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REVIEW

Risk of recurrence in patients with colon cancer stage II and III: A systematic review and meta-analysis of recent literature

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ABSTRACT

Background. Adjuvant chemotherapy is established routine therapy for colon cancer (CC) patients with radically resected stage III and 'high-risk' stage II disease. The decision on recommending adjuvant chemotherapy, however, is based on data from older patient cohorts not reflecting improvements in pre-operative staging, surgery, and pathological examination. The aim is to review the current risk of recurrence in stage II and III patients and second, to estimate the relative importance of routinely assessed clinico-pathological variables.

Methods. The PubMed/MEDLINE and the Cochrane databases were systematically searched for randomized controlled studies and observational studies published after 1 January 2005 with patients included after January 1995 on prognosis in surgically treated stage II and III CC patients.

Results. Of 2596 studies identified, 37 met the inclusion criteria and 25 provided data for meta-analysis. The total patient sample size in the 25 studies reporting either disease-free (DFS) or recurrence-free survival was 15 559 in stage II and 18 425 in stage III. Five-year DFS for stage II patients operated without subsequent adjuvant chemotherapy was 81.4% [95% confidence interval (CI) 75.4–87.4; in studies with good/very good quality of reporting 82.7%, (95% CI 80.8–84.6)]. For stage II patients treated with adjuvant chemotherapy, the five-year DFS was 79.3% (95% CI 75.6–83.1). For stage III patients without chemotherapy, five-year DFS was 49.0% (95% CI 23.2–74.8) and for those treated with adjuvant chemotherapy, 63.6% (95% CI 59.3–67.9). The prognostic impact of commonly investigated clinico-pathological parameters, (pT-stage, pN-stage, differentiation, number of lymph nodes studied, MMR-status, and emergency surgery) were confirmed.

Conclusions. In this meta-analysis, studies with good quality of reporting show a five-year DFS of 82.7% for stage II CC without adjuvant chemotherapy, whereas the five-year DFS is 63.8% for stage III CC with adjuvant chemotherapy. Due to insufficient reporting on treatment quality the presented DFS is likely an under-estimation of what is achieved at high-quality centers today.

The risk of post-surgical recurrence for patients with stage II or III colon cancer (CC) is influenced by the quality of pre-operative staging, surgery, and pathological examination. The quality of these interventions has improved in recent years. The decision on recommending adjuvant chemotherapy, however, is still based on data from older patient cohorts not reflecting the improvements. Consequently, an updated analysis of recent studies with state-of-the-art patient care will be of great use to guide physicians and patients in their treatment decisions.

In 1990, a large randomized trial demonstrated that 12 months of adjuvant 5-fluorouracil (FU) with levamisol significantly improved overall and disease-free survival (DFS) in CC patients with metastatic involvement of regional lymph nodes (stage III) [1].

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Later studies established six months of adjuvant therapy with FU and leucovorin (LV) as standard of care [2]. The positive results of the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial [3] led to approval of oxaliplatin plus FU/LV (FOLFOX) for patients with stage III CC in 2004. Today, six months of combination therapy with FOLFOX or capecitabine plus oxaliplatin (CAPOX) is recommended for curatively resected stage III CC patients in virtually all clinical guidelines [4–6], including the Nordic countries [7–10].

In patients with stage II CC the role of adjuvant chemotherapy is less clear, partly due to the smaller number of stage II patients enrolled in randomized studies. A gain was shown in a pooled analysis of data from seven randomized studies demonstrating a significant benefit from FU-based adjuvant therapy across stages, but to a lesser degree in stage II than in stage III CC [11]. A Cochrane-analysis demonstrated that different types of adjuvant chemotherapy reduce the risk of recurrence in completely resected stage II CC in the order of 20–25% and improve overall survival with 5–10% [12]. The Adjuvant Colon Cancer Endpoints (ACCENT) group noted that the survival benefit after adjuvant FU-based chemotherapy is 'primarily driven by stage III patients', estimating an absolute 10% improvement in the eight-year survival rate in stage III, compared to 5% in stage II [13].

Over time, the surgical techniques, pathological staging, pre-operative imaging, and the oncologic treatments have improved. When comparing patients enrolled in adjuvant trials before and after 1995, Shi et al. [14] found data supporting stage-migration [15] from stage II to stage III, probably due to improved lymph node staging after 1995, with lower recurrence rates in stage II as a consequence. A further consequence is that recurrence rates will be lower also in stage III (often denoted the Will-Rogers phenomenon). A recent population-based Danish study reported on similar signs of stage migration from stage II to stage III [16]. Assignment of patients to adjuvant chemotherapy must be based on current data on recurrence risks for best estimates of the potential benefit.

The purpose of this study is, first, to define the risk of recurrence in recent, as proxy for improved care, patient cohorts, and second, to estimate the relative importance of routinely assessed clinicopathological variables.

Methods

All authors agreed on a pre-specified protocol according to the guidelines of the Cochrane handbook for systematic reviews [17,18] before the literature review began.

The primary outcome measure was risk of recurrence for operated colon adenocarcinoma stage II and III patients. Secondary outcome measures were quantitative influence of commonly registered clinical and histopathological factors on the risk of recurrence.

Criteria for inclusion of studies

Randomized controlled studies and observational studies published after 1 January 2005 (with patients enrolled after January 1995) on prognosis in surgically treated CC stage II and III patients were identified. The date for patient enrollment was after initial screening of titles changed from 2000 to 1995 to include more studies and not to miss relevant studies. The outcome of interest was recurrence, defined as local, regional, or distant recurrence after surgery. Studies where colon and rectal tumors could not be distinguished, duplicates, or studies comprising 20 patients or less were excluded.

Search methods for identification of studies

An experienced healthcare librarian was consulted for the search strategy of PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. The PubMed/MEDLINE search was constructed of combining specific Medical Subject Heading (MeSH)-words with key words on the title relating to colon or colorectal cancer and recurrence or prognosis (Supplemenary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839). The Cochrane search was performed with word search using a closeness operator (Supplementary Appendix 2, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839). The reference lists of relevant reviews were screened for relevant studies. In addition, reference lists of relevant studies were screened and abstracts were hand-searched. There were no language restrictions; however, two studies in Japanese and one in Chinese were excluded due to lack of translation resources.

Data collection

In the initial stage four researches (BEE, BG, CB, and TK) screened titles and subsequently selected abstracts in pairs according to the inclusion criteria. The potentially relevant full articles were then read (by BEE, CB, TH, and TK) in pairs to reach consensus on which articles to include.

Disagreements about study eligibility were resolved by discussion. All authors agreed on included studies before data extraction began. Reasons for exclusion were documented and presented according to the PRISMA flow diagram (Figure 1) [17,18]. The following trial characteristics were extracted: time period and country, study design, sample size, intervention (including adjuvant treatment, if given), and outcome measure, including DFS or relapse-free survival (RFS), and univariable and multivariable hazard ratio (HR) for common clinico-pathological risk factors for recurrence. Information on the following risk factors for recurrence were collected [5,19]: pT-category, pN-category, number of lymph nodes examined, differentiation grade, vascular and neural invasion, perforation, obstruction, mismatch repair (MMR) status, preoperative carcinoembrogenic antigen (CEA) level, and *KRAS*-mutation status.

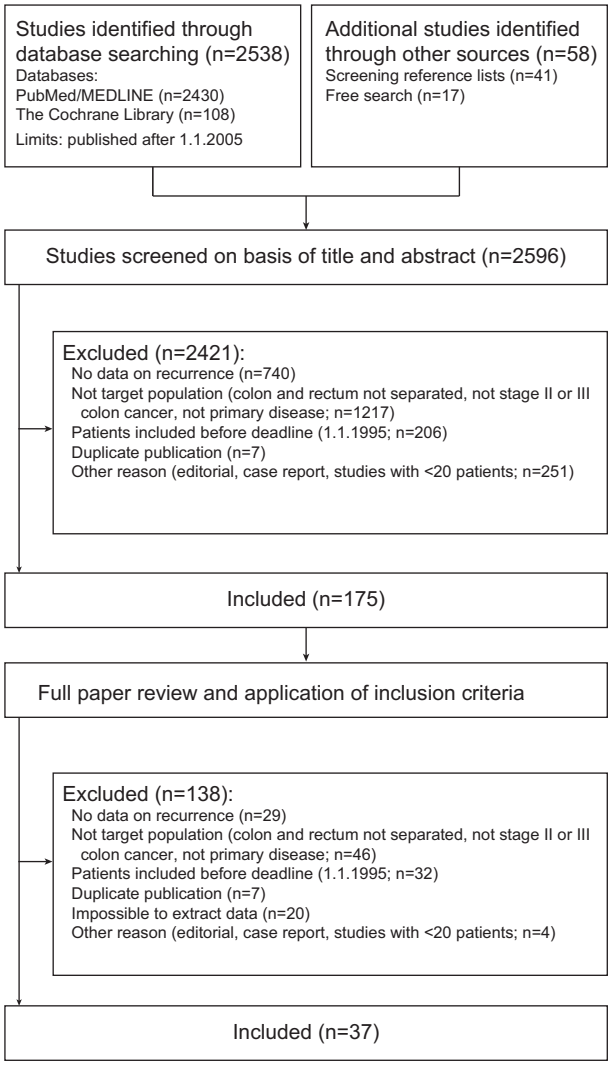

Figure 1. Flow chart of study selection.

Assessment of quality and risk of bias

The quality of reporting was assessed with a scoring tool, based on 5 subscales regarding: 1) reporting of the study results; 2) external validity; 3) bias in measurement and outcomes; 4) bias in the selection of study subjects; and 5) the power of the study [20]. We used a simplified version with a maximum obtainable score of 28 [21]. Studies were grouped qualitatively (≥ 20: very good; 15–19: good; 11–14: fair; ≤ 10: poor) [22].

In order to address the quality of the medical care administered to the included patients, articles were searched for information on pre-operative staging, surgical procedures, patho-anatomical staging, and follow-up (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839).

Statistical analyses

The most sensitive endpoint for evaluating the need for adjuvant chemotherapy is risk of recurrence, or time to recurrence (TTR), but these are rarely reported [23]. For the purpose of the review, time to recurrence was extracted as DFS or RFS. When using the definition by Punt et al. [23], RFS is more sensitive as an endpoint estimating the need for adjuvant therapy than DFS, as it ignores second primary same cancers and other primary cancers. However, the definitions of DFS (and RFS) sometimes differ from the consensus statement [23] or are not given. We use only the term DFS well aware that different studies did not consider exactly the same events. When both DFS and RFS were reported, the figure for DFS was used. We computed 95% confidence intervals (CI) and standard errors (SE) from the number of patients and rates using exact binomial CI. The studies were grouped according to stage (II or III) and adjuvant treatment given (yes, no, unclear). The category 'adjuvant treatment unclear' was used for studies where treatment was given only to a proportion of the patients or was not clearly described. The overall DFS and 95% CI were estimated by the random effects meta-analysis model. Meta-regression was used to analyze the effect of study quality on DFS. In a similar way available uni- and multivariable hazard ratios (HR) and CIs for important clinico-pathological variables were extracted. Significance levels and study population sizes were used to calculate missing CIs. The overall effect of each clinico-pathological variable was estimated with the random effects meta-analysis model (DerSimonian-Laird) including both three- and five-year HR values. A p-value of < 0.05 was considered statistically significant. All statistical analyses were done with STATA 11.0 software.

Results

Eligible studies

We identified 2596 potentially eligible studies that provided data on prognosis of patients operated for stage II or III CC. Of these, 37 met the inclusion criteria (Table I) [11,24–60]. Reasons for exclusion at each stage are presented in Figure 1. We excluded 1263 otherwise eligible studies because they did not present stage-specific survival data, presented combined data on patients with colorectal cancers, or on recurrent or metastatic disease. Of the 37 included studies, 25 studies with survival data specific for either stage II or III CC were eligible for meta-analysis (Table II, Supplementary Table II, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839). Eight studies provided univariable HR (Table III, Supplementary Table III, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839) and 17 multivariable HR (Supplementary Tables IV and V, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839) for important clinico-pathological factors.

Study characteristics

Characteristics of the included 37 studies are presented in Table I. The majority of the studies were published between 2009 and 2012. Eighty-four percent of the patients were operated on after the year 2000. Ten studies originated from European centers, six from North America, 11 from Asian countries, and three included patients from multiple countries. There were 16 single center studies. Five studies reported on clinical trials whereas seven studies were biomarker-based aiming for the identification of prognostic markers in selected cohorts of patients.

Eight studies presented data on the untreated course of resected stage II and III CC.

The total patient sample size in the 25 studies reporting DFS was 15 559 in stage II and 18 425 in stage III. The mean number of patients per study was 1722 (range 49–9645) in stage II, and 1036 (range 34–8616) in stage III. The total patient sample in the eight studies reporting univariable HRs for risk of recurrence was 3330. The mean number of patients per study was 370 (range 141–1404).

Disease-free survival at five years

Five-year DFS for stage II patients operated without subsequent adjuvant chemotherapy was 81.4% (95% CI 75.4–87.4), and for stage III 49.0% (95% CI 23.2–74.8) (Table II). Considering stage II patients who were treated with adjuvant chemotherapy, five-year DFS was 79.3% (95% CI 75.6–83.1) and for stage III 63.6% (95% CI 59.3–67.9). For patients with unclear adjuvant status, five-year DFS was 81.1 (95% CI 77.3–84.8) for stage II patients and 58.7 (95% CI 50.0–67.5) for stage III. Reported original data of DFS-rates from the included studies are presented in Supplementary Table II (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839).

Influence by clinico-pathological variables

Results of a meta-analysis of the HRs for recurrence for clinico-pathological parameters are presented in Table III, with the underlying original HRs in Supplementary Tables III and V to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839. A higher pT-stage indicates approximately a two-fold risk of recurrence (pT1-2 vs. pT3 and pT3 vs. pT4). The data extracted from studies only presenting multivariable analyses also support these findings (Supplementary Table IV to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839). Higher pN-stage (pN1 vs. pN2) increases the risk of tumor recurrence, whereas a higher number of sampled lymph nodes decrease the risk, as seen in analyses based on both uni-and multivariable data (Table III, Supplementary Table IV to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839). Low histological differentiation also implies a higher risk of recurrence supported by both uni- and multivariable data.

Perforation and/or obstruction indicating emergency surgery also increase the risk of recurrence supported by both uni- and multivariable data. Tumor invasion into neural structures indicates a higher risk of recurrence, however being statistically significant only in analysis of the multivariable data. Results regarding vascular invasion are similar, but also statistically significant in the univariable data. Deficient MMR-status nearly halves the risk of recurrence. Elevated pre-operative CEA-level is related to higher risk of recurrence, albeit being statistically significant only in the analyses of the multivariable data. A mutation in the *KRAS*-gene increased the risk of tumor recurrence according to multivariable, but not univariable data.

Quality assessment

No study reported all relevant aspects of the quality of care (Table IV). Of the 37 studies included in this review, none was scored as poor, 16 as fair, 17 as good, and four as very good according to the quality assessment score [20,21]. Five-year DFS in stage II

Table I. Main characteristics of eligible studies identifying risk of recurrence in patients with colon cancer stage II or III.

First author, year of publication	Period of patient inclusion	Country	Study design	Study characteristics	Sample size
André, 2007 [24]	1996–1999	France, Belgium	Randomized trial	2×2 factorial comparison of adjuvant FU/LV semi-monthly vs. monthly and 24 weeks vs. 36 weeks (GERCOR C96.1)	Stage II: 319 Stage III: 514
André, 2009 [25]	1998–2001	Worldwide	Randomized trial	Adjuvant LV5FU2 vs. oxaliplatin and infusional FU and LV (Multi-center International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial)	Stage II: 899 Stage III: 1347
Belt, 2012 [26]	1996–2005	The Netherlands, single center	Observational cohort	Prognostic value of biomarkers	Stage II: 226 Stage III: 160
Chin, 2010 [27]	1995–2005	China, single center	Retrospective	Prognostic value of colon obstruction in proximal colon cancer	Stage II: 598 Stage III: 424
Cho, 2008 [28]	1996–2003	South Korea, single center	Retrospective	Prognostic value of colon obstruction in left-sided colon cancer	Stage II: 374 Stage III: 368
Coco, 2012 [29]	2000–2003	Italy, single center	Retrospective	Prognostic value of CD133 expression	Stage II: 43 Stage III: 69
Derwinger, 2008 [30]	1999–2003	Sweden, single center	Retrospective	Prognostic value of LN ratio	Stage III: 265
Ding, 2010 [31]	2002–2006	China, single center	Retrospective	Prognostic value of neutrophil to lymphocytic ratio	Stage III: 141
Faerden, 2011 [32]	2000–2005	Norway, multicenter	Observational cohort	Prognostic value of micrometastases/isolated tumor cells	Stage II: 87 Stage III: 126
Fariña-Sarasqueta, 2010 [33]	1996–2004	The Netherlands, multicenter	Retrospective	Prognostic value of BRAF	Stage II: 106 Stage III: 258
Fernandez-Cebrian, 2007 [34]	1998–2002	Spain, single center	Observational cohort	Prognostic value of Ki-67, p53	Stage II: 162
Galizia, 2009 [35]	1996–2007	Italy, single center	Retrospective	Prognostic value of LN ratio	Stage III: 145
Gill 2011 [11]	1995–2003	Canada, multicenter	Observational cohort	Evaluation of web-based prognostic models	Stage II: 814 Stage III: 1228
Giráldez, 2013 [36]	1998–2005	Spain, single center	Observational cohort	Prognostic value of gene-expression signatures	Stage II: 78 Stage III: 150
Huh, 2010 [37]	1999–2008	South Korea, single center	Retrospective	Prognostic value of pre-operative carcinoembryonic antigen	Stage II: 236 Stage III: 191
Huh, 2010 [38]	2001–2006	South Korea, single center	Retrospective	Prognostic value of perineural invasion	Stage II: 190
Huh, 2012 [39]	1999–2007	South Korea, single center	Retrospective	Prognostic factors in stage I-III colon cancer with <12 LN retrieved	Stage II: 75 Stage III: 78
Kandemir, 2005 [40]	Not reported[1]	Turkey, single center	Retrospective	Prognostic value of thrombocytosis	Stage II: 137
Kang, 2011 [41]	1995–2007	South Korea, single center	Retrospective	Prognostic value of inferior mesenteric artery LN metastasis	Stage III: 206
Kjaer-Frifeldt, 2012 [42]	2003	Denmark, multicenter	Population based study, retrospective	Prognostic value of microRNA-21	Stage II: 520
Kumar, 2009 [43]	2001–2004	USA, single center	Retrospective	Prognostic value of microsatellite instability and lymphocytic infiltration	Stage II: 56 Stage III: 34
Lee, 2007 [44]	1995–2001	South Korea, single center	Retrospective	Prognostic value of LN ratio	Stage III: 201

(*Continued*)

Table I. (*Continued*)

First author, year of publication	Period of patient inclusion	Country	Study design	Study characteristics	Sample size
Mroczkowski, 2012 [45]	2000–2004	Germany, multicenter	Observational cohort	Prognostic value of clinico-pathological parameters	Stage II: 9645 Stage III: 8616
Niedzwiecki, 2011 [46] and Venook, 2013 [47]	1997–2002	USA, UK, Canada, Belgium, France	Randomized trial	Adjuvant edrecolomab vs. no treatment; 12-gene recurrence score validation in subgroup (Cancer and Leukemia Group B (CALGB) 9581)	Stage II: 1738 Subgroup analysis: Stage II: 690
Oh, 2012 [48]	2000–2002	South Korea, single center	Retrospective	Prognostic value of fascin-1 expression	Stage III: 47
Park, 2008 [49]	1996–2005	South Korea, single center	Retrospective	Prognostic value of LN micrometastases	Stage II: 126
Saltz, 2007 [50]	1999–2001	USA, Canada	Randomized trial	Adjuvant chemotherapy with FU/LV ± irinotecan (CALGB 89803)	Stage III: 1264
Sargent 2011 [51]	1999–2006	Canada, multicenter	Observational cohort	Prognostic value of guanylate cyclase C LN status	Stage II: 241
Tanaka, 2011 [52]	1999–2007	USA, single center	Retrospective	Prognostic value of DNA methylation biomarkers	Stage II: 28 Stage III: 54
Twelves, 2005 [53]	1998–2001	Worldwide	Randomized trial	Phase III trial comparing LV5FU2 vs. capecitabine (Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial)	
Van Cutsem, 2009 [54] and Roth, 2012 [55]	2000–2002	31 European countries	Randomized trial	Phase III trial comparing adjuvant infusional FU/LV ± irinotecan; prognostic value of KRAS, BRAF, 18qLOH, microsatellite instability, SMAD4 in subgroup (Pan European Trial Adjuvant Colon Cancer (PETACC)-3)	Stage III: 3278 Subgroup analysis: Stage II: 420 Stage III: 984
Xing, 2009 [56]	1996–2002	China, single center	Retrospective	Prognostic value of PRL-3	Stage II: 97 Stage III: 83
Yan, 2010 [57]	2001–2003	China, single center	Retrospective	Prognostic value of ubiquitin D	Stage II: 81 Stage III: 80
Yothers, 2011 [58]	2000–2002	USA, multicenter	Randomized trial	Adjuvant FU/LV vs. oxaliplatin and bolus FU/LV (National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07)	Stage II: 695 Stage III: 1702[2]
Zaanan, 2011 [59]	1998–2007	France, multicenter	Observational cohort	Prognostic value of mismatch repair system -status	Stage III: 303

[1] Manuscript received for publication by journal in 2004, up to 100 months of follow-up; [2] Derived from percentages given in the original study by Kuebler et al. [60].
FU, 5-fluorouracil; LV, leukovorin; LN, lymph nodes.

patients in studies with fair quality of reporting was 75.4% (95% CI 68.3–82.5) and significantly lower than for studies with good/very good quality of reporting with DFS of 82.7% (95% CI 80.8–84.6) (Table IV). Comparing DFS in stage II patients by meta-regression we found a statistically significant difference between fair and good/very good quality studies (regression coefficient 0.067; 95% CI 0.037–0.1312, $p = 0.039$). In stage III patients having received adjuvant therapy the result was similar, but when the use of adjuvant therapy was unclear, the result was the opposite (Table IV).

Discussion

Disease-free survival in stage II and III colon cancer patients

This systematic review and meta-analysis based on more than 15 000 patients with stage II CC operated in 1995 or later showed a five-year DFS of 81.4%

Table II. Five-year disease-free survival in colon cancer stratified according to stage and adjuvant treatment.

Stage	Patients (n)	DFS (%), 95% CI[1]	Included studies
Without adjuvant therapy			
II	2250	81.4 (75.4–87.4)	[11,31–34,43,46,51]
III	312	49.0 (23.2–74.8)	[11,43]
With adjuvant therapy			
II	2655	79.3 (75.6–83.1)	[11,24,25,43,46,58]
III	8624	63.6 (59.3–67.9)	[11,24–26,32,33,35,38,43,44,48,50,54,58,59]
Adjuvant status unclear[2]			
II	10654	81.1 (77.3–84.8)	[27,37,45,49,56]
III	9489	58.7 (50.0–67.5)	[26,27,41,45,56]

[1]Meta-analysis was done with the random effects model; [2] Adjuvant status unclear refers to studies where adjuvant chemotherapy was given only to a proportion of patients or was not clearly described.
CI, confidence interval; DFS, disease-free survival; n, number.

(95% CI 75.4–87.4) for patients not treated with adjuvant chemotherapy. For stage II CC patients who received adjuvant treatment, the five-year DFS was 79.3% (95% CI 75.6–83.1). For all stage II CC patients from studies with good/very good quality of reporting [20], the DFS was 82.7% (95% CI 80.8–84.6). In 8624 patients with stage III CC treated with adjuvant chemotherapy the five-year DFS was 63.6% (95% CI

Table III. Univariable risk of recurrence for colon cancer stage II–III.

Clinicopathological parameter	HR (95% CI)[1]	Patients (n)	Studies
pT-stage			
T1–2	1	1167	[55]
T3	1.85 (1.10–3.23)		
pT-stage			
T3	1	2411	[34,47,51,55]
T4	1.90 (1.08–3.32)		
pN-stage			
N1	1	1707	[55,59]
N2	2.27 (1.89–2.73)		
Lymph nodes studied (n)			
≥12 (15)	1	1052	[31,47,51]
<12 (15)	1.96 (1.09–3.57)		
Differentiation			
Well/moderate	1	2795	[34,47,51,55,59]
Low	1.58 (1.08–2.33)		
Perforation or obstruction			
No	1	539	[51,59]
Yes	1.97 (1.11–3.51)		
Neural invasion			
No	1	162	[34]
Yes	1.99 (0.84–4.74)		
Vascular invasion			
No	1	1281	[34,47,51,57]
Yes	2.08 (1.26–3.43)		
MMR-status			
Proficient (MSI-stable)	1	2854	[36,47,51,55,59]
Deficient (MSI-unstable)	0.54 (0.41–0.68)		
CEA-level			
<5 ng/ml	1	162	[34]
≥5 ng/ml	1.85 (0.27–12.6)		
KRAS-status			
Wildtype	1	1404	[55]
Mutation	1.04 (0.85–1.28)		

[1]Pooled univariable values for risk of recurrence. Both 3- and 5-year hazard ratios were included in this table. Random effects model was used for the meta-analysis.
CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; MMR, mismatch repair system; MSI, microsatellite instability; n, number; pN-stage, pathological nodal stage; pT-stage, pathological tumor stage.

Table IV. Five-year disease-free survival in colon cancer stratified according to disease stage, adjuvant treatment, and study quality[1].

Stage, adjuvant treatment	Fair quality[1] DFS % (95% CI)	Studies (n); patients (n)	Studies [references]	Good/very good quality[1] DFS % (95% CI)	Studies (n); patients (n)	Studies [references]
Stage II						
All	75.4 (68.3–82.5)	6; 1377	[11,31,32,34,43,49]	82.7 (80.8–84.6)	8; 14 182	[25,27,33,38,45–47,51,58]
Stage III						
With adjuvant therapy	61.6 (55.8–67.5)	5; 1327	[11,32,43,44,48]	63.8 (58.6–69.0)	9; 7523	[25,26,33,35,37,50,54,58,59]
Unclear[2]	77.2 (71.5–82.9)	1; 206	[41]	54.9 (49.5–60.4)	4; 9283	[26,27,45,56]

[1]Study quality according to Downs and Black quality score [20], Supplementary Table I; [2]Adjuvant status unclear refers to studies where adjuvant chemotherapy was given only to a proportion of patients or was not clearly described.
CI, confidence interval; DFS, disease-free survival; n, number.

59.3–67.9), whereas the natural course of the disease in 312 patients not receiving adjuvant chemotherapy led to a five-year DFS of 49.0% (95% CI 23.2–74.8). Stage II CC patients in studies where chemotherapy administration was not clearly described showed a five-year DFS of 81.1% (95% CI 77.3–84.8) and for stage III CC patients 58.7% (95% CI 50.0–67.5). All studies providing patients for the 'unclear' group are observational or retrospective [26,27,37,41,45,49,56], and probably a significant proportion of patients in these series did not receive any chemotherapy. It is therefore remarkable that the five-year DFS for stage II CC patients in the studies with 'unclear' chemotherapy assignment seems no worse and actually slightly better than for adjuvantly treated patients. As expected, in stage III CC adjuvant treatment shows a trend towards a positive effect on DFS according to these data. Evaluation of the benefit from adjuvant therapy, however, was not the scope of this review.

In line with our results, Haller et al. [61] found that five-year DFS for stage III CC patients treated with CAPOX was 66.1% and for those receiving bolus FU 59.8%. Shi et al. [14] reported a five-year RFS for stage II CC of 80.5%, and for stage III 61.5% in the older trials in the ACCENT database, whereas patients in the newer trials had a five-year RFS of 84.7% for stage II and 61.7% for stage III. The outcome measure RFS ignores secondary primary same cancers, which are included in the events used to calculate DFS [23]. The difference between DFS and RFS is larger in stage II than in stage III and becomes larger with longer follow-up. A difference of 10% between five-year DFS and five-year RFS was estimated in stage II CRC in a recent population-based Swedish study [62]. The five-year DFS for stage II CC patients found in this systematic review is in agreement with the five-year RFS in the newer trials of the ACCENT database, whereas the five-year DFS of 63.6% in stage III CC patients demonstrated here appears better than what was shown in the newer trials of the ACCENT database [14].

The endpoints TTR and RFS include fewer event categories than DFS and are thus more sensitive to the effects of adjuvant chemotherapy; however, DFS is more widely used and acknowledged in guidelines as the most appropriate primary endpoint for trials of adjuvant treatment [23]. The results of this systematic review can therefore easily be compared to data in literature, even if DFS is not ideal to estimate the need for adjuvant therapy.

Our estimate of DFS could be higher than in daily clinical practice due to a selection bias of healthier patients into trials. Furthermore, our meta-analysis includes data from two large studies that use RFS as endpoint [11,51], thereby 'boosting' DFS. However, several aspects imply that the DFS presented here are lower than can be expected for patients treated according to guidelines today. No study recruited patients later than 2008. More recent cohorts, e.g. with data from quality registries after quality assurance of all important parts of the care, may show the full extent of the benefits of state-of-the-art treatment with patients adequately staged, operated by specialized surgeons, the surgical specimen investigated according to modern standards [63], and the patients adequately followed up. It was impossible to evaluate the quality of care in a meaningful way since few studies reported on more than single aspects of intervention and patient care. We applied a validated scoring tool [20] in order to grade the quality of the reporting of studies. Patients with stage II disease from studies with good/very good quality of reporting [20] had significantly better DFS of 82.7% (95% CI 80.8–84.6) compared to patients from studies with fair quality with DFS of 75.4% (95% CI 68.3–82.5). The category good/very good is dominated by randomized controlled trials, likely ensuring better quality of diagnostic work-up and follow-up, but not necessarily surgical intervention and pathological examination. However, they mostly include a selected patient cohort and selection bias could explain the better survival in studies with good/very good quality

of reporting. It is not easy to explain, however, why this is not seen in stage III patients.

Taken together, there are several reasons to regard the presented DFS results as an under-estimation of what should be possible to achieve today. Based on the results from studies with good/very good quality of reporting, current treatment of CC can be improved. Still, the five-year DFS of 82.7% for stage II in the group of studies with the best quality of reporting is a valuable starting point for calculations of the current benefit of adjuvant treatment in curatively resected CC without lymph node metastases. Furthermore, the recent introduction of multidisciplinary treatment decisions will hopefully improve the overall outcome as well.

Prognostic value of clinical and histopathological factors

Survival varies widely for patients within the same disease stage [64], and identification of those that benefit from adjuvant chemotherapy cannot be done without an individual risk assessment. In this systematic review, data from patients treated after 1995 confirm the prognostic impact of a number of commonly investigated parameters. The overall more favorable prognosis for patients with tumors harboring a deficient MMR-system is comparable to recent reports [65–67], although one study suggests that the prognostic value of the MMR-status is limited to proximal tumors only [68]. Emergency surgery due to obstruction or perforation is associated with a high degree of surgical morbidity and mortality, and, as demonstrated here, with an increased risk of recurrence (HR = 1.97). Presence of mutated *KRAS* had no prognostic impact (HR = 1.04) in our data. This could be due to a small sample size; a prognostic impact of *KRAS* mutations, if present, is probably not as large as for the clinico-pathological parameters, with HRs around 1.40 found in the literature [65,68,69].

For the meta-analysis of the impact of prognostic factors we pooled data across stages. This assumption of stage-independent prognostic value may not be valid in all cases, as reported for the prognostic importance of MMR in stage II versus III in one study [68]. For the rest of the markers, well documented differences between the prognostic importance in stage II and III are missing, and the assumption of stage independence is probably valid.

The initial search identified almost 2600 studies for screening. It seems likely that all key publications were identified. There were no language restrictions, and the included studies represent patients from North American, European, and Asian populations. The number of studies finally included in this review is limited, reflecting strict inclusion criteria in accordance with the aim of the study. The strict inclusion criteria, however, could exclude potentially informative studies. The large multicenter randomized QUASAR trial, comparing surgery alone with surgery and adjuvant chemotherapy, initiated patient inclusion in May 1994 prior to our (extended) time limit of this review [67]. The QUASAR study would have substantially increased the number of patients. The absolute recurrence risk of 17% in the surgery-only arm fits well with the good/high quality studies included in our meta-analysis (DFS of 82.7%, Table IV). The HRs for risk factors of recurrence reported from the QUASAR study are not fundamentally different, and the overall conclusions would likely not have changed.

Perspectives: Risk stratification in curatively resected stage II–III colon cancer

With a five-year DFS of 82.7% for stage II, as seen in the studies with good/very good quality of reporting, it is our best estimate that the recurrence risk after five years in pT3N0 without any risk factor is (at the most) 10% in hospitals with high quality of the care. Adding one risk factor could increase the risk to about 15% for poor differentiation or few sampled lymph nodes, or up to 20% for vascular invasion, pT4, vessel or neural invasion, obstruction, or N1. Since independent prognostic importance has been reported in the multivariable analyses in several of the studies, as well as in an older study not included [70], two or more risk factors increase the risk further, although not said precisely by how much. Gertler et al. [70] report that five-year RFS decreased from 91% in stage II with no risk factor to 88% with one, 82% with two and 75% with three risk factors, although the latter estimate was based on very few individuals. Even simple calculations, however, indicate that the recurrence risk in pT4N0M0 (stage II) must be roughly the same as in stage III disease (pT3N1) without additional risk factors, and that pT4N0M0 disease with additional risk factors can carry a much higher recurrence risk than pT3N1M0 without other risk factors. Should all these patients then receive the same treatment with a doublet of chemotherapy [4–9]? 5-FU-based monotherapy represents a less toxic alternative for low- (and moderate-?) risk patients where the absolute gain from the added therapy is small. The current evidence does not identify any of the commonly assessed clinical and histopathological features as individually powerful enough for further risk stratification in high-risk stage II and stage III CC. A weighted contribution of the individual markers, as seen in a prognostic index, may provide a more clinically relevant stratification, but such attempts have not been done. The

prognostic value of new, additional molecular markers, however, has been explored in hundreds of studies. In this perspective, it is striking that it was difficult to find recent reports on the prognostic value of standard clinico-pathological variables, the backbone of all routine care. The knowledge-base for this systematic review would have been much larger if the prognostic value of commonly assessed factors had been presented in the many publications where new markers are explored.

Conclusions

In conclusion, this systematic review and meta-analysis shows a five-year DFS of slightly above 80% for stage II CC, regardless of post-operative treatment, and a five-year DFS of 64% for stage III CC treated with adjuvant chemotherapy. The impact of commonly investigated clinical and histopathological factors on these survival rates was confirmed. The effects of ongoing efforts towards optimized patient management on recurrence rates should be further evaluated in prospective preferably population-based studies, and the results published.

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Supplementary material available online

Supplementary Appendix 1 and 2, Tables I–V to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.975839.