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META-ANALYSIS

Intensive follow-up *vs* conventional follow-up for patients with non-metastatic colorectal cancer treated with curative intent: A meta-analysis

Li-Li Cui, Shi-Qi Cui, Zhong Qu, Zhen-Qing Ren

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Li-Li Cui, Department of Operating Room, Jiangsu Taizhou People's Hospital, Taizhou 225300, Jiangsu Province, China

Shi-Qi Cui, Department of Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310020, Zhejiang Province, China

Zhong Qu, Department of Endoscopy Center, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310020, Zhejiang Province, China

Zhen-Qing Ren, Department of Nursing, Jiangsu Taizhou People's Hospital, Taizhou 225300, Jiangsu Province, China

Corresponding author: Zhen-Qing Ren, MA, Department of Nursing, Jiangsu Taizhou People's Hospital, No. 366 Taihu Road, Pharmaceutical and High-tech Zone, Taizhou 225300, Jiangsu Province, China. 635818285@qq.com

Abstract

BACKGROUND

The frequency and content of follow-up strategies remain controversial for colorectal cancer (CRC), and scheduled follow-ups have limited value.

AIM

To compare intensive and conventional follow-up strategies for the prognosis of non-metastatic CRC treated with curative intent using a meta-analysis.

METHODS

PubMed, Embase, and the Cochrane Library databases were systematically searched for potentially eligible randomized controlled trials (RCTs) from inception until April 2023. The Cochrane risk of bias was used to assess the methodological quality of the included studies. The hazard ratio, relative risk, and 95% confidence interval were used to calculate survival and categorical data, and pooled analyses were performed using the random-effects model. Additional exploratory analyses were performed for sensitivity, subgroups, and publication bias.

RESULTS

Eighteen RCTs involving 8533 patients with CRC were selected for the final

analysis. Intensive follow-up may be superior to conventional follow-up in improving overall survival, but this difference was not statistically significant. Moreover, intensive follow-up was associated with an increased incidence of salvage surgery compared to conventional follow-up. In addition, there was no significant difference in the risk of recurrence between intensive and conventional follow-up strategies, whereas intensive follow-up was associated with a reduced risk of interval recurrence compared to conventional follow-up. Finally, the effects of intensive and conventional follow-up strategies differed when stratified by tumor location and follow-up duration.

CONCLUSION

Intensive follow-up may have a beneficial effect on the overall survival of patients with non-metastatic CRC treated with curative intent.

Key Words: Intensive follow-up; Conventional follow-up; Colorectal cancer; Curative intent; Meta-analysis

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Core Tip: This systematic review and meta-analysis aimed to determine the effects of intensive *vs* conventional follow-up strategies on the prognosis of patients with colorectal cancer (CRC) treated with curative intent by examining randomized controlled trials (RCTs). This study found that an intensive follow-up strategy might have beneficial effects on overall survival. Moreover, an intensive follow-up strategy was associated with an increased incidence of salvage surgery and a reduced risk of interval survival. Further large-scale RCTs should assess the effects of intensive follow-up with a specific frequency and content for non-metastatic CRC treated with curative intent.

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INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer, which accounted for more than 1.9 million cases and 900000 cancer-related deaths worldwide in 2000, thereby causing a great public health burden[1,2]. The incidence and prognosis of CRC have improved because of the use of population-based screening programs and understanding the necessity of a healthy lifestyle. Early diagnosis and treatment are significantly related to CRC prognosis[3]. The 5-year survival rate is 90% for stage I-II CRC and is reduces to 14% for stage IV CRC[4]. The standard treatment for early-stage CRC is curative surgery, and tumor node metastasis is an important predictor of early-stage CRC prognosis and other prognostic factors, including tumor location and clinicopathological results[5-7]. Nevertheless, 10%-20% of patients develop recurrent disease, and an additional follow-up strategy should be applied to improve CRC prognosis.

Curative surgery aims for the early detection of treatable recurrence and improving CRC prognosis. Generally, there is a long follow-up duration for patients with CRC treated through curative surgery. However, the frequency and content of follow-ups remain controversial for CRC, and scheduled follow-ups have limited value[8-10]. A prior meta-analysis found that the use of intensive follow-up strategies could improve overall survival compared to conventional follow-up strategies. However, the pooled analyses did not yield a conclusive solution[11]. Moreover, stratified analyses based on studies and patient characteristics were not performed. Therefore, this systematic review and meta-analysis was conducted to determine the effects of intensive *vs* conventional follow-up strategies on the prognosis of patients with CRC treated with curative intent. The study chose randomized controlled trials (RCTs) for its data.

MATERIALS AND METHODS

Search strategy and selection criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[12]. RCTs comparing the effects of intensive and conventional follow-up strategies for non-metastatic CRC treated with curative intent were eligible for our study, and the publication language was restricted to English. We systematically searched PubMed, Embase, and the Cochrane library for eligible trials throughout April 2023, and we used the following search terms: ("colorectal neoplasms") AND ("recurrence" OR "metastasis" OR "survival analysis" OR "mortality" OR "prognosis") AND ("follow up" OR "episode of care" OR "surveillance") AND ("randomized controlled trials"). Trials that had already been completed but had not yet been published were also searched on the ClinicalTrials.gov website (NIH, United States). Manual searches were also performed on the reference lists of the relevant reviews to identify any new trials that met the inclusion criteria.

Two reviewers independently conducted the literature search and trial screening, and conflicts between the reviewers were resolved *via* discussions. Studies were included if they met the following criteria: (1) Patients: All patients with non-metastatic CRC who were treated with curative intent surgery; (2) Intervention: Intensive follow-up strategy; (3) Control: Conventional follow-up strategy; (4) Outcome: The study should report at least one outcome of overall survival, cancer-specific survival, relapse-free survival, salvage surgery, recurrence, and interval recurrences; and (5) Study design: All included studies had to have an RCT design.

Data collection and quality assessment

The following data were independently collected from the included trials: First author's name, publication year, region, sample size, mean age, proportion of males, tumor stage (Dukes' stage A/B/C), tumor location (colon cancer/rectal cancer), treatments (curative intent surgery and subsequent adjuvant treatments), intervention, control, follow-up, and reported outcomes (overall survival, cancer-specific survival, relapse-free survival, salvage surgery, recurrence, and interval recurrences). The Cochrane risk of bias was used to assess methodological quality, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases[13]. Each item was defined as having a low, high, or an unclear risk of bias. Two reviewers independently performed the abstracted data and methodological quality assessments, and a third reviewer who referred to the original article settled inconsistent results.

Statistical analysis

The effects of intensive *vs* conventional follow-up strategies on survival and categorical data were assigned as hazard ratios (HR), relative risks (RR), and 95% confidence intervals (CI), and pooled analyses were performed using the random-effects model because it considers the underlying variations across the included trials[14,15]. Heterogeneity among the included trials was evaluated using I^2 and Q statistics, and significant heterogeneity was defined as $I^2 > 50\%$ or $P < 0.10$[16,17]. The stability of the pooled analyses were determined using sensitivity analysis through the sequential removal of a single trial[18]. Subgroup analyses of the investigated outcomes were performed based on sample size, mean age, proportion of males, tumor location, and follow-up duration, and the differences between subgroups were assessed using the interaction t-test, which assumes that the data distribution was normal[19]. Moreover, the ratio of HR (RHR) to RR (RRR) between the subgroups was assessed among patients without specific characteristics[20]. Funnel plots, Egger's test, and Begg's test were used to assess potential publication bias[21,22]. All reported P values for the pooled analyses were 2-sided, and the inspection level was 0.05. Statistical analyses were performed using the STATA software (version 10.0; Stata Corporation, College Station, TX, United States).

RESULTS

Literature search and study selection

A total of 2671 articles were identified from the initial electronic search, and 1743 studies were retained after duplicate articles were removed. Subsequently, 1698 studies were excluded because they reported irrelevant topics, and the remaining 45 studies were retrieved for full-text evaluation. Reviewing the reference lists yielded two potentially eligible studies, and 46 articles were subjected to detailed evaluation. After this, 28 studies were excluded because they reported the same population (n = 15), did not have an RCT design (n = 9), or included cancers at other stages (n = 4). The remaining 18 RCTs were included in the final meta-analysis[23-40]. Details of the study selection process are shown in Figure 1.

Trials' characteristics

Table 1 summarizes the baseline characteristics of the identified trials and patients involved. A total of 8533 patients with CRC were included from 18 RCTs, and the sample sizes ranged from 106 to 2509. Seventeen of the included trials were performed in Western countries, including Australia and European countries, whereas the remaining one trial was conducted in China. The follow-up duration ranged from 1.0-10.0 years. Details of the methodological quality of the included trials are listed in Table 2. Most of the included trials were of moderate to high quality, and three were of low quality.

Overall survival

Sixteen trials reported the effects of intensive *vs* conventional follow-up strategies on overall survival. There was no significant difference between intensive and conventional follow-up strategies for the improvement of overall survival (HR = 0.90; 95%CI: 0.81-1.01; P = 0.062; Figure 2A), and no evidence of heterogeneity was observed across the included trials (I^2 = 0.0%; P = 0.643). Sensitivity analysis indicated that an intensive follow-up strategy might be associated with an improvement in overall survival compared to a conventional follow-up strategy (Supplementary material). Subgroup analyses found that intensive follow-up was superior to conventional follow-up in overall survival if the sample size was < 500, proportion of males was < 60.0%, and follow-up duration was ≥ 5.0 years (Table 3). There were no significant differences between subgroups when stratified by sample size (RHR = 1.19; 95%CI: 0.95-1.48; P = 0.135), mean age (RHR = 1.07; 95%CI: 0.84-1.35; P = 0.584), proportion of males (RHR = 1.11; 95%CI: 0.89-1.39; P = 0.339), tumor location (RHR = 1.07; 95%CI: 0.84-1.36; P = 0.584), and follow-up (RHR = 0.86; 95%CI: 0.69-1.06; P = 0.163). No significant publication bias for overall survival was observed (P value for Egger's test: 0.753; P value for Begg's test: 0.558; Supplementary material).

Table 1 The baseline characteristics of included trials and recruited patients

Ref.	Region	Sample size	Age (yr)	Male (%)	Stage (A/B/C)	Tumor location (C/R)	Treatments	Intervention	Control	Follow-up duration
Mäkelä *et al* [23], 1995	Finland	106	66.0	49.1	(A/B/C) 28/48/30	75/31	Radical resection denotes surgical removal of all macroscopic tumor tissue with microscopically evaluated clearance of the surgical margins	Flexible sigmoidoscopy with video imaging every 3 mo, colonoscopy at 3 mo, then annually. They also had ultrasound of the liver and primary site at 6 mo, then annually	Rigid sigmoidoscopy and barium enema annually	5.0 yr
Ohlsson *et al* [24], 1995	Sweden	107	65.6	47.7	(A/B/C) 19/47/41	71/36	Resection with curative intent and early postoperative colonoscopy	Performed at each visit were clinical exam, rigid proctosigmoidoscopy, CEA, alkaline phosphatase, gamma-glutaryl transferase, faecal haemoglobin, and CXR. Examination of anastomosis was performed at 9, 21, and 42 mo. Colonoscopy was performed at 3, 15, 30, and 60 mo. CT of the pelvis was performed at 3, 6, 12, 18, and 24 mo	Written instructions recommending that they leave faecal samples with the district nurse for examination every 3 mo during the first 2 yr then once a year. They contact the surgical department if they had any symptoms	5.5-8.8 yr
Kjeldsen *et al* [25], 1997	Denmark	597	< 76.0	54.6	(A/B/C) 138/293/166	314/283	Radical primary surgery and no residual neoplasia was detected by complete colonoscopy or incomplete colonoscopy plus double-contrast barium enema, chest radiograph, histological examination of all resection margins in surgical specimens, biopsy of lesions, and inspection and palpation of the liver during surgery	Examinations at 6, 12, 18, 30, 36, 48, 60, 120, 150, and 180 mo after radical surgery (medical history, clinical examination, digital rectal examination, gynaecological examination, Haemoccult-II test, colonoscopy, CXR, haemoglobin level, erythrocyte sedimentation rate, and liver enzymes)	Examinations at 60, 120, and 180 mo (medical history, clinical examination, digital rectal examination, gynaecological examination, Haemoccult-II test, colonoscopy, CXR, haemoglobin level, erythrocyte sedimentation rate, and liver enzymes)	5.0-10.0 yr
Pietra *et al* [26], 1998	Italy	207	63.3	53.6	(A/B/C) 0/122/85	139/68	Curative resection defined as one in which no macroscopic tumor remained at the end of the operation and in which histopathologic examination of the operative specimen showed no tumor at the lines of resection	Examinations at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 mo, then annually thereafter. There was clinical examination, ultrasound, CEA, and CXR at each visit. Annual CT of the liver and colonoscopy were performed	Examinations at 6 and 12 mo, then annually. At each visit, clinical examination, CEA, and ultrasound were performed. They had annual CXR, yearly colonoscopy, and CT scan	5.0 yr
Schoemaker *et al*[27], 1998	Australia	325	68.0	63.7	(A/B/C) 71/153/101	238/87	Curative resection	Yearly CXR, CT of the liver, and colonoscopy	Clinical grounds or after screening test abnormality, and at 5 yr of follow-up, to exclude a reservoir of undetected recurrences	5.0 yr
Secco *et al* [28], 2002	Italy	337	65.1	48.4	(A or B/C) 201/136	NA	Putative curative surgery alone, which defined as macriscopic excision of the primary tumour, peritumoral tissues and palpable locoregional lymph nodes	Clinic visits and serum CEA, abdomen/pelvic US scans, and CXR. Participants with rectal carcinoma had rigid sigmoidoscopy and CXR	Minimal follow-up programme performed by physicians	4.0-5.1 yr
Rodríguez-Moranta *et al* [29], 2006	Spain	259	68.0	62.2	(II/III) 157/102	194/65	Curative resection, complete colon study was achieved with colonoscopy to determine the presence of synchronous lesions. If colonoscopy of the entire bowel could not be performed before resection, a postoperative colonoscopy was	Seen with history, examination, and bloods (including CEA) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 mo; US/CT at 6, 12, 18, 24, 30, 36, 42, 48, and 56 mo; CXR and colonoscopy at 12, 24, 36, 48, and 56 mo	Seen with history, examination, and bloods (including CEA) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 mo	4.0 yr

							warranted			
Wattchow *et al*[30], 2006	Australia	203	NA	53.6	(A/B/C) 47/96/60	203/0	Curative surgery and completion of postsurgical chemotherapy	Every 3 mo for the first 2 yr postoperatively, then every 6 mo for the next 3 yr	Asking a list of set questions about symptoms, physical examination, annual faecal occult blood testing, and colonoscopy every 3 yr	2.0 yr
Sobhani *et al* [31], 2008	France	130	60.1	NA	IV: 17	75/55	Curative surgery, compliance with adjuvant chemotherapy, and the absence of disease progression and/or missed synchronous metastases were checked	PET performed at 9 and 15 mo and conventional follow-up	Conventional follow-up	2.0 yr
Wang *et al* [32], 2009	China	326	54.5	54.3	(A/B/C) 100/133/93	171/155	Curative surgery, which was defined as one in which no macroscopic tumor remained at the end of the operation and in which histopathologic examination of the operative specimen demonstrated no tumor at the margins of resection	Colonoscopy at each visit	Colonoscopy at 6 mo, 30 mo, and 60 mo from randomisation	5.3-6.5 yr
Strand *et al* [33], 2011	Sweden	110	68.0	53.6	(I/II/III/IV) 26/40/36/8	0/110	Curative surgery, all patients had a first postoperative visit with the surgeon for information on histology and adjuvant therapy. Consecutive patients were asked to participate at various postoperative controls starting after the adjuvant chemotherapy was terminated	Surgeon-led follow-up	Nurse-led follow-up	5.0 yr
Augestad *et al*[34], 2013	Norway	110	65.4	59.1	(A/B/C) 24/55/32	110/0	Surgery and received postsurgical adjuvant chemotherapy	Surgeon follow-up	GP follow-up	2.0 yr
Primrose *et al* [35], 2014	United Kingdom	1202	69.2	61.2	(A/B/C) 254/553/354	811/359	Curative surgery, and adjuvant treatment if indicated, with no evidence of residual disease on investigation	CEA testing every 3 mo for 2 yr, then every 6 mo for 3 yr with a single CT scan of the chest/abdomen/pelvis if requested at study entry by clinician; CT scan of the chest/ abdomen/pelvis every 6 mo for 2 yr, then annually for 3 yr, plus colonoscopy at 2 yr; CEA and CT follow-up: Both blood and imaging as above, plus colonoscopy at 2 yr	No scheduled follow-up except a single CT scan of the chest/ abdomen/pelvis if requested at study entry by a clinician	3.4 yr
Treasure *et al* [36], 2014	United Kingdom	216	63.0	59.3	(A/B/C) 10/95/101	NA	Curative resection for adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the postoperative monitoring routine	CEA rise triggered the "second-look" surgery, with intention to remove any recurrence discovered	Conventional follow-up	2.0 yr
Rosati *et al* [37], 2016	Italy	1228	63.9	60.7	(B/C) 617/611	933/295	Curative intent, with adjuvant radio-chemotherapy if indicated	4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 60 monthly office visits and history and clinical examination, FBC, CEA, and CA 19-9; colonoscopy and CXR at 12, 24, 36, 48, and 60 mo; liver US at 4, 8, 12, 16, 24, 36, 48, and 60 mo; for rectal participants, pelvic CT at 4, 12, 24, and 48 mo	4, 8, 12, 16, 20, 24, 30, 42, 48, and 60 monthly office visits, including history, examination, and CEA; colonoscopy at 12 and 48 mo; liver US at 4 and 16 mo; rectal cancer participants in addition had rectoscopy at 4 mo, CXR at 12 mo, and liver US at 8 and 16 mo. A single pelvic CT was allowed if a radiation oncologist required it as baseline following adjuvant treatment	5.2 yr

Wille-Jørgensen *et al* [38], 2018	Denmark and Uruguay	2509	64.9	55.0	(II/III) 1352/1157	884/1625	Curative intent, with adjuvant treatment if indicated, a colon and rectum free of neoplasia verified by perioperative barium enema or a colonoscopy within 3 mo after surgery	Multislice contrast-enhanced CT of the thorax and abdomen and CEA at 6, 12, 18, 24, and 36 mo after surgery	Multislice contrast-enhanced CT of the thorax and abdomen and CEA at 12 and 36 mo after surgery	3.0 yr
Rahr *et al* [39], 2019	Denmark	196	70.0	63.8	(I/II/III/IV) 47/66/49/16	140/56	Elective surgery for verified or suspected CRC were screened by a study nurse for cardiopulmonary comorbidity at the preoperative visit	Routine follow-up with one extra medical visit and additional visits to the Cardiology and Respiratory Medicine Clinics 1 and 3 mo postoperatively	Routine follow-up	1.0 yr
Monteil *et al* [40], 2021	France	365	65.0	54.8	(I/II/III/IV) 2/176/185/2	290/75	Curative surgery, with adjuvant treatment if indicated	PET/CT and conventional follow-up every 3 mo	CEA, liver echography, and alternated between lung radiography and CT scans	3.0 yr

PET-CT: Positron emission tomography/computed tomography; CXR: Chest radiography; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; US: Ultrasound.

Cancer-specific survival

Ten trials reported the effects of intensive *vs* conventional follow-up strategies on cancer-specific survival. No significant difference between intensive and conventional follow-up strategies was observed for improvement in cancer-specific survival (HR = 0.98; 95%CI: 0.83-1.15; P = 0.785; Figure 2B), and unimportant heterogeneity was detected across the included trials (I^2 = 17.8%; P = 0.280). Sensitivity analysis indicated that the pooled analyses were stable and not altered by the sequential removal of a single trial (Supplementary material). The results of the subgroup analyses were consistent with those of the overall analysis in all subgroups (Table 3). Moreover, the differences between subgroups were not statistically significant when stratified by sample size (RHR = 1.04; 95%CI: 0.70-1.54; P = 0.837), mean age (RHR = 1.23; 95%CI: 0.84-1.79; P = 0.281), proportion of males (RHR = 1.09; 95%CI: 0.75-1.60; P = 0.645), tumor location (RHR = 1.35; 95%CI: 0.89-2.05; P = 0.155), and follow-up (RHR = 0.82; 95%CI: 0.58-1.15; P = 0.245). There was no significant publication bias for cancer-specific survival (P value for Egger's test: 0.492; P value for Begg's test: 0.858; Supplementary material).

Relapse-free survival

Fifteen trials reported the effects of intensive *vs* conventional follow-up strategies on relapse-free survival. There was no significant difference between intensive and conventional follow-up strategies for improvement in relapse-free survival (HR = 1.08; 95%CI: 0.97-1.22; P = 0.168; Figure 2C), and non-significant heterogeneity was observed among the included trials (I^2 = 10.8%; P = 0.333). Sensitivity analysis revealed that intensive follow-up may be associated with poor relapse-free survival after excluding the trial performed by Schoemaker *et al*[27] (Supplementary material). Subgroup analyses indicated that an intensive follow-up strategy was associated with poor relapse-free survival when the sample size was ≥ 500 (Table 3). Furthermore, there were no significant differences between subgroups when stratified by sample size (RHR = 1.24; 95%CI: 0.99-1.56; P = 0.063), mean age (RHR = 1.02; 95%CI: 0.79-1.31; P = 0.885), proportion of males (RHR = 1.08; 95%CI: 0.80-1.45; P = 0.633), tumor location (RHR = 1.04; 95%CI: 0.81-1.32; P = 0.778), and follow-up (RHR = 0.87; 95%CI: 0.68-1.11; P = 0.265). No significant publication bias was observed for relapse-free survival (P value for Egger's test: 0.189; P value for Begg's test: 0.621; Supplementary material).

Salvage surgery

Fourteen trials reported the effects of intensive *vs* conventional follow-up strategies on the incidence of salvage surgery. We noted that intensive follow-up significantly increased the risk of salvage surgery compared to a conventional follow-

Table 2 The methodological quality assessment of included trials

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Mäkelä *et al*[23], 1995	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear
Ohlsson *et al*[24], 1995	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear
Kjeldsen *et al*[25], 1997	Unclear	Unclear	Unclear	High risk	Low risk	Unclear	Unclear
Pietra *et al*[26], 1998	Unclear	Unclear	Low risk	Unclear	High risk	Unclear	Unclear
Schoemaker *et al* [27], 1998	Low risk	High risk	Low risk	Low risk	Low risk	Unclear	Unclear
Secco *et al*[28], 2002	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Rodríguez-Moranta *et al*[29], 2006	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Wattchow *et al* [30], 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Sobhani *et al*[31], 2008	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear
Wang *et al*[32], 2009	Unclear	Unclear	High risk	High risk	Unclear	Unclear	Unclear
Strand *et al*[33], 2011	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear
Augestad *et al* [34], 2013	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Primrose *et al*[35], 2014	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear
Treasure *et al*[36], 2014	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Rosati *et al*[37], 2016	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Wille-Jørgensen *et al*[38], 2018	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Rahr *et al*[39], 2019	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Monteil *et al*[40], 2021	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear

up strategy (RR = 1.99; 95%CI: 1.57-2.53; $P < 0.001$; Figure 2D), and unimportant heterogeneity was detected among the included trials ($I^2 = 25.0\%$; $P = 0.184$). The pooled analyses for the incidence of salvage surgery were robust and not altered by any specific trial (Supplementary material). The results of the subgroup analyses were consistent with those of the overall analysis, and significant differences between the intensive and conventional follow-up strategies were observed in all subgroups (Table 3). We noted that intensive *vs* conventional follow-up strategies on salvage surgery in tumor location [colon/rectal ratio (C/R)] ≥ 70.0% was lower than tumor location (C/R) < 70.0% (RRR = 0.54; 95%CI: 0.31-0.92; $P = 0.022$). There was no significant publication bias for salvage surgery (P value for Egger's test: 0.419; P value for Begg's test: 1.000; Supplementary material).

Recurrence

Fifteen trials reported the effects of intensive *vs* conventional follow-up strategies on the risk of recurrence. We noted that the intensive follow-up strategy had no significant effect on the risk of recurrence (RR = 1.13; 95%CI: 0.98-1.31; $P = 0.094$; Figure 2E), and significant heterogeneity was observed across the included trials ($I^2 = 51.6\%$; $P = 0.011$). Sensitivity analysis indicated that the intensive follow-up strategy was associated with an elevated risk of recurrence when the trial conducted by Secco *et al*[28] was excluded (Supplementary material). Subgroup analyses suggested that the intensive follow-up strategy was associated with an increased risk of recurrence when the sample size was ≥ 500 and the mean age was < 65.0 years (Table 3). Moreover, the differences between subgroups were not statistically significant when stratified

Table 3 Subgroup analyses for investigated outcomes

Outcomes	Factors	Subgroups	No. of studies	HR or RR and 95%CI	*P* value	I^2 (%)	P value for I^2	Interaction *P* value	RHR or RRR with 95%CI
Overall survival	Sample size	≥ 500	4	0.96 (0.84-1.10)	0.579	0.0	0.581	0.135	1.19 (0.95-1.48)
		< 500	12	0.81 (0.68-0.97)	0.019	0.0	0.693		
	Mean age (yr)	≥ 65.0	9	0.94 (0.78-1.14)	0.538	0.0	0.563	0.584	1.07 (0.84-1.35)
		< 65.0	6	0.88 (0.77-1.02)	0.082	7.7	0.367		
	Male (%)	≥ 60.0	5	0.97 (0.81-1.16)	0.758	0.0	0.503	0.339	1.11 (0.89-1.39)
		< 60.0	11	0.87 (0.76-0.99)	0.035	0.0	0.620		
	Tumor location (C/R)	≥ 70.0	8	0.93 (0.78-1.11)	0.429	0.0	0.742	0.584	1.07 (0.84-1.36)
		< 70.0	7	0.87 (0.74-1.02)	0.082	16.9	0.301		
	Follow-up (yr)	≥ 5.0	8	0.84 (0.72-0.97)	0.017	0.0	0.635	0.163	0.86 (0.69-1.06)
		< 5.0	8	0.98 (0.84-1.15)	0.837	0.0	0.658		
Cancer-specific survival	Sample size	≥ 500	4	0.99 (0.83-1.17)	0.866	0.0	0.804	0.837	1.04 (0.70-1.54)
		< 500	6	0.95 (0.67-1.36)	0.782	49.4	0.079		
	Mean age (yr)	≥ 65.0	5	1.12 (0.80-1.57)	0.515	29.3	0.226	0.281	1.23 (0.84-1.79)
		< 65.0	5	0.91 (0.77-1.08)	0.276	0.0	0.510		
	Male (%)	≥ 60.0	3	1.05 (0.77-1.43)	0.750	0.0	0.603	0.645	1.09 (0.75-1.60)
		< 60.0	7	0.96 (0.77-1.20)	0.732	37.6	0.142		
	Tumor location (C/R)	≥ 70.0	4	1.23 (0.84-1.81)	0.281	23.9	0.268	0.155	1.35 (0.89-2.05)
		< 70.0	6	0.91 (0.78-1.07)	0.254	0.0	0.560		
	Follow-up (yr)	≥ 5.0	5	0.89 (0.72-1.10)	0.288	0.0	0.464	0.245	0.82 (0.58-1.15)
		< 5.0	5	1.09 (0.83-1.42)	0.552	35.9	0.182		
Relapse-free survival	Sample size	≥ 500	4	1.18 (1.02-1.36)	0.025	18.8	0.296	0.063	1.24 (0.99-1.56)
		< 500	11	0.95 (0.80-1.14)	0.589	0.0	0.583		
	Mean age (yr)	≥ 65.0	9	1.10 (0.89-1.36)	0.388	23.5	0.234	0.885	1.02 (0.79-1.31)
		< 65.0	6	1.08 (0.95-1.23)	0.220	3.6	0.394		
	Male (%)	≥ 60.0	4	1.14 (0.87-1.50)	0.340	51.1	0.105	0.633	1.08 (0.80-1.45)
		< 60.0	11	1.06 (0.94-1.20)	0.364	0.0	0.569		
	Tumor location (C/R)	≥ 70.0	6	1.15 (0.94-1.40)	0.171	9.5	0.355	0.778	1.04 (0.81-1.32)
		< 70.0	7	1.11 (0.96-1.28)	0.159	6.2	0.380		
	Follow-up (yr)	≥ 5.0	8	1.01 (0.86-1.18)	0.917	0.0	0.597	0.265	0.87 (0.68-1.11)
		< 5.0	7	1.16 (0.96-1.39)	0.120	27.9	0.215		
Salvage surgery	Sample size	≥ 500	3	2.12 (1.05-4.29)	0.036	71.7	0.029	0.990	1.00 (0.48-2.11)
		< 500	11	2.11 (1.67-2.66)	< 0.001	0.0	0.567		
	Mean age (yr)	≥ 65.0	8	1.95 (1.42-2.69)	< 0.001	0.0	0.910	0.675	0.89 (0.50-1.56)
		< 65.0	6	2.20 (1.38-3.50)	0.001	65.8	0.012		
	Male (%)	≥ 60.0	4	1.64 (1.06-2.53)	0.026	38.1	0.183	0.256	0.75 (0.45-1.23)
		< 60.0	9	2.19 (1.72-2.80)	< 0.001	0.0	0.726		
	Tumor location (C/R)	≥ 70.0	6	1.44 (1.08-1.91)	0.013	0.0	0.759	0.022	0.54 (0.31-0.92)
		< 70.0	6	2.69 (1.71-4.24)	< 0.001	24.0	0.254		
	Follow-up (yr)	≥ 5.0	7	1.69 (1.15-2.48)	0.007	28.2	0.213	0.189	0.73 (0.46-1.16)
		< 5.0	7	2.30 (1.79-2.97)	< 0.001	0.0	0.591		

Recurrence	Sample size	≥ 500	4	1.38 (1.00-1.89)	0.048	82.1	0.001	0.075	1.37 (0.97-1.93)
		< 500	11	1.01 (0.89-1.15)	0.891	0.0	0.585		
	Mean age (yr)	≥ 65.0	8	1.23 (0.87-1.73)	0.238	75.4	< 0.001	0.645	1.09 (0.76-1.56)
		< 65.0	6	1.13 (1.01-1.26)	0.027	0.0	0.808		
	Male (%)	≥ 60.0	3	1.54 (0.71-3.30)	0.273	89.7	< 0.001	0.357	1.44 (0.66-3.12)
		< 60.0	11	1.07 (0.97-1.18)	0.185	0.0	0.618		
	Tumor location (C/R)	≥ 70.0	6	1.13 (0.96-1.32)	0.130	0.0	0.461	0.583	0.92 (0.68-1.24)
		< 70.0	8	1.23 (0.95-1.59)	0.116	64.3	0.006		
	Follow-up (yr)	≥ 5.0	8	1.09 (0.95-1.25)	0.223	0.0	0.715	0.317	0.85 (0.62-1.17)
		< 5.0	7	1.28 (0.97-1.71)	0.085	76.3	< 0.001		
Interval recurrence	Sample size	≥ 500	3	0.74 (0.45-1.20)	0.221	74.8	0.019	0.060	1.76 (0.98-3.18)
		< 500	4	0.42 (0.30-0.58)	< 0.001	0.0	0.557		
	Mean age (yr)	≥ 65.0	3	0.45 (0.34-0.60)	< 0.001	0.0	0.423	0.173	0.65 (0.35-1.21)
		< 65.0	4	0.69 (0.40-1.19)	0.182	62.0	0.048		
	Male (%)	≥ 60.0	2	0.77 (0.32-1.85)	0.558	86.9	0.006	0.424	1.48 (0.57-3.87)
		< 60.0	4	0.52 (0.35-0.77)	0.001	47.6	0.126		
	Tumor location (C/R)	≥ 70.0	2	1.12 (0.75-1.67)	0.586	0.0	0.435	0.007	1.96 (1.21-3.20)
		< 70.0	4	0.57 (0.43-0.75)	< 0.001	0.0	0.412		
	Follow-up (yr)	≥ 5.0	4	0.76 (0.47-1.23)	0.265	57.1	0.072	0.044	1.77 (1.02-3.07)
		< 5.0	3	0.43 (0.33-0.57)	< 0.001	0.0	0.795		

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio; RHR: Ratio of hazard ratio; RRR: Ratio of risk ratio; C/R: Colon/rectal ratio.

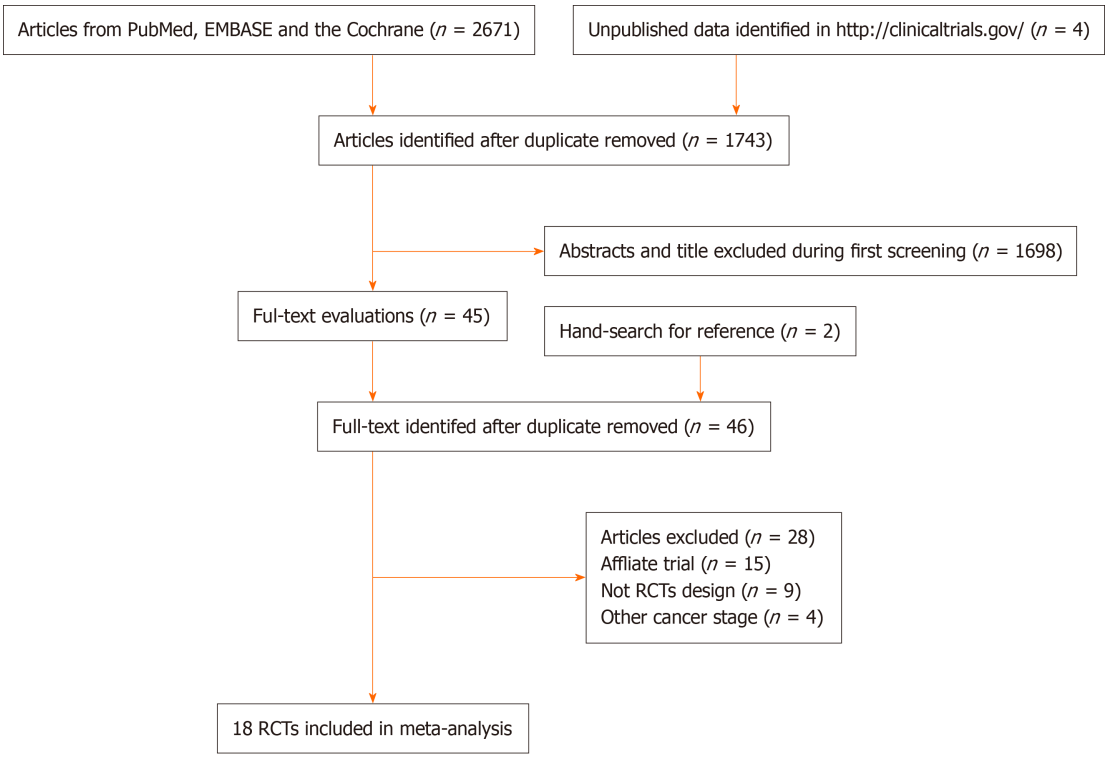

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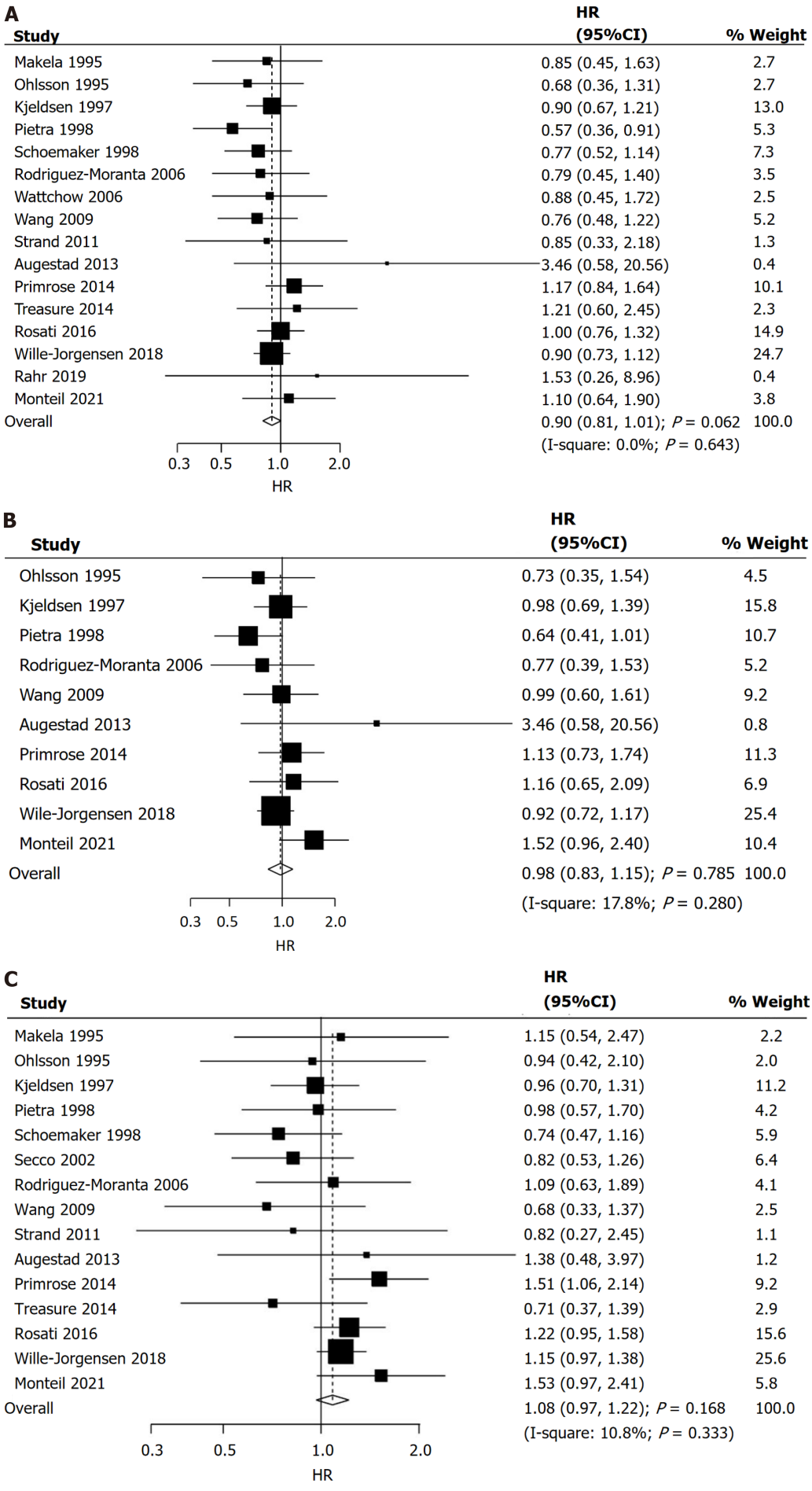
Figure 1 The PRISMA flowchart for the literature search and study selection process. RCT: Randomized controlled trial.


A
Study
HR (95%CI)
% Weight
Makela 1995 0.85 (0.45, 1.63) 2.7
Ohlsson 1995 0.68 (0.36, 1.31) 2.7
Kjeldsen 1997 0.90 (0.67, 1.21) 13.0
Pietra 1998 0.57 (0.36, 0.91) 5.3
Schoemaker 1998 0.77 (0.52, 1.14) 7.3
Rodriguez-Moranta 2006 0.79 (0.45, 1.40) 3.5
Wattchow 2006 0.88 (0.45, 1.72) 2.5
Wang 2009 0.76 (0.48, 1.22) 5.2
Strand 2011 0.85 (0.33, 2.18) 1.3
Augestad 2013 3.46 (0.58, 20.56) 0.4
Primrose 2014 1.17 (0.84, 1.64) 10.1
Treasure 2014 1.21 (0.60, 2.45) 2.3
Rosati 2016 1.00 (0.76, 1.32) 14.9
Wille-Jorgensen 2018 0.90 (0.73, 1.12) 24.7
Rahr 2019 1.53 (0.26, 8.96) 0.4
Monteil 2021 1.10 (0.64, 1.90) 3.8
Overall 0.90 (0.81, 1.01); P = 0.062 100.0
(I-square: 0.0%; P = 0.643)
0.3 0.5 1.0 2.0
HR
B
Study
HR (95%CI)
% Weight
Ohlsson 1995 0.73 (0.35, 1.54) 4.5
Kjeldsen 1997 0.98 (0.69, 1.39) 15.8
Pietra 1998 0.64 (0.41, 1.01) 10.7
Rodriguez-Moranta 2006 0.77 (0.39, 1.53) 5.2
Wang 2009 0.99 (0.60, 1.61) 9.2
Augestad 2013 3.46 (0.58, 20.56) 0.8
Primrose 2014 1.13 (0.73, 1.74) 11.3
Rosati 2016 1.16 (0.65, 2.09) 6.9
Wile-Jorgensen 2018 0.92 (0.72, 1.17) 25.4
Monteil 2021 1.52 (0.96, 2.40) 10.4
Overall 0.98 (0.83, 1.15); P = 0.785 100.0
(I-square: 17.8%; P = 0.280)
0.3 0.5 1.0 2.0
HR
C
Study
HR (95%CI)
% Weight
Makela 1995 1.15 (0.54, 2.47) 2.2
Ohlsson 1995 0.94 (0.42, 2.10) 2.0
Kjeldsen 1997 0.96 (0.70, 1.31) 11.2
Pietra 1998 0.98 (0.57, 1.70) 4.2
Schoemaker 1998 0.74 (0.47, 1.16) 5.9
Secco 2002 0.82 (0.53, 1.26) 6.4
Rodriguez-Moranta 2006 1.09 (0.63, 1.89) 4.1
Wang 2009 0.68 (0.33, 1.37) 2.5
Strand 2011 0.82 (0.27, 2.45) 1.1
Augestad 2013 1.38 (0.48, 3.97) 1.2
Primrose 2014 1.51 (1.06, 2.14) 9.2
Treasure 2014 0.71 (0.37, 1.39) 2.9
Rosati 2016 1.22 (0.95, 1.58) 15.6
Wille-Jorgensen 2018 1.15 (0.97, 1.38) 25.6
Monteil 2021 1.53 (0.97, 2.41) 5.8
Overall 1.08 (0.97, 1.22); P = 0.168 100.0
(I-square: 10.8%; P = 0.333)
0.3 0.5 1.0 2.0
HR

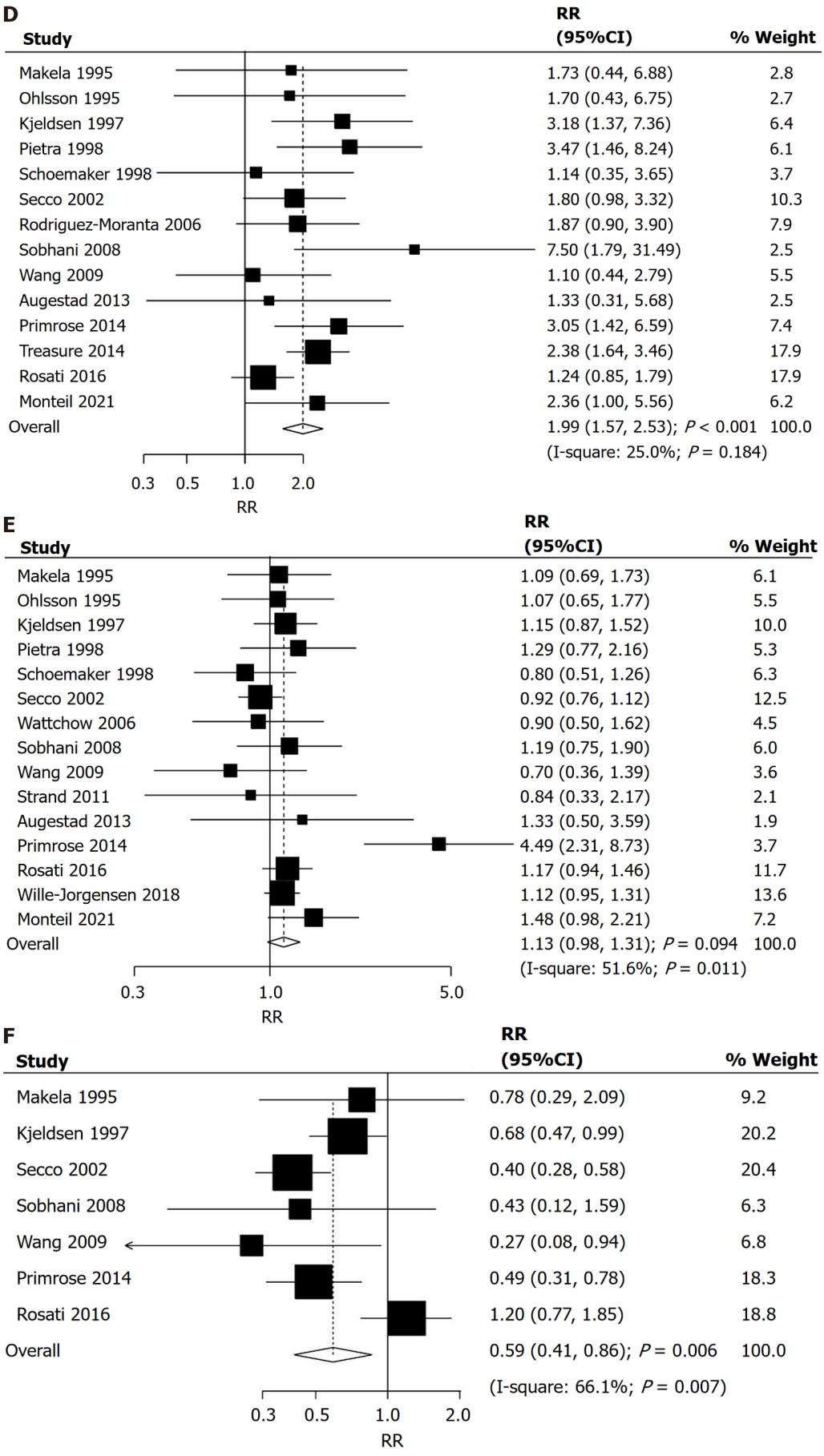


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Figure 2 Intensive *vs* conventional follow-up strategies. A: On overall survival; B: On cancer-specific survival; C: On relapse-free survival; D: On salvage

surgery; E: On recurrence; F: On interval recurrences. HR: Hazard ratio; CI: Confidence interval; RR: Risk ratio.

by sample size (RRR = 1.37; 95%CI: 0.970-1.93; P = 0.075), mean age (RRR = 1.09; 95%CI: 0.76-1.56; P = 0.645), proportion of males (RRR = 1.44; 95%CI: 0.66-3.12; P = 0.357), tumor location (RRR = 0.92; 95%CI: 0.68-1.24; P = 0.583), and follow-up (RRR = 0.85; 95%CI: 0.62-1.17; P = 0.317). No significant publication bias was observed for recurrence (P value for Egger's test: 0.492; P value for Begg's test: 0.843; Supplementary material).

Interval recurrence

Seven trials reported the effects of intensive *vs* conventional follow-up strategies on the risk of interval recurrence. We noted that intensive follow-up significantly reduced the risk of interval recurrence compared to conventional follow-up (RR = 0.59; 95%CI: 0.41-0.86; P = 0.006; Figure 2F), and significant heterogeneity was observed among the included trials (I^2 = 66.1%; P = 0.007). The sensitivity analysis indicated that the pooled analyses were not altered when a particular trial was excluded (Supplementary material). Subgroup analyses found that intensive *vs* conventional follow-up strategies were associated with a lower risk of interval recurrence if the sample size was < 500, mean age was ≥ 65.0, proportion of males was < 60.0, tumor location (C/R) was < 70.0%, and follow-up duration was < 5.0 years (Table 3). Moreover, the effects of intensive *vs* conventional follow-up strategies on the risk of interval recurrence in the subgroups of tumor location (C/R) ≥ 70.0% (RRR = 1.96; 95%CI: 1.21-3.20; P = 0.007) and follow-up ≥ 5.0 years (RRR = 1.77; 95%CI: 1.02-3.07; P = 0.044) were greater than the corresponding subgroups. There was no significant publication bias for interval recurrence (P value for Egger's test: 0.790; P value for Begg's test: 1.000; Supplementary material).

DISCUSSION

Numerous studies have addressed the effects of intensive *vs* conventional follow-up strategies on the prognosis of patients with non-metastatic CRC treated with curative intent. However, the study results are controversial. This comprehensive quantitative meta-analysis identified 8533 patients with CRC from 18 RCTs, and the patients had a broad range of characteristics. We noted that the intensive follow-up strategy was not associated with overall survival, cancer-specific survival, relapse-free survival, or recurrence compared to the conventional follow-up strategy. Moreover, intensive follow-up significantly increased the incidence of salvage surgery and reduced the risk of interval recurrence compared to conventional follow-up. Finally, the effects of intensive and conventional follow-up strategies differed when stratified by tumor location and follow-up duration.

Several systematic reviews and meta-analyses have compared the effects of intensive treatment with those of conventional follow-up strategies on the prognosis of patients with non-metastatic CRC treated with curative intent[11,41]. The results of a meta-analysis conducted by Zhao *et al*[11] were consistent with those of a Cochrane review, and the investigated outcomes were similar. A Cochrane review found that using an intensive follow-up strategy did not affect survival outcomes but could increase the incidence of salvage surgeries[41]. Although the analysis in this study was comprehensive, stratified analyses were performed only through the intervention protocol and according to the study or patient characteristics. Therefore, this study was conducted to compare the effects of intensive *vs* conventional follow-up strategies on the prognosis of non-metastatic CRC treated with curative intent by examining published RCTs.

The summary result did not reveal significant differences between intensive and conventional follow-up strategies for improving overall survival. However, this pooled analysis was not stable, and the sensitivity analysis revealed a potentially beneficial role of intensive follow-up on overall survival. A potential reason for this could be that recurrent cases can be detected early and further curative procedures can be applied among patients who receive an intensive follow-up strategy, which could improve the prognosis of CRC after curative surgery. Moreover, patients in the intensive follow-up group showed an increased frequency of clinic visits, tests, and examinations, which could improve CRC prognosis[41]. Furthermore, subgroup analyses found that the beneficial effects of intensive follow-up strategies were mainly relevant when the sample size was < 500, proportion of males was < 60.0%, and follow-up duration was ≥ 5.0, which could be explained by the fact that patients with rectal cancer need longer follow-up durations owing to the delayed liver and lung recurrences[42]. Finally, intensive follow-up might be superior to conventional follow-up among women because the difference in lifestyle and compliance among women was better than that among men.

There were no significant differences between the intensive and conventional follow-up strategies in improving cancer-specific survival and relapse-free survival. These results were consistent with those of prior meta-analyses[11,41]. However, subgroup analyses found that intensive follow-up was associated with poor relapse-free survival when the sample size was ≥ 500 patients. The potential reason for this could be the large sample size with sufficient power to detect potential differences, and that residual cancer could be detected through a more thorough follow-up[43]. Similar to a previous meta-analysis, we noted that intensive follow-up significantly increased the incidence of salvage surgery, which could be explained by the early detection of recurrent cases, and salvage surgery was performed for patients with recurring issues.

Although there was no significant difference in the risk of recurrence between groups, intensive follow-up significantly reduced the risk of interval recurrence. Moreover, intensive follow-up was associated with an increased risk of recurrence when the sample size was ≥ 500 and the mean age was < 65.0 years. A potential reason for the risk of recurrence could be that the recurrent cases were consistent and could be affected by the colon/rectal cancer ratio[42]. Moreover, most recurrent cases occurred within 36 mo, and the mean age of the patients was significantly related to the tumor stage[44].

Interval recurrence was defined as symptomatic recurrence, and recurrent presentation in asymptomatic cases was observed when using an intensive follow-up strategy.

This study has several limitations. First, the disease status and treatments across the included trials were different, which could affect the prognosis of CRC after curative surgery. Second, the follow-up protocol differed among the included trials, and the frequency and content of examination could affect the prognosis of CRC. Third, there was substantial heterogeneity for recurrence and interval recurrence, which was not fully explained using sensitivity and subgroup analyses. Finally, there are inherent limitations of meta-analyses on published articles, including inevitable publication bias and restricted detailed analyses.

CONCLUSION

This study found that an intensive follow-up strategy might have beneficial effects on the overall survival of patients with CRC. Moreover, an intensive follow-up strategy was associated with an increased incidence of salvage surgery and a reduced risk of interval survival. Further large-scale studies should be performed to explore suitable follow-up plans after CRC surgery.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is the third most frequently diagnosed cancer, and the prognosis of CRC at early stage was relative better. The frequency and content of follow-up strategies play an important role on the prognosis of CRC, and intensive follow-up may improve the prognosis of CRC.

Research motivation

Assess the effects of intensive with conventional follow-up strategies for CRC patients after curative intention using a meta-analysis.

Research objectives

This study aimed to compare the overall survival, cancer-specific survival, relapse-free survival, salvage surgery, recurrence, and interval recurrences between intensive and conventional follow-up strategies for non-metastatic CRC treated with curative intent.

Research methods

The eligible trials were identified from PubMed, Embase, and the Cochrane Library databases from inception until April 2023. All of pooled analyses were calculated using the random-effects model, which considering the underlying varies across included trials.

Research results

We noted intensive follow-up play a beneficial effects in improving overall survival, and interval recurrence as compared with conventional follow-up. Moreover, the incidence of salvage surgery was significantly increased for patients received intensive follow-up.

Research conclusions

This study found intensive follow-up was superior than conventional follow-up for CRC patients after curative intention, which should introduce in clinical practice.

Research perspectives

The results of this study based on randomized controlled trials, and the evidence level for pooled conclusions was high.

FOOTNOTES

Author contributions: Cui LL and Ren ZQ conceived the study concept and participated in its design, data extraction, statistical analysis; Cui LL, Cui SQ, Qu Z, and Ren ZQ contributed to the manuscript drafting, and editing; Cui SQ and Qu Z participated in the literature research; and all authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Li-Li Cui 0009-0002-6404-5884; Shi-Qi Cui 0009-0006-4950-6063; Zhong Qu 0009-0002-5608-9633; Zhen-Qing Ren 0000-0003-2816-5395.

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