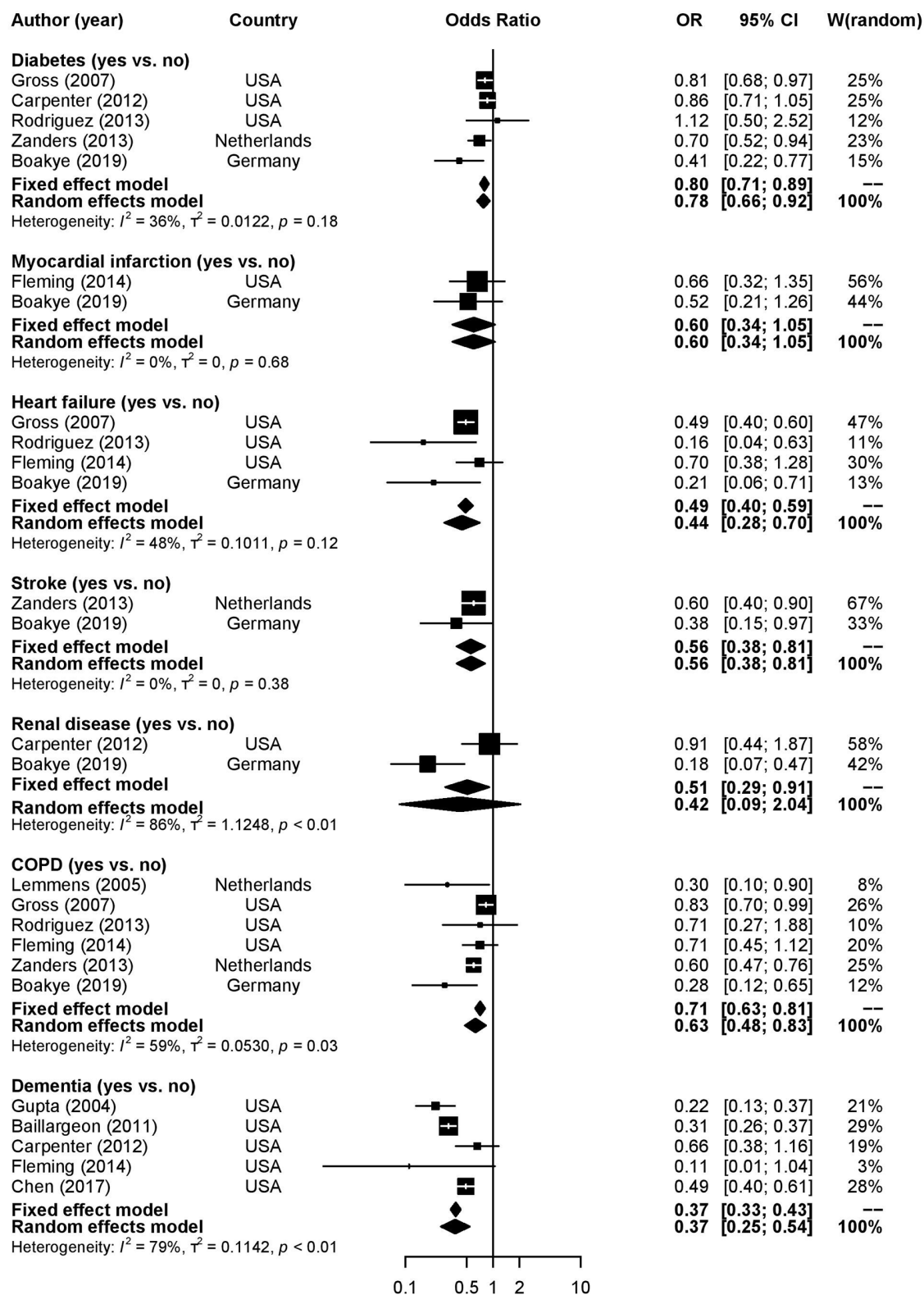


Figure 4. Meta-analysis of specific comorbidities and chemotherapy administration. ORs and 95% CIs were calculated indirectly and might differ slightly from the original values (OR < 1.00 indicates lower likelihood of receiving chemotherapy). Size of data markers indicates the weight of each study in the analysis. CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; OR, Odds ratio; USA, United States of America; W, Weight.

received chemotherapy less often, but the associations with myocardial infarction and renal disease were not statistically significant. Associations varied by comorbid condition and were strongest for dementia (OR = 0.37, 95% CI = 0.33–0.54), followed by heart failure (OR = 0.44, 95% CI = 0.28–0.70) and stroke (OR = 0.56, 95% CI = 0.38–0.81). We observed no indication of publication bias (Egger's test $p > 0.13$), but the associations for renal disease, COPD, and dementia were heterogeneous. Meta-regression analysis suggested that interactions of COPD with age and year of colon cancer diagnosis accounted for all the between-study heterogeneity (~100%) in the associations for COPD ($p_{\text{moderation}} = 0.018$; data not shown). For the associations with dementia, interaction with year of colon cancer diagnosis explained about 80% of the between-study heterogeneity ($p_{\text{moderation}} = 0.035$).

Subgroup analyses of overall comorbidity and chemotherapy administration

Age at colon cancer diagnosis. Three studies conducted subgroup analyses by age (<75 and 75+ years, Supplemental Table S2).^{10,27,33} While comorbidity was inversely associated with chemotherapy use in younger patients (<75 years), no associations were seen in older patients (75+ years). In one of the studies, there was a significant interaction between comorbidity and age ($p_{\text{interaction}} = 0.004$).³³

Comorbidity assessment time, year of diagnosis, geographical region, and quality score. Inverse associations between CCI score and chemotherapy use were observed irrespective of timing of comorbidity assessment, year of colon cancer diagnosis, geographical region, or quality score (Table 3). The results from the studies determining comorbidities before/at colon cancer surgery, referring to patients diagnosed in 2001–2010, and from North America were heterogeneous. Meta-regression analysis showed that interactions of CCI score with timing of comorbidity assessment and year of colon cancer diagnosis explained all the between-study heterogeneity (~100%) in the associations for CCI 2+ (*versus* 0, $p_{\text{moderation}} < 0.001$), with year of diagnosis alone explaining about 70% of the between-study heterogeneity ($p_{\text{moderation}} = 0.003$). The between-study heterogeneity in the associations for CCI 1 (*versus* 0) was not explained by these factors (data not shown).

Discussion

We summarized evidence on the associations between comorbidities and chemotherapy administration in stage III colon cancer patients in a systematic review and meta-analysis, with a particular focus on potential variations in the associations by specific comorbidities. We observed a strong inverse association between comorbidity and chemotherapy use, but the association differed by comorbid condition. Comorbidities showing the strongest associations with chemotherapy non-use were dementia, followed by heart failure and stroke.

Our meta-analysis demonstrated that the prevalence of comorbidity differed by geographical region, even among studies using the CCI. For example, comorbidities were higher in Europe than in North America. A possible explanation is that the majority of the studies from North America evaluated comorbidities from administrative data, which have been suggested to mostly underestimate the prevalence of comorbidities.⁵⁸ Our meta-analysis also showed improvement in comorbidity assessment or documentation over time, as comorbidities were higher in the studies that included patients with more recent years of colon cancer diagnosis. This may also explain the observed higher comorbidities in Europe than in North America because the studies from Europe included patients with more recent years of diagnosis.

Our study showed that chemotherapy administration has increased over time—from 57% in patients diagnosed before 2001 to 66% in patients diagnosed after 2010. However, we found that merely 60% of the patients received chemotherapy, despite the established benefits of chemotherapy for stage III colon cancer cases.^{4,5,44,59} Our meta-analysis of 15 cohort studies including 177,018 patients showed that patients with mild (CCI 1) and moderate–severe comorbidity (CCI 2+) had 21% and 51% lower odds of receiving chemotherapy, respectively. Similar patterns of inverse associations between comorbidity and chemotherapy use were observed across subgroups defined by timing of comorbidity assessments, calendar year of diagnosis, and geographical region. Concerns about efficacy and less tolerability of chemotherapy might explain the observed disproportionately lower chemotherapy use in comorbid patients. However, evidence on the risk–benefit ratio of chemotherapy in stage III colon cancer patients is still sparse. Data from three cohort studies^{24,25,60}

Table 3. Subgroup analysis of studies^a on associations between overall comorbidity quantified by the Charlson comorbidity index and chemotherapy administration.

Groups	<i>n</i>	OR (95% CI)	<i>I</i> ²	<i>p</i> _{heterogeneity}	<i>p</i> _{moderator} ^c (CCI 1, 2+)
Overall	13 ^a				
CCI 1		0.81 (0.74–0.89)	89%	<0.01	
CCI 2+		0.52 (0.46–0.59)	80%	<0.01	
Comorbidity assessment time					0.69, 0.74
Before or at diagnosis	3				
CCI 1		0.78 (0.66–0.92)	40%	0.19	
CCI 2+		0.49 (0.41–0.60)	43%	0.17	
Before or at surgery	5				
CCI 1		0.84 (0.71–0.99)	95%	<0.01	
CCI 2+		0.55 (0.43–0.71)	93%	<0.01	
Not reported	5				
CCI 1		0.79 (0.66–0.95)	29%	0.23	
CCI 2+		0.54 (0.51–0.57)	0%	0.79	
Year of diagnosis					0.94, 0.003
Before 2001	3				
CCI 1		0.82 (0.75–0.89)	0%	0.98	
CCI 2+		0.54 (0.49–0.59)	0%	0.46	
2001–2010	5				
CCI 1		0.86 (0.78–0.94)	60%	0.04	
CCI 2+		0.61 (0.52–0.71)	72%	<0.01	
2011–2017	2				
CCI 1		0.80 (0.72–0.89)	0%	1.00	
CCI 2+		0.50 (0.44–0.58)	0%	0.61	
Multiple decades	3				
CCI 1		0.70 (0.47–1.07)	97%	<0.01	
CCI 2+		0.39 (0.31–0.51)	40%	0.19	
Geographical region					0.64, 0.87
North America	7				
CCI 1		0.83 (0.74–0.93)	93%	<0.01	
CCI 2+		0.52 (0.44–0.61)	87%	<0.01	

(Continued)

Table 3. (Continued)

Groups	<i>n</i>	OR (95% CI)	<i>I</i> ²	<i>p</i> _{heterogeneity}	<i>p</i> _{moderator} ^c (CCI 1, 2+)
Europe	5				
CCI 1		0.81 (0.74–0.89)	3%	0.39	
CCI 2+		0.53 (0.41–0.67)	71%	<0.01	
Oceania	1				
CCI 1		0.34 (0.16–0.72)	–	–	
CCI 2+		0.50 (0.24–1.04)	–	–	
Quality score ^b					0.82, <0.001
Low (≤6)	5				
CCI 1		0.82 (0.68–0.99)	50%	0.09	
CCI 2+		0.63 (0.56–0.71)	0%	0.62	
Moderate (7)	4				
CCI 1		0.84 (0.81–0.86)	0%	0.81	
CCI 2+		0.56 (0.50–0.62)	71%	0.02	
High (8–9)	4				
CCI 1		0.73 (0.51–1.03)	96%	<0.01	
CCI 2+		0.38 (0.33–0.45)	11%	0.34	

Reference group is patients with CCI score 0 (OR <1.00 indicates lower likelihood of receiving chemotherapy).
^aTwo studies reporting crude results only were excluded (van den Broek *et al.*⁴⁷ and Yamano *et al.*¹⁰).
^bBased on the Newcastle–Ottawa scale.
^c*p*-values assess between-study heterogeneity of associations in the subgroups and were calculated from the random-effects meta-regression using the restricted maximum likelihood method for estimation of between-study variance.
CCI, Charlson comorbidity index; CI, Confidence interval, *n*, Number of studies; OR, Odds ratio.

suggest that some patients with comorbidities may derive similar survival benefits from chemotherapy as those not having comorbidities. A pooled analysis of four trials also suggested that patients with comorbidities experience comparable adverse treatment effects as non-comorbid patients.⁶¹ In the clinical trials, the incidence of grade 3/4 adverse effects in patients with CCI scores 0–1 and 2+ who received oxaliplatin-based treatments were 54% *versus* 56%, respectively. However, the trials sampled relatively healthy patients. Also, the CCI is only a summary measure of a broad and heterogeneous group of comorbidities. It is thus not clear which specific comorbidities (type, severity) have an impact on the risk of severe adverse effects. The observational studies also did not consider severity of comorbid conditions, frailty, or functional status.^{24,25,60} Thus, confounding by indication and

residual confounding due to insufficient adjustment for comorbidities may have led to biased results in these studies. Further studies overcoming these important limitations are required to clarify in which comorbid patients and to what extent application of chemotherapy may improve health outcomes. Also, the majority of the studies assessing the effect of chemotherapy have focused on survival as an endpoint,^{4–6,44,59} but evaluation of quality of life is also important.

Among the included studies reporting age-stratified analysis,^{10,27,33} comorbidities were associated with chemotherapy non-use in patients aged <75 years, whereas no associations were seen in older patients (75+ years). Although there is no upper age limit for administration of chemotherapy,^{2,62} several studies have demonstrated substantially less

frequent chemotherapy administration in older patients,^{6,8,9} due to concerns about the risk–benefit relation of chemotherapy in this patient group. Our results indicate that comorbidities might play more important roles in treatment decisions in younger than in older patients. However, the lack of significant associations among older adults might be due to small number of patients without comorbidities or receiving chemotherapy in this age group. Further research providing age-stratified analysis is thus needed to clarify whether and to what extent the association between comorbidity and chemotherapy use differs by age.

Although comorbidity was inversely associated with chemotherapy use irrespective of how overall comorbidity was quantified, the associations were generally modest for the ACE-27 score. This indicates that the effects of comorbidity on treatment administration may differ by summary scores and appear to be more pronounced for the CCI score. Reasons for this disparity are unclear, but a possible explanation may be the inclusion of a large number of comorbidities in the ACE-27,⁵¹ some of which may be less correlated with chemotherapy use, unlike the CCI which considers only 19 comorbidities.⁵⁰ Also, in one of the included studies, comorbidities obtained from outpatient records only were not associated with chemotherapy use, whereas strong associations were reported for those obtained from in-patient records.²¹ This suggests that studies using information from outpatient records only for risk adjustment may less accurately estimate the effect of comorbidities, leading to residual confounding. Further research comparing the predictive capacities of various comorbidity scores and information sources regarding treatment use will be useful, as lower comorbidity of chemotherapy recipients has been suggested to be associated with better survival.⁴⁸

Because summary scores provide little information on the specific diseases that mainly affect treatment administration, we additionally conducted a meta-analysis on individual comorbidities. We found that the associations between comorbidities and chemotherapy use differed by comorbid condition. Dementia was the strongest predictor of chemotherapy non-use, followed by heart failure and stroke. Reasons for the stronger association with dementia are unclear, but mediation by patient refusal may play a key role. Patient refusal is one of the common reasons for chemotherapy non-use,⁸ and cognitive impairment due

to dementia could result in patient refusal, by interfering with patient communication, consent for treatment, or adherence to therapeutic advice.³⁰ Another important finding that warrants further investigation is the appropriateness of using summary scores for confounder adjustment in studies whose outcomes are not related to mortality. For instance, in the CCI, heart failure, COPD, diabetes, and dementia have a weight of one, whereas renal disease has a weight of two.⁵⁰ We, however, observed that the associations of dementia and heart failure with chemotherapy non-use were stronger than that of renal disease. Because the CCI weights were derived from mortality risk estimates, it is possible that the risk estimates for treatment use vastly differ from those for mortality, as observed in our study. This suggests that using information on type and severity of comorbidities, rather than summary scores, may provide better adjustment for confounding in observational studies.

There are several other possible mechanisms through which comorbidities may affect chemotherapy administration. First, evidence suggests that patients with comorbidities are less likely to be referred for oncological assessment and chemotherapy treatment,^{63,64} both of which are associated with chemotherapy use.⁶⁵ Second, patients with comorbidities have increased risk of postoperative complications after colon cancer surgery,³⁵ which have also been suggested to be strongly associated with chemotherapy non-use.^{35,41} Third, in many countries, contraindications of chemotherapy include poor functional status,⁶² which strongly correlates with comorbidity.⁶⁶

Our findings highlight differences in important characteristics such as comorbidities between recipients and non-recipients of chemotherapy. Yet, many observational studies evaluating the effects of chemotherapy in colon cancer patients lack information on comorbidities.^{6,67} Also, most studies adjusting for comorbidities have only considered those relevant for calculating specific summary scores.^{44,48,59} For example, although psychotic disorders such as schizophrenia are associated with increased mortality in colon cancer patients,^{30,68} they are not part of the CCI.⁵⁰ This may explain in part why estimates of chemotherapy benefits are usually larger in observational studies^{6,44,59} than in clinical trials.⁴⁵ Treatment effect estimates from observational studies should thus be interpreted with caution, as they may be affected by residual confounding due to suboptimal ascertainment of

comorbidities and rarely measured factors such as frailty.

Our study was the first to quantify to what extent comorbidities influence chemotherapy administration in colon cancer patients in a meta-analysis. The quality of the included studies was high, and the majority adjusted for at least age, the main predictor of chemotherapy use.^{6,8,9} There was, however, heterogeneity in some of the results, mainly due to differences in year of colon cancer diagnosis possibly because of changing treatment recommendations.⁶⁹ Because treatment regimens vary by age or year of diagnosis,⁶⁹ we defined the outcome of this review as receipt of any chemotherapy regimen. For instance, the efficacy and safety of oxaliplatin-based therapies in older patients are still controversial and hence rarely applied in this patient group.⁷⁰ Older patients are thus often given less aggressive treatments (e.g. capecitabine monotherapy, a 5-fluorouracil pro-drug), but survival benefits of different regimens in older patients are comparable.⁷¹ Also, the inverse associations between comorbidity and treatment administration might be stronger for aggressive (e.g. oxaliplatin-based therapies) than for less aggressive treatments, which might explain in part the observed stronger associations in younger patients. Future studies should assess this knowledge gap.

Our study has some limitations. First, even though we did not restrict our electronic literature search to specific languages, it is possible that some relevant studies (e.g. those published in languages other than English or German) were missed. Also, like all reviews, our results might be affected by selective reporting arising from unpublished studies with non-significant results. However, the funnel plot suggested only mild publication bias in the results for CCI score. Second, the use of various comorbidity scores and groupings precluded us from combining results from all the included studies. However, similar patterns of inverse association between comorbidity and chemotherapy administration were also reported by those studies that could not be included in this meta-analysis.^{7,26,29,31,33,45,46} Third, about one-third of the studies did not report when comorbidities were determined,^{10,25,34–37,39,40,42,46,49} and one study determined comorbidities up to the time of chemotherapy administration.⁴⁵ These might result in reverse causality (e.g. comorbidities due to chemotherapy treatment), but the meta-regression

analysis showed no indication of significant effect modification by timing of comorbidity assessments. Lastly, other factors such as microsatellite instability⁷² and functional status⁶² also affect treatment decisions, but only three studies adjusted for functional status.^{9,48,49}

Conclusion

Results from this first systematic review and meta-analysis suggest that comorbidities are strong predictors of chemotherapy non-use in stage III colon cancer patients besides older age. The association differs by comorbid condition and is strongest with dementia. Given the survival disadvantage of colon cancer patients with comorbidities, further evidence is needed on the risk–benefit ratio of chemotherapy according to the type and severity of comorbidity. Also, quantifications of the proportions of chemotherapy non-use that are attributable to comorbidities and the extent to which the survival disadvantage of comorbidity is explained by less use or lower tolerability of chemotherapy are research gaps. Dedicated studies answering these important questions could provide further evidence to foster personalized medical care in patients with comorbidities.

Author contributions

Study concept and design: DB and KG. *Search strategy development and literature search:* DB. *Extraction, analysis, and interpretation of data:* DB, RN, WA, UH, and KG. *Drafting of the manuscript:* DB. *Critical revision of the manuscript for important intellectual content:* DB, RN, WA, UH, and KG. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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References

- Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
- American Cancer Society. Treatment of colon cancer, by stage: American Cancer Society, <https://www.cancer.org/cancer/colon-rectal-cancer/treating/by-stage-colon.html> (accessed 27 April 2020).
- Zhang C, Yin S, Tan Y, *et al.* Patient selection for adjuvant chemotherapy in high-risk stage II colon cancer: a systematic review and meta-analysis. *Am J Clin Oncol* 2020; 43: 279–287.
- Sargent DJ, Goldberg RM, Jacobson SD, *et al.* A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *New Engl J Med* 2001; 345: 1091–1097.
- Sargent D, Sobrero A, Grothey A, *et al.* Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2009; 27: 872–877.
- Babaei M, Balavarca Y, Jansen L, *et al.* Administration of adjuvant chemotherapy for stage II–III colon cancer patients: an European population-based study. *Int J Cancer* 2018; 142: 1480–1489.
- Minicozzi P, Vicentini M, Innos K, *et al.* Comorbidities, timing of treatments, and chemotherapy use influence outcomes in stage III colon cancer: a population-based European study. *Eur J Surg Oncol* 2020; 46: 1151–1159.
- Walter V, Boakye D, Weberpals J, *et al.* Decreasing use of chemotherapy in older patients with stage III colon cancer irrespective of comorbidities. *J Natl Compr Cancer Netw* 2019; 17: 1089–1099.
- Boyle JM, Kuryba A, Cowling TE, *et al.* Determinants of variation in the use of adjuvant chemotherapy for stage III colon cancer in England. *Clin Oncol* 2020; 32: e135–e144.
- Yamano T, Yamauchi S, Kimura K, *et al.* Influence of age and comorbidity on prognosis and application of adjuvant chemotherapy in elderly Japanese patients with colorectal cancer: a retrospective multicentre study. *Eur J Cancer* 2017; 81: 90–101.
- van Leersum NJ, Janssen-Heijnen ML, Wouters MW, *et al.* Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995–2010. *Int J Cancer* 2013; 132: 2157–2163.
- Fowler H, Belot A, Ellis L, *et al.* Comorbidity prevalence among cancer patients: a population-based cohort study of four cancers. *BMC Cancer* 2020; 20: 2.
- Boakye D, Rillmann B, Walter V, *et al.* Impact of comorbidity and frailty on prognosis in colorectal cancer patients: a systematic review and meta-analysis. *Cancer Treat Rev* 2018; 64: 30–39.
- Chen YJ, Cress RD, Stewart SL, *et al.* Mediating effect of postsurgical chemotherapy on presence of dementia and survival among patients 65 and older with stage III colon cancer. *Cancer Epidemiol Biomarkers Prev* 2017; 26: 1558–1563.
- Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Med* 2009; 6: 2–28.
- Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
- Hamaker ME, Stauder R and van Munster BC. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the national institutes of health clinical trial registry. *Oncologist* 2014; 19: 1069–1075.
- Hanlon P, Hannigan L, Rodriguez-Perez J, *et al.* Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. *BMC Med* 2019; 17: 201.
- Unger JM, Hershman DL, Fleury ME, *et al.* Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol* 2019; 5: 326–333.
- Wells GA, O’Connell D, Peterson J, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (accessed 28 April 2020).
- Gupta SK and Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. *J Am Geriatr Soc* 2004; 52: 1681–1687.
- Lemmens VE, Janssen-Heijnen ML, Verheij CD, *et al.* Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. *Br J Surg* 2005; 92: 615–623.
- McGory ML, Zingmond DS, Sekeris E, *et al.* A patient’s race/ethnicity does not explain the

- underuse of appropriate adjuvant therapy in colorectal cancer. *Dis Colon Rectum* 2006; 49: 319–329.
24. Gross CP, McAvay GJ, Guo Z, *et al.* The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. *Cancer* 2007; 109: 2410–2419.
 25. Cress RD, Sabatino SA, Wu XC, *et al.* Adjuvant chemotherapy for patients with stage III colon cancer: results from a CDC-NPCR patterns of care study. *Clin Med Oncol* 2009; 3: 107–119.
 26. Sarfati D, Hill S, Blakely T, *et al.* The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. *BMC Cancer* 2009; 9: 116.
 27. Kahn KL, Adams JL, Weeks JC, *et al.* Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. *JAMA* 2010; 303: 1037–1045.
 28. van Steenbergen LN, Rutten HJ, Creemers GJ, *et al.* Large age and hospital-dependent variation in administration of adjuvant chemotherapy for stage III colon cancer in southern Netherlands. *Ann Oncol* 2010; 21: 1273–1278.
 29. Winget M, Hossain S, Yasui Y, *et al.* Characteristics of patients with stage III colon adenocarcinoma who fail to receive guideline-recommended treatment. *Cancer* 2010; 116: 4849–4856.
 30. Baillargeon J, Kuo YF, Lin YL, *et al.* Effect of mental disorders on diagnosis, treatment, and survival of older adults with colon cancer. *J Am Geriatr Soc* 2011; 59: 1268–1273.
 31. Foley KL, Tooze JA, Klepin HD, *et al.* Adjuvant chemotherapy among medicaid-enrolled patients diagnosed with nonmetastatic colon cancer. *Am J Clin Oncol* 2011; 34: 120–124.
 32. Hu CY, Delclos GL, Chan W, *et al.* Assessing the initiation and completion of adjuvant chemotherapy in a large nationwide and population-based cohort of elderly patients with stage-III colon cancer. *Med Oncol* 2011; 28: 1062–1074.
 33. Quipourt V, Jooste V, Cottet V, *et al.* Comorbidities alone do not explain the undertreatment of colorectal cancer in older adults: a French population-based study. *J Am Geriatr Soc* 2011; 59: 694–698.
 34. Carpenter WR, Meyer AM, Wu Y, *et al.* Translating research into practice: the role of provider-based research networks in the diffusion of an evidence-based colon cancer treatment innovation. *Med Care* 2012; 50: 737–748.
 35. van der Geest LG, Portielje JE, Wouters MW, *et al.* Complicated postoperative recovery increases omission, delay and discontinuation of adjuvant chemotherapy in patients with Stage III colon cancer. *Colorectal Dis* 2013; 15: e582–e591.
 36. Hoeben KW, van Steenbergen LN, van de Wouw AJ, *et al.* Treatment and complications in elderly stage III colon cancer patients in the Netherlands. *Ann Oncol* 2013; 24: 974–979.
 37. Hermosillo-Rodriguez J, Anaya DA, Sada Y, *et al.* The effect of age and comorbidity on patient-centered health outcomes in patients receiving adjuvant chemotherapy for colon cancer. *J Geriatr Oncol* 2013; 4: 99–106.
 38. Zanders MM, van Steenbergen LN, Haak HR, *et al.* Diminishing differences in treatment between patients with colorectal cancer with and without diabetes: a population-based study. *Diabet Med* 2013; 30: 1181–1188.
 39. Fleming ST, Mackley HB, Camacho F, *et al.* Clinical, sociodemographic, and service provider determinants of guideline concordant colorectal cancer care for Appalachian residents. *J Rural Health* 2014; 30: 27–39.
 40. Jorgensen ML, Young JM, Dobbins TA, *et al.* Does patient age still affect receipt of adjuvant therapy for colorectal cancer in New South Wales, Australia? *J Geriatr Oncol* 2014; 5: 323–330.
 41. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, *et al.* Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer. *Ann Surg* 2014; 259: 930–938.
 42. Becerra AZ, Probst CP, Tejani MA, *et al.* Opportunity lost: adjuvant chemotherapy in patients with stage III colon cancer remains underused. *Surgery* 2015; 158: 692–699.
 43. Murphy CC, Harlan LC, Lund JL, *et al.* Patterns of colorectal cancer care in the United States: 1990–2010. *J Natl Cancer Inst* 2015; 107: djv198.
 44. Booth CM, Nanji S, Wei XJ, *et al.* Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. *J Natl Compr Cancer Netw* 2016; 14: 47–56.
 45. Hsieh MC, Thompson T, Wu XC, *et al.* The effect of comorbidity on the use of adjuvant chemotherapy and type of regimen for curatively resected stage III colon cancer patients. *Cancer Med* 2016; 5: 871–880.
 46. Guerrero W, Wise A, Lim G, *et al.* Better late than never? Adherence to adjuvant therapy guidelines for stage III colon cancer in an underserved region. *J Gastrointest Surg* 2018; 22: 138–145.
 47. van den Broek CBM, Puylaert C, Breugom AJ, *et al.* Administration of adjuvant chemotherapy

- in older patients with stage III colon cancer: an observational study. *Colorectal Dis* 2017; 19: O358–O364.
48. Boakye D, Walter V, Martens UM, *et al.* Treatment selection bias for chemotherapy persists in colorectal cancer patient cohort studies even in comprehensive propensity score analyses. *Clin Epidemiol* 2019; 11: 821–832.
 49. Sarasqueta C, Perales A, Escobar A, *et al.* Impact of age on the use of adjuvant treatments in patients undergoing surgery for colorectal cancer: patients with stage III colon or stage II/III rectal cancer. *BMC Cancer* 2019; 19: 735.
 50. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
 51. Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope* 2000; 110: 593–602.
 52. Higgins JP, White IR and Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Stat Med* 2008; 27: 6072–6092.
 53. DerSimonian R and Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
 54. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
 55. Sterne JA and Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; 54: 1046–1055.
 56. Duval S and Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56: 455–463.
 57. Schwarzer G. General package for meta-analysis, version 4.12-0, <https://cran.r-project.org/web/packages/meta/meta.pdf> (accessed 21 May 2020).
 58. Powell H, Lim LL and Heller RF. Accuracy of administrative data to assess comorbidity in patients with heart disease. An Australian perspective. *J Clin Epidemiol* 2001; 54: 687–693.
 59. Sanoff HK, Carpenter WR, Stürmer T, *et al.* Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012; 30: 2624–2634.
 60. Wildes TM, Kallogjeri D, Powers B, *et al.* The benefit of adjuvant chemotherapy in elderly patients with stage III colorectal cancer is independent of age and comorbidity. *J Geriatr Oncol* 2010; 1: 48–56.
 61. Haller DG, O’Connell MJ, Cartwright TH, *et al.* Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. *Ann Oncol* 2015; 26: 715–724.
 62. Schmiegel W, Pox C, Reinacher-Schick A, *et al.* S3 guidelines for colorectal carcinoma. *Z Gastroenterol* 2010; 48: 65–136.
 63. Gilbar P, Lee A and Pokharel K. Why adjuvant chemotherapy for stage III colon cancer was not given: reasons for non-recommendation by clinicians or patient refusal. *J Oncol Pharm Pract* 2017; 23: 128–134.
 64. Krzyzanowska MK, Regan MM, Powell M, *et al.* Impact of patient age and comorbidity on surgeon versus oncologist preferences for adjuvant chemotherapy for stage III colon cancer. *J Am Coll Surg* 2009; 208: 202–209.
 65. Kutner JS, Vu KO, Prindiville SA, *et al.* Patient age and cancer treatment decisions. Patient and physician views. *Cancer Pract* 2000; 8: 114–119.
 66. Garman KS, Pieper CF, Seo P, *et al.* Function in elderly cancer survivors depends on comorbidities. *J Gerontol A Biol Sci Med Sci* 2003; 58: M1119–M1124.
 67. Boland GM, Chang GJ, Haynes AB, *et al.* Association between adherence to national comprehensive cancer network treatment guidelines and improved survival in patients with colon cancer. *Cancer* 2013; 119: 1593–1601.
 68. Ni L, Wu J, Long Y, *et al.* Mortality of site-specific cancer in patients with schizophrenia: a systematic review and meta-analysis. *BMC Psychiatry* 2019; 19: 323.
 69. Gustavsson B, Carlsson G, Machover D, *et al.* A review of the evolution of systemic chemotherapy in the management of colorectal cancer. *Clin Colorectal Cancer* 2015; 14: 1–10.
 70. André T, Boni C, Navarro M, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; 27: 3109–3116.
 71. Kim CAK, Spratlin JL, Armstrong DE, *et al.* Efficacy and safety of single agent or combination adjuvant chemotherapy in elderly patients with colon cancer: a Canadian cancer institute experience. *Clin Colorectal Cancer* 2014; 13: 199–206.
 72. Webber EM, Kauffman TL, O’Connor E, *et al.* Systematic review of the predictive effect of MSI status in colorectal cancer patients undergoing 5FU-based chemotherapy. *BMC Cancer* 2015; 15: 156.