Review

# Follow-up strategy and survival for five common cancers: A meta-analysis

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**Abstract** *Background:* This meta-analysis aimed to evaluate the effectiveness of intensive follow-up after curative intent treatment for five common solid tumours, in terms of survival and treatment of recurrences.

*Methods:* A systematic literature search was conducted, identifying comparative studies on follow-up for colorectal, lung, breast, upper gastro-intestinal and prostate cancer. Outcomes of interest were overall survival (OS), cancer specific survival (CSS), and treatment of recurrences. Random effects meta-analyses were conducted, with particular focus on studies at low risk of bias.

*Results:* Fourteen out of 63 studies were considered to be at low risk of bias (8 colorectal, 4 breast, 0 lung, 1 upper gastro-intestinal, 1 prostate). These studies showed no significant impact of intensive follow-up on OS (hazard ratio, 95% confidence interval) for colorectal (0.99; 0.92—1.06), breast 1.06 (0.92—1.23), upper gastro-intestinal (0.78; 0.51—1.19) and prostate cancer (1.00; 0.86—1.16). No impact on CSS (hazard ratio, 95% confidence interval) was found for colorectal cancer (0.94; 0.77—1.16). CSS was not reported for other cancer types. Intensive follow-up increased the rate of curative treatment (relative risk; 95% confidence interval) for colorectal cancer recurrences (1.30; 1.05—1.61), but not for upper gastro-intestinal cancer recurrences (0.92; 0.47—1.81). For the other cancer types, no data on treatment of recurrences was available in low risk studies.

*Conclusion:* For colorectal and breast cancer, high quality studies do not suggest an impact of intensive follow-up strategies on survival. Colorectal cancer recurrences are more often treated locally after intensive follow-up. For other cancer types evaluated, limited high quality

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## 1. Introduction

Most cancer survivors receive regular follow-up care after being treated with curative intent. Traditionally, follow-up is performed for a period of 5 years or longer for most types of solid tumours. Guidelines differ between tumour types, but generally advocate regular hospital visits, imaging, and serum tumour marker measurements when available [1—4].

The main rationale behind oncologic follow-up is to detect metastases or novel primary tumours early, since prompt treatment of cancer relapses is deemed important for the likelihood of cure and survival. Next to this, follow-up can be used to address patients' needs with regards to psychosocial counselling, to evaluate treatment effects and complications, and to inform patients on their disease status and risk of recurrence [5].

The debate surrounding oncological follow-up practices has existed for many years. It is associated with a considerable use of hospital resources and costs, may have impact on quality of life, while the effect of follow-up intensity on survival outcomes remains equivocal [6,7]. Given that the number of cancer survivors will continue to grow [8], improvements of follow-up practices should be pursued. Many studies evaluate the effectiveness of follow-up for individual tumours types, but a broad oncological perspective remains lacking.

We therefore sought to systematically assess and meta-analyse available literature on follow-up after curative intent treatment for five types of solid tumours (colorectal, lung, breast, upper gastro-intestinal, and prostate cancers) in order to determine the impact of different follow-up strategies on survival outcomes and treatment of recurrent disease.

## 2. Methods

### 2.1. Search strategy

This study was performed in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis, www.prisma-statement.org) guidelines. Pubmed/MEDLINE, Embase, Web of Science, the Cochrane database, and Google Scholar were systematically searched for studies published prior to the 12th of May 2020. The search terms are provided in supplementary table A.1. Reference lists from eligible articles were also reviewed to identify additional publications.

### 2.2. Study selection

Screening for eligible studies was performed by two authors (BG, DH), independently. Studies were included when comparing follow-up approaches after curative intent treatment for colorectal, lung, breast, upper gastro-intestinal or prostate cancer, in light of overall survival (OS) or cancer specific survival (CSS) outcomes. Treatment intent for recurrent disease (i.e. curative or palliative) was also evaluated. Both randomised controlled trials (RCTs) and observational studies (cohort and case—control) were considered. Inclusion was restricted to articles written in English. Non-original studies (e.g. reviews, editorials) were excluded, as were non-comparative studies and studies using simulation techniques (e.g. Markov modelling).

### 2.3. Data extraction and presentation

Data were extracted by two reviewers (BG, DH), independently. Studies were categorised based on the aspect of follow-up evaluated, being the frequency of testing, setting of follow-up (e.g. in-hospital or general practitioner), diagnostic modalities used, or a combination of the aforementioned categories. Data on survival (hazard ratios (HR) including 95% confidence intervals (95% CI) for OS and CSS) and the probability of treatment with curative intent for recurrent disease (relative risk (RR) including 95% CI) were collected. When no ratios were reported, data were extracted from Kaplan—Meier figures, tables, and text. Multi-layered circle plots were created to visualise all aspects in relation to outcomes and the risk of bias.

### 2.4. Quality assessment

Quality assessment was performed by two reviewers (BG, DH), independently. The Cochrane tools ROBINS-I (for observational studies) and RoB2 (for randomised studies) were used [9,10]. Studies were considered to be at low risk of bias when qualified as either 'low' to 'moderate' using ROBINS-I, or as 'low risk' to 'some concerns' using RoB2.

### 2.5. Quantitative assessment

A random effects meta-analysis was conducted per tumour type and stratified for study risk of bias, using the generic inverse variance method (survival) or the

Mantel-Haenszel method (treatment of recurrences). Methods described by Tierney et al. were applied to calculate log HRs and corresponding standard errors, in case these were not reported [11]. Both HRs and RRs were reported using the least intensive approach (e.g. lowest frequency, non-hospital setting) as a reference. In studies with multiple groups (i.e. >2 follow-up approaches), the most intensive approaches were combined to create a single pair-wise comparison with the least intensive approach, as recommended by the Cochrane Handbook [12]. The R Project for Statistical Computing version 4.1.0 (https://www.r-project.org/) was used for both the statistical analyses and visualisation of the data (packages: meta (v4.18-1), ggplot2 (v3.3.2); circlize (v0.4.11) [13]).

## 3. Results

The screening and selection process is illustrated in Fig. 1. After screening 4538 studies, 167 were screened full-text. Ultimately, 63 studies were deemed eligible for inclusion [14−76]. For quantitative analyses, 61 studies were eligible.

### 3.1. Study characteristics and outcomes

Fig. 2 visualises the studies obtained. Thirty-three original studies (52%) reported on the effect of follow-up in colorectal [14−46], 13 (21%) in lung [47−59], 11 (18%) in breast [60−70], five (8%) in upper gastro-intestinal [71−75], and one (2%) in prostate cancer patients [76].
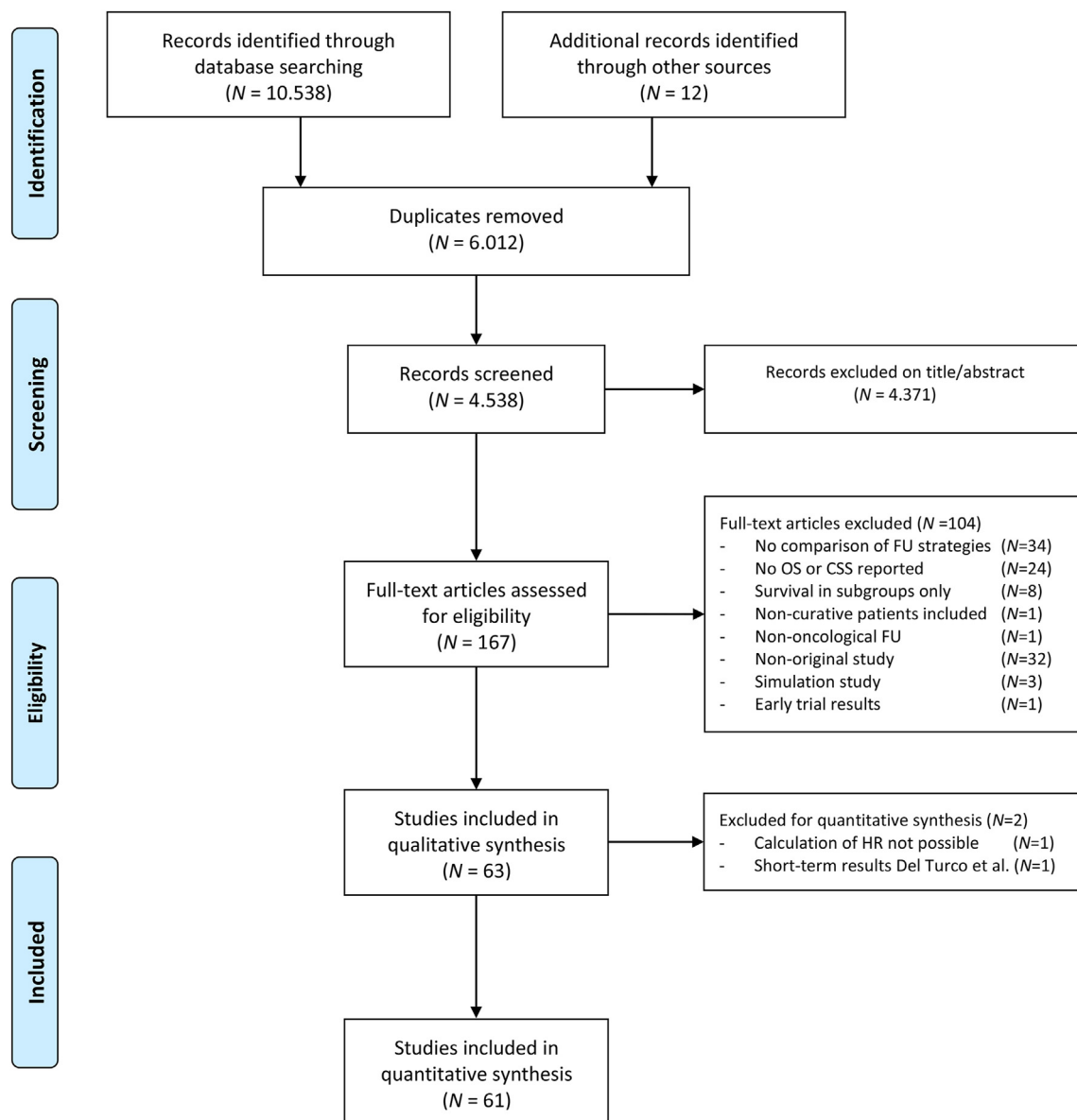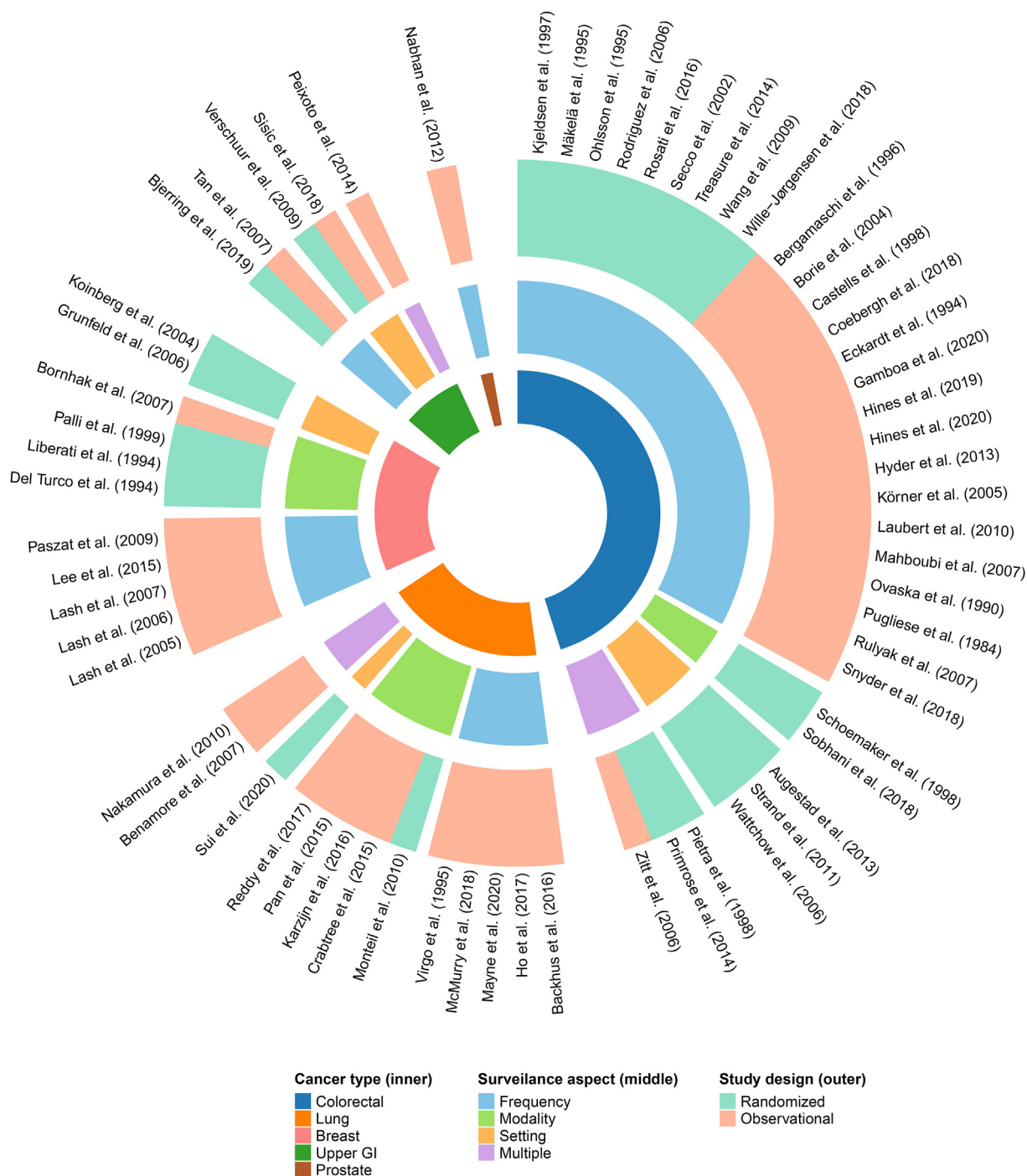


Fig. 1. PRISMA flowchart.

Fig. 2. Multi-layered circle plot displaying all 63 included studies by cancer type (inner circle), aspect of follow-up investigated (middle circle), and study design (outer circle).

The majority of studies evaluated frequency of follow-up (N = 38, 60%) [14,16−21,23−37,39,40,42,47,50,52,-53,59,66−71,74,76]. A total of 89,154 patients were included. Twenty-five RCTs (40%) were identified, including one long-term update [62], and comprised 12,458 patients in total [14−17,19−22,32,36,38,41−45,-54,58,61−65,71,75]. Tables 1 and 2 provide detailed overviews of the low and high risk of bias studies. Risk of bias assessment is provided in supplementary table A.2.

Fig. 3 visualises outcomes per study. The results of the meta-analysis per tumour type, including stratified analyses are reported in Table 3.

### 3.2. Colorectal cancer

The 33 colorectal cancer studies comprised 50,431 patients in total (Tables 1 and 2). Across all studies, intensive follow-up led to improved OS (HR 0.82, 95%

Table 1
Studies at low risk of bias.

| Author (year) | N | Cancer type, stage | Follow-up duration | Intensive follow-up approach | Comparison (reference) |
|---|---|---|---|---|---|
| Ohlsson (1995) [14] | 107 | CRC, Dukes A-C | Range 5.5−8.8 y | Clin exam/CEA/CXR/proctoscopy: every 3 m Y1-2, 6 m Y3-4, 12 m Y5 CT pelvis: every 6 m Y1-2 Colonoscopy: 3, 15, 30 and 60 m | No organised follow-up |
| Primrose (2014) [15] | 1202 | CRC, Dukes A-C | Mean 3.7 y | CEA-only: every 3 m Y1-2, every 6 m Y3-5[a] CT-only: CT chest, abd, pelvis every 6 m Y1-2, every 12 m Y3-5 CT + CEA: protocols combined | No scheduled follow-up[a] |
| Rodriguez (2006) [16] | 259 | CRC, II−III | Median 49 m and 45 m | Clin exam/CEA: every 3 m Y1-2, every 6 m Y 3-5 Abd CT or US: every 6 m Y1-2, every 12 m Y3-5 CXR/colonoscopy: every 12 m Y1-5 | Clin exam/CEA: every 3 m Y1-2, every 6 m Y3-5 Colonoscopy: @ 12 and 36 m ** |
| Rosati (2016) [17] | 1228 | CRC, Dukes B2−C | Minimum 5 y | Clin exam/CEA and CA 19-9: every 4 m Y1-2, every 6 m Y3-4, every 12 m Y5 CXR/colonoscopy: every 12 m Y1-5 Liver US: @ 4, 8, 12, 16, 24, 16, 48 and 60 m | Clin exam/CEA: every 4 m Y1-2, every 6 m Y3-4, every 12 m Y5 Colonoscopy: @ 12 and 48 m Liver US: @ 4 and 16 m |
| Snyder (2018) [18] | 8529 | CRC, I−III | Minimum 5 y | High-frequency CT and CEA *** | Low-frequency CT and CEA *** |
| Treasure (2014) [19] | 216 | CRC, Dukes A-C | Minimum 18 y | Second look surgery upon CEA rise Clin exam: every 3 m Y1-2, every 6 m Y3-5 CEA: every month Y1-3, every 3 m Y4-5 | No additional diagnostics upon CEA rise Clin exam: every 3 m Y1-2, every 6 m Y3-5 |
| Wang (2009) [20] | 326 | CRC, Dukes A-C | Median 74 m | Colonoscopy/clin exam/CEA/abd CT or US/CXR: every 3 m Y1, every 6 m Y2-3, every 12 m Y4-5 | Colonoscopy: @ 6, 30 and 60 months Clin exam/CEA/abd CT or US/CXR: every 3 m Y1, every 6 m Y2-3, every 12 m Y4-5 |
| Wille-Jørgensen (2018) [21] | 2509 | CRC, II−III | Median 5 y | CT/CEA: @ 6, 12, 18, 24 and 36 m | CT/CEA: @ 12 and 36 m |
| Bornhak (2007) [60] | 670 | Breast, T1-4, N0-2 | Almost all patients 5 y | Clin exam/blood tests: every 3 m Y1-3, every 6 m Y4-5 Liver US/CXR: every 6 m Y1-5 Mammography: every 6 m Y1-3, every 12 m Y4-5 | Clin exam: every 3 m Y1-3, every 6 m Y4-5 Mammography: every 6 m Y1-3, every 12 m Y4-5 |
| Del Turco (1994) [61] Palli (1999) [62] | 1243 | Breast, T1-4, N−/+ | Almost all patients 10 y | Clin exam: every 3 m Y1-2, every 6 months Y3-5 Mammography: every 12 m Y1-5 CXR/bone scan: every 6 m Y1-5 | Clin exam: every 3 m Y1-2, every 6 months Y3-5 Mammography: every 12 m Y1-5 |
| Liberati (1994) [63] | 1320 | Breast, T1-3, N0-1 | Median 71 m | Clin exam/blood tests: every 3 m Y1-2, every 6 m Y3-5 Mammography/liver US/bone scan: every 12 m Y1-5 CXR: every 6 m Y1-5 | Clin exam/blood test: every 3 m Y1-2, every 6 m Y3-5 Mammography: every 12 m Y1-5 |
| Bjerring (2019) [71] | 183 | GOJ, gastric, pancreatic, I-III | Almost all patients 2 y | Clin exam/PET-CT/endoscopic US: every 3 m Y1, every 6 m Y2 | Clin exam: every 3 m Y1, every 6 m Y2 |
| Nabhan (2012) [76] | 703 | Prostate, I−III | Median 6.7 y | PSA test within 2 y after treatment | No PSA test within 2 y after treatment |

Abd = abdominal, CA 19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, clin exam = clinical examination, CRC = colorectal cancer, CT = computed tomography, CXR = chest x-ray, GOJ = gastro-oesophageal junction, m = months, MRI = magnetic resonance imaging, NR = not reported, NSCLC = non-small cell lung cancer, PET-CT = positron emission tomography − computed tomography, PSA = prostate specific antigen, US = ultrasound, w = weeks, y = years.

[a] Single chest, abdomen, and pelvis CT scan at 12−18 months if requested at study entry by hospital clinician; ** Only performed in patients at high risk for metachronous lesions (hereditary cancer, synchronous colorectal neoplasms); *** Classification of follow-up facility based. Expected number of scans/CEA measurements calculated through 2-level random intercept negative binomial model. High frequency facility defined as observed:expected ratio ≥1.

Table 2
Studies at high risk of bias.

| Author (year) | N | Cancer type, stage | Follow-up duration | Intensive follow-up approach | Comparison (reference) |
|---|---|---|---|---|---|
| Augestad (2013) [22] | 110 | Colon, Dukes A-C | 58% completed 2 y follow-up | Surgeon-led | General practitioner-led |
| Bergamaschi (1996) [23] | 800 | CRC, I-III | Minimum 60 m | Clin exam/CEA/liver US: every 3 m Y1, every 6 m Y2-5 CXR: every 3 m Y1, every 6 m Y2, every 12 m Y3-5 Endoscopy: every 12 m Y1-5 | Symptom-based |
| Borie (2004) [24] | 231 | CRC, Dukes A-C | NR | Clin exam: every 3 m Y1-2, every 6 m Y3-5 CEA/US: every 4−6 m Y1-3, every 12 m Y4-5 CXR: every 12 m Colonoscopy: every 36 m | Clin. Exam: at most every 6 m Y1-5 CEA/US: at most every 12 m Y1-3 CXR: at most every 12 m Y1-2 Colonoscopy: at most every 36 m |
| Castells (1998) [25] | 199 | CRC, I-III | Median 51 m | Compliant (>70% adherence) to follow-up | Non-compliant (<70% adherence) to follow-up |
| Coebergh (2018) [26] | 681 | CRC, I-III | Median 68 m for OS Median 34 m for DFS | Intensive (≥3 follow-up moments in first year) | Minimal (≤2 follow-up moments in first year) |
| Eckardt (1994) [27] | 212 | CRC, Dukes A-C | Mean 91 m and 94 m | Full compliance to endoscopic follow-up | Non-compliance to endoscopic follow-up |
| Gamboa (2020) [28] | 239 | CRC, IV (peritoneal) | Median 17 m | High frequency follow-up (every 2−4 months) | Low-frequency follow-up (every 6−12 months) |
| Hines (2019) [29] | 17,860 | CRC, II-III | Median 9.0 y and 9.6 y | More adherent to guideline recommendations | Less adherent to guideline recommendations |
| Hines (2020) [30] | 8783 | CRC, I | Median >10 y | 1 colonoscopy during follow-up or ≥2 colonoscopies during follow-up | No colonoscopy during follow-up |
| Hyder (2013) [31] | 507 | CRC, IV (liver) | NR | Follow-up with imaging (≥1 scan) | No imaging during follow-up |
| Kjeldsen (1997) [32] | 597 | CRC, Dukes A-C | NR | Clin exam/blood analysis without CEA/CXR/ colonoscopy: every 6 m Y1-3, every 12 m Y4-5, every 5 y Y6-15 | Clin exam/blood analysis without CEA/CXR/ colonoscopy: every 5 y Y1-15 |
| Körner (2005) [33] | 314 | CRC, Dukes A-C | Median 66 m | Guideline follow-up | No follow-up |
| Laubert (2010) [34] | 1469 | CRC, I-IV | Median 70 m | Intensive follow-up (>70% adherence) or Minimal follow-up (<70% adherence) | No follow-up |
| Mahboubi (2007) [35] | 389 | CRC, I-IV | NR | Regular (≥1 per 6 months) follow-up at GP or Occasional (<1 per 6 months) follow-up at GP | No follow-up |
| Mäkelä (1995) [36] | 106 | CRC, Dukes A-C | NR | Clin exam/CEA/CXR: every 3 m Y1-2, every 6 m Y3-5 Liver US: every 6 m Y1-5 CT abd/colonoscopy: every 12 m Y1-5 Sigmoidoscopy[a]: every 3 m Y1-5 | Clin exam/CEA/CXR/ sigmoidoscopy[a]: every 3 m Y1-2, every 6 m Y3-5 Barium enema: every 12 m Y1-5 |
| Ovaska (1990) [37] | 507 | CRC, Dukes A-C | 85% 5 y | Clin exam/CEA/ sigmoidoscopy: @3, 6, 12, 18, 24, 36, 48 and 60 m CXR/colography: every 6 m Y1, every 12 m Y2-5 | No follow-up |
| Pietra (1998) [38] | 207 | CRC, Astler-Coller B1−C2 | NR | Clin exam/CEA/US: every 3 m Y1-2, every 6 m Y3-4, every 12 m thereafter CXR/CT/colonoscopy: every 12 m Y1-5 | Clin exam/CEA/US: every 6 m Y1, every 12 m Y2-5 CXR/colonoscopy: every 12 m Y1-5 |
| Pugliese (1984) [39] | 177 | CRC, Dukes B−C | Median 33 m | Clin exam/blood tests - later including CEA: every 3 m Y1-2, every 6 m Y3-5 CXR/liver US/colonoscopy: | No follow-up |

Table 2 (*continued*)

| Author (year) | N | Cancer type, stage | Follow-up duration | Intensive follow-up approach | Comparison (reference) |
|---|---|---|---|---|---|
| | | | | every 6 m Y1-2, every 12 m Y3-5 | |
| Rulyak (2007) [40] | 1002 | CRC, 0-III | Median 3.6 y | ≥1 colonoscopies during follow-up | No colonoscopy during follow-up |
| Schoemaker (1998) [41] | 325 | CRC, Dukes A-C | 94% 60 m | Clin exam/CEA: every 3 m Y1-2, every 6 m Y3-5 CXR/liver CT/colonoscopy: every 12 m Y1-5 | Clin exam/CEA: every 3 m Y1-2, every 6 m Y3-5 |
| Secco (2002) [42] | 358 | CRC, Dukes A-C | Median 61.5 m (high-risk) and 42 m (low-risk) | High risk patients Clin exam/CEA: every 3 m Y1-2, every 4 m Y3, every 6 m Y4-5 Abd and pelvic US: every 6 m 1-3Y, every 12 m Y4-5 CXR/rectosigmoidoscopy[a]: every 12 m Y1-5 Low risk patients Clin exam/CEA: every 6 m Y1-2, every 12 m Y3-5 Abd and pelvic US: every 6 m 1-2Y, every 12 m Y3-5 CXR: every 12 m Y1-5 Rectosigmoidoscopy[a]: every 12 m Y1-2, every 24 m Y3-5 | Minimal follow-up not clearly defined |
| Sobhani (2018) [43] | 239 | CRC, II-IV | NR | Follow-up with whole body CT and PET-CT: every 6 m Y1-3 | Follow-up with whole body CT: every 6 m Y1-3 |
| Strand (2011) [44] | 110 | CRC, I-IV | NR | Surgeon-led | Nurse-led |
| Wattchow (2006) [45] | 203 | CRC, Dukes A-C | 87% 2 y | Surgeon-led | General practitioner-led |
| Zitt (2006) [46] | 430 | CRC, I-IV | Mean 49 m | Clin exam/CEA: every 3 m Y1-2, every 6 m Y3-5 CXR + abd US/ CT + colonoscopy: every 6 m Y1-5 (alternating per 6 m) Rectoscopy @ 3, 6 and 9 months or Non-standardised follow-up in hospital or at GP | No follow-up |
| Backhus (2016) [47] | 18,406 | NSCLC, I-II | NR | Clinical visitation within 4−8 m after treatment | No clinical visitation within 4−8 m after treatment |
| Benamore (2007) [48] | 75 | NSCLC, III | Median 77 m and 44 m | Follow-up within clinical trial Clin exam/blood analysis/CXR: every 2/3 m Y1-2, every 6 m thereafter CT chest and upper abd/MRI brain: every 6 m Y1-3, every 12 m thereafter | Non-trial follow-up Clin exam/blood analysis/CXR: every 3 m Y1-2/3, every 6 m Y3/4-5 |
| Crabtree (2015) [49] | 554 | NSCLC, I | NR | Routine CT-based follow-up | Routine CXR-based follow-up |
| Ho (2017) [50] | 263 | NSCLC, IB-II | NR | Frequency CT and/or clinical visits per or above guidelines | Frequency CT and/or clinical visits below guidelines |
| Karzijn (2016) [51] | 73 | NSCLC, I-II | NR | Follow-up with CT imaging | Follow-up with CXR only |
| Mayne (2020) [52] | 187 | NSCLC, IA | Median 36 m and 56.4 m | Early (6 ± 3 months) start of CT surveillance | Late (12 ± 3 months) start of CT surveillance |
| McMurry (2018) [53] | 4463 | NSCLC, I-III | Minimum 60 m | 3 months CT-imaging interval | 6 or 12 months CT-imaging interval |
| Monteil (2010) [54] | 69 | NSCLC, I-IIIA | Median 25 m and 29 m | PET-CT/Brain CT | Brain, chest and upper abd CT/ abd US/bone scintigraphy ** |
| Nakamura (2010) [55] | 1398 | NSCLC, I-III | Median 79 m | Follow-up by chest physician Clin exam/CXR: every 3−4 m Y1-3 CT: every 6 m Y1-3 | Follow-up by thoracic surgeon Clin exam/CXR: every 3−4 m Y1-3 |
| Pan (2015) [56] | 92 | NSCLC, IIB-IIIB | Median 23 m | Follow-up with CT imaging and a single PET-CT @ 9 m | Follow-up with CT imaging only |
| Reddy (2017) [57] | 200 | NSCLC, III | Median 59.4 m | Follow-up with PET-CT and CT alternating in Y1-2 | Follow-up with CT only |
| Sui (2020) [58] | 200 | NSCLC, I-III | 85% 5 y | WeChat app-based education | Regular rehabilitation program |

Table 2 (*continued*)

| Author (year) | N | Cancer type, stage | Follow-up duration | Intensive follow-up approach | Comparison (reference) |
|---|---|---|---|---|---|
| | | | | and rehabilitation program - including disease related education (once a week for 12w), rehabilitation exercise guidance (once a week for 40w), daily activity supervision (once a week for 12 m), and psychosocial support (every 2 weeks for 12 m) | |
| Virgo (1995) [59] | 182 | Lung (subtype NR), I-IIIA | Mean 3.3 y | Intensive follow-up, any of the following criteria: ≥4 visits and/or blood tests and/or CXR per year, ≥1 CT per year, or any bronchoscopy and/or sputum cytology | Non-intensive follow-up (none of the criteria met) |
| Grunfeld (2006) [64] | 968 | Breast, early stage | Median 3.5 y | Guideline follow-up carried out by cancer specialist | Guideline follow-up carried out by family physician |
| Koinberg (2004) [65] | 264 | Breast, I-II | NR | Physician-led Clin exam: every 3 m Y1-2, every 6 m Y3-5, and yearly thereafter Mammography: every 12 m Y1-5 | Nurse-led Clin exam: on-demand Mammography: every 12 m Y1-3, screening-programme thereafter |
| Lash (2005) [66] | 303 | Breast, I-II | Median 7.4 y | Number of consecutive years of guideline surveillance | (continuous analysis, no separate comparison group) |
| Lash (2006) [67] | 334 | Breast, I-IIIA | NR | One or more mammograms during follow-up | No mammograms during follow-up |
| Lash (2007) [68] | 812 | Breast, I-II | NR | Number surveillance mammograms received | (continuous analysis, no separate comparison group) |
| Lee (2015) [69] | 3770 | Breast, I-III | Median 7.1 y | Clin exam/blood analysis/ mammography/CXR/breast, abd and pelvic US/bone scans: every 3–6 m Y1-5, and yearly thereafter | Control group of patients lost to follow-up after adjuvant therapy |
| Paszat (2009) [70] | 901 | Breast, I-II | Median 141 m and 29 m | ≥1 surveillance mammography | No surveillance mammography |
| Peixoto (2014) [72] | 292 | Gastroesophageal, I-III | NR | Oncologist follow-up with Clin exam or Blood analysis or Imaging or endoscopy | Discharge to general practitioner |
| Sisic (2018) [73] | 587 | Gastroesophageal, I-III | Median 60.5 m and 68.5 m | Follow-up in cancer centre Clin exam/CT abd or abd US and endoscopy (alternating): every 3 m Y1-2, every 6 m Y3-4, every 12 m Y5 | Individual follow-up by other physicians |
| Tan (2007) [74] | 102 | Gastric, I-IV | Mean 3.4 y | >1 CT scans per year | ≤1 CT scans per year |
| Verschuur (2009) [75] | 109 | Gastroesophageal, I-IV | 98% 1 y | Physician-led follow-up | Nurse-led follow-up |

Abd = abdominal, CA 19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, clin exam = clinical examination, CRC = colorectal cancer, CT = computed tomography, CXR = chest x-ray, GOJ = gastro-oesophageal junction, m = months, MRI = magnetic resonance imaging, NR = not reported, NSCLC = non-small cell lung cancer, PET-CT = positron emission tomography – computed tomography, PSA = prostate specific antigen, US = ultrasound, w = weeks, y = years.
  [a] For rectal and sigmoid cancer patients only. ** Only in patients with symptoms possibly related to bone metastases.

CI 0.73–0.91) and an increased probability of curative intent treatment for recurrences (RR 1.60, 95% CI 1.21–2.11). An equally large, but non-significant, impact on CSS (HR 0.80, 95% CI 0.63–1.01) was observed. Considerable heterogeneity was present ($I^2$ 66–85% for the three outcomes) (Table 3).

In the eight studies (24%) considered to be at low risk of bias, including seven RCTs [14–17,19–21], no significant impact on OS (HR 0.99, 95% CI 0.92–1.06) and CSS (0.94, 95% CI 0.77–1.16) was observed with little to no heterogeneity ($I^2$ 7% and 0%). All low risk studies evaluated frequency of follow-up, of which three evaluated a symptom-based approach without use of diagnostics [14,15,19]. Primrose et al. also compared CT and CEA as diagnostic modalities during surveillance [15]. Although survival was not significantly impacted
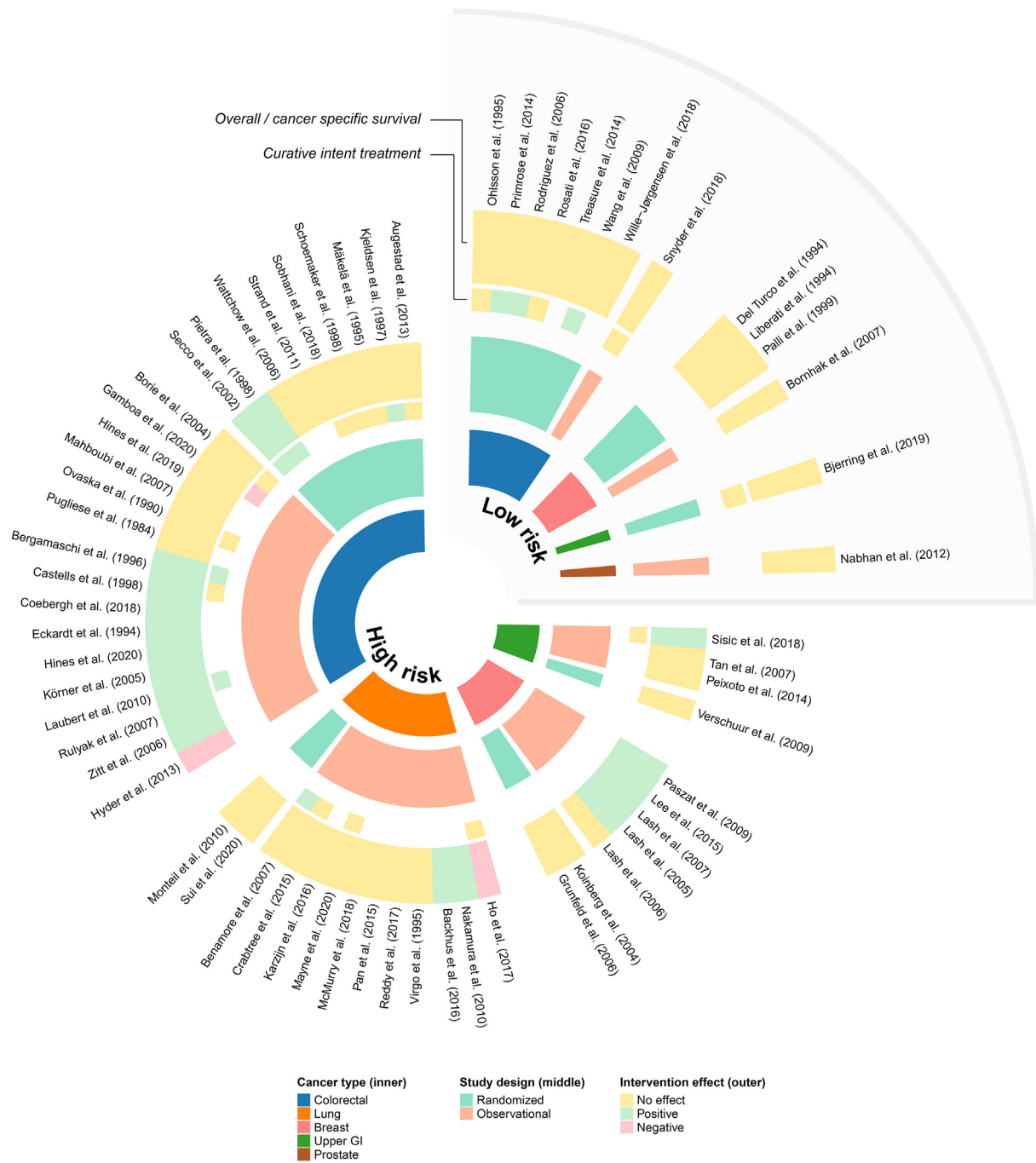
Fig. 3. Multi-layered circle plot summarising the reported effect in all 63 included studies, stratified by risk of bias. The inner circle represents cancer type, the middle circle study design, and the outer circle the effect of the intervention on overall or cancer specific survival, and treatment intent.

by follow-up strategy, intensive follow-up remained significantly associated with the probability of curative intent treatment for recurrences (RR 1.30, 95% CI 1.05−1.61) in low risk studies (I$^2$ 28%).

Twenty-five studies (76%) were deemed to be at high risk of bias, the majority being observational (N = 16, 64%) [22,32,36,38,41−45]. Most high risk studies evaluated frequency of follow-up (N = 18, 72%) [23−37,39,40,42]. Pooled effect estimates in high risk

colorectal cancer studies were larger for all outcomes evaluated, with considerable heterogeneity (Table 3).

### 3.3. Lung cancer

Within the thirteen lung cancer studies, 26,162 patients were included (Table 2). All of the studies identified were considered to be at high risk of bias, including two RCTs [54,58]. Five studies assessed frequency of follow-

Table 3
Meta-analysis per tumour type.

| Cancer type | OS | | | CSS | | | Curative treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | HR [95% CI] | $I^2$ | N | HR [95% CI] | $I^2$ | N | RR [95% CI] | $I^2$ |
| *All studies* | | | | | | | | | |
| Colorectal | 30 | 0.82 [0.73−0.91][a] | 85% | 11 | 0.80 [0.63−1.01] | 84% | 19 | 1.60 [1.21−2.11][a] | 66% |
| Lung | 12 | 0.94 [0.84−1.05] | 49% | 1 | 1.45 [0.84−2.5] | NA | 4 | 1.34 [0.82−2.20] | 39% |
| Breast | 8 | 0.80 [0.54−1.18] | 92% | 3 | 0.52 [0.27−1.02] | 94% | − | − | − |
| Upper GI | 5 | 0.79 [0.66−0.95][a] | 0% | | − | − | 2 | 1.25 [0.62−2.52] | 50% |
| Prostate | 1 | 1.00 [0.86−1.16] | NA | | − | − | − | − | − |
| *Low risk of bias* | | | | | | | | | |
| Colorectal | 8 | 0.99 [0.92−1.06] | 7% | 3 | 0.94 [0.77−1.16] | 0% | 6 | 1.30 [1.05−1.61][a] | 28% |
| Lung | − | − | − | − | − | − | − | − | − |
| Breast | 3[b] | 1.06 [0.92−1.23] | 0% | − | − | − | − | − | − |
| Upper GI | 1 | 0.78 [0.51−1.19] | NA | − | − | − | 1 | 0.92 [0.47−1.81] | NA |
| Prostate | 1 | 1.00 [0.86−1.16] | NA | − | − | − | − | − | − |
| *High risk of bias* | | | | | | | | | |
| Colorectal | 22 | 0.75 [0.65−0.86][a] | 87% | 8 | 0.74 [0.54−1.02] | 88% | 13 | 1.77 [1.06−2.94][a] | 74% |
| Lung | 12 | 0.94 [0.84−1.05] | 49% | 1 | 1.45 [0.84−2.5] | NA | 4 | 1.34 [0.82−2.20] | 39% |
| Breast | 5 | 0.68 [0.41−1.14] | 91% | 3 | 0.52 [0.27−1.02] | 94% | − | − | − |
| Upper GI | 4 | 0.79 [0.65−0.97][a] | 0% | − | − | − | 1 | 1.73 [0.84−3.59] | NA |
| Prostate | − | − | − | − | − | − | − | − | − |

CI = confidence interval, CSS = cancer specific survival, HR = hazard ratio, N = number of studies reporting on outcome, NA = not applicable, OS = overall survival, RR = relative risk, Upper GI = upper gastrointestinal.

[a] Statistically significant result.

[b] Long-term updates [62] from the study by Del Turco et al. [61] were used for the meta-analysis in breast cancer patients.

up [47,50,52,53,59], five the modalities used [49,51,54,56,57], one the setting in which follow-up was performed [58], and two evaluated multiple aspects [48,55]. Follow-up did not significantly impact OS (HR 0.94, 95% CI 0.84−1.05) (Table 3). Heterogeneity was moderate ($I^2$ 49%). Only one study reported on CSS, in which no significant survival difference was obtained [49]. Intensive follow-up did not increase curative treatment rates (RR 1.34, 95% CI 0.82−2.20, $I^2$ 39%), as reported in four studies [48−50,52].

### 3.4. Breast cancer

In total 10,585 breast cancer patients were included in eleven studies (Tables 1 and 2). Across all studies no significant impact of intensive follow-up on OS (HR 0.80, 95% CI 0.54−1.18) or CSS (HR 0.52, 95% CI 0.27−1.02) was observed (Table 3). Heterogeneity was considerable for both outcomes ($I^2$ 92% and 94%). None of the studies reported on the (curative) treatment for local recurrence or metastatic disease.

Four studies (36%) were considered to be at low risk of bias, including two RCTs [61,63], one long-term update of an RCT [62], and one prospective observational study [60]. All low risk studies compared different modalities used in the same frequency, generally every 3−6 months. When pooling the effects of individual studies, no impact on OS was observed (pooled HR 1.06, 95% CI 0.92−1.23), with no heterogeneity ($I^2$ 0%). None observed significant additional value of using multiple diagnostics (e.g. liver ultrasonography, chest radiography, laboratory tests) next to clinical examinations and mammography's. None of the studies reported on CSS.

Most of the seven high risk studies were observational (71%) [64,65]. In contrast to the low risk studies, all of the observational studies evaluated the frequency of follow-up, while the RCTs evaluated setting of follow-up. The randomised studies found no impact on OS when follow-up was performed by the family physician (HR 1.05, 95% CI 0.60−1.84) or the nurse practitioner (HR 1.22, 95% CI 0.58−2.57), compared to the standard hospital-based physician-led approach [64,65]. The studies evaluating the frequency of follow-up all assessed the impact of receiving one or more diagnostic evaluations (i.e. mammography or multiple diagnostics) to a nihilistic approach [66−70]. All but one study (80%) found that any follow-up significantly improved survival. Pooled OS (HR 0.68, 95% CI 0.41−1.14) and CSS (HR 0.52, 95% CI 0.27−1.02) estimates were non-significant, and high heterogeneity was observed ($I^2$ 91% and 94%).

### 3.5. Upper gastro-intestinal cancer

Five studies were identified in patients with upper gastro-intestinal cancers, including 1,273 patients in total (Tables 1 and 2). A significant benefit from intensive follow-up was observed, in terms of OS (HR: 0.79, 95% CI 0.66−0.95), with no heterogeneity ($I^2$ 0%). Intensive follow-up was not significantly associated with treatment intent (RR 1.25, 95% CI 0.62−1.52, $I^2$ 50%). None of the studies reported on CSS (Table 3).

Bjerring et al. conducted the only study in patients with upper-gastrointestinal cancers considered to be at low risk of bias, comparing imaging based to symptom based follow-up in patients with oesophageal, gastric,

and pancreatic cancer [71]. No significant difference in OS (HR 0.78, 95% CI 0.51−1.19), nor in the probability of being treated with curative intent for isolated locoregional disease (RR 0.92, 95% CI 0.47−1.81) could be demonstrated.

High risk studies were again mostly observational (75%) [72−74]. One study evaluated the frequency of follow-up [74], two the setting of follow-up [73,75], and one study evaluated multiple aspects [72]. When pooling the high risk studies, intensive follow-up significantly improved OS (HR 0.79, 95% CI 0.65−0.97, $I^2$ 0%) (Table 3).

### 3.6. Prostate cancer

Only one study evaluating follow-up in terms of survival was identified in patients with prostate cancer (Table 1) [76]. The study was observational and considered to be at low risk of bias. Nahban et al. performed a two-year landmark analysis, evaluating the frequency of prostate specific antigen (PSA) testing after prostatectomy or radiotherapy. Frequent PSA testing within the first two years after treatment did not impact OS (Table 3), neither in patients undergoing resection (HR 0.95, 95% CI 0.70−1.30), nor in patients receiving radiotherapy (HR 1.01, 95% CI 0.86−1.21) (combined HR 1.00, 95% CI 0.86−1.16).

### 4. Discussion

This meta-analysis provides a general overview on the impact of follow-up strategies on survival and treatment outcomes for five common tumour types. We found that for tumours other than colorectal and breast cancer, little to no high quality evidence is available to formulate evidence based follow-up guidelines upon. The impact of different follow-up strategies on CSS and treatment for recurrences could only be evaluated for colorectal cancer, as these outcomes were hardly reported in high quality studies for the other types of cancer.

When pooling the eight available colorectal cancer studies at low risk of bias, no significant OS (HR 0.99, 95% CI 0.92−1.06) or CSS (0.94, 95% CI 0.77−1.16) benefit was observed after intensive surveillance (i.e. more frequent imaging). These results are consistent with previous meta-analyses which only included RCTs [77,78]. Other meta-analyses did find a survival benefit in terms of OS, but none regarding CSS [79−84]. In line with our results, all available meta-analyses evaluating colorectal cancer follow-up found that intensive follow-up increases the probability of receiving curative intent treatment for recurrent disease, leading to several hypotheses. The consistently higher curative intent treatment rates suggest that intensive follow-up after colorectal cancer surgery successfully meets its main objective (i.e. early detection of relapses to increase

treatment possibilities). Nevertheless, this does not translate in a survival benefit at a population level. The cure rate of approximately twenty percent after local treatment for metastatic colorectal disease shows the need for some form of follow-up [85]. Both intensive and less intensive follow-up approaches (e.g. mostly based on sequential CEA measurements) may however both be equally able to identify those patients that will benefit most from local therapies. Other factors (e.g. pre-existing tumour biology, host immune response) than the timely detection of recurrences may ultimately have a larger impact on survival after colorectal cancer resection [86].

In breast cancer, the low risk studies strongly suggest that frequent, multimodality follow-up (i.e. including MRI, bone scans, and laboratory assessments) does not provide benefits for patients in terms of survival, compared to a mammography based approach (HR 1.06, 95% CI 0.92−1.23 for OS). Low-frequency imaging surveillance using mammograms is being advocated by the majority of guidelines [87,88], but has mostly been compared to symptom-based follow-up in observational studies prone to bias (HR 0.68 (95% CI 0.41−1.14) for OS, 0.52 (95% CI 0.27−1.02) for CSS) [64−70]. The effectiveness of annual mammography surveillance therefore remains questionable, especially since none of the breast cancer studies report data on the (curative) treatment of recurrent disease or novel primary tumours. Despite the lack of evidence, a mammography frequency similar to that of most breast cancer screening programs (e.g. every 1−3 years) [89] seems acceptable from both a medical and an economic point of view. Interestingly, no high quality data is available on the relationship between follow-up strategy and the other outcomes evaluated in this study (i.e. CSS, treatment intent). Such data would provide additional insights regarding follow-up in this population.

The quality of the 13 identified lung cancer and the 5 upper-gastrointestinal cancer studies was mostly poor, with 100% and 80% of studies being at high risk of bias. A potential OS benefit was observed in upper-gastrointestinal cancer studies (HR 0.79, 95% CI 0.66−0.95). For both tumours, most guidelines either refrain from advising on the frequency of diagnostic or clinical evaluations, or continue to advise imaging, blood tests, and clinical evaluations every 3−6 months during the first years after surgery [90−95]. This meta-analysis shows that any policy making with regards to follow-up for these cancer types is not based on robust evidence. Given the outcomes in breast and colorectal cancer, no large effect is to be expected from frequent multimodality follow-up. So while high quality studies are formally needed to evaluate effectiveness of intensive follow-up in lung and upper gastro-intestinal cancers, combining survival with other relevant end-points (e.g. quality of life, cost-effectiveness) should be considered to maximise return of investment.

For prostate cancer only one study was identified. Follow-up for prostate cancer differs from other types of cancer, as the strategy solely relies on serum tumour marker measurements (i.e. PSA). Intensive prostate cancer follow-up thus remains relatively non-intensive, when compared to follow-up for other cancers. In addition, serum PSA measurements are relatively cheap and can easily be performed in a general practitioner setting. As only 1−10% of deaths in prostate cancer patients relate to cancer progression, little may be expected from a highly frequent oncological follow-up program in this population as a whole, at least in terms of a survival benefit [96]. After a median follow-up of 6.7 years, Nabhan et al. indeed found no impact of frequent PSA testing during the first two years, neither after resection (HR 0.95, 95% CI 0.70−1.30) nor radiotherapy (HR 1.01, 95% CI 0.86−1.21). None of the follow-up guidelines for prostate cancer make recommendations on the actual frequency of follow-up, but all advocate a frequency depending on patient characteristics and preference. A more frequent approach may be applied in patients needing reassurance and vice versa. Such an approach may also be suitable in patients with other types of cancer, especially when a reliable serum tumour marker is available (e.g. CEA in colorectal cancer and gastric cancer). Dutch and Scandinavian national guidelines for colorectal cancer are currently moving in this direction, with only one or two scheduled imaging procedures advocated during follow-up [97−99]. The lack of evidence favouring such an approach in non-colorectal cancer patients remains however.

Multiple studies comparing different diagnostic modalities in multiple types of cancer were identified in this review, including several high quality RCTs [15,61−63]. None of these studies demonstrated that the addition of more sensitive diagnostics actually improves survival outcomes, while they are associated with increasing health costs. During follow-up, adding and combining several different diagnostics apparently does not provide the expected survival benefit. Given the currently presented lack of evidence it might be worthwhile to reconsider the frequent and combined use of multiple diagnostics during follow-up, especially in colorectal cancer patients. Importantly, it has to be stressed that these results do not declare oncological follow-up practices futile, and certainly do not propose a nihilistic, symptom-based, follow-up approach for all cancer patients. However, a change of approach may be necessary and beneficial. For instance, out-of-hospital follow-up (or at least partly), in close collaboration with the general practitioner, could be an appealing alternative from a patient wellbeing and economic point of view [100,101]. Both of these outcomes should play a major role in deciding which type of follow-up is most appropriate for cancer patients. Adequate (meta-analytic) data on quality of life and cost-effectiveness is currently lacking, but one could assume an impact of follow-up on both. Anxiety, patient satisfaction, costs, but also physical wellbeing and post treatment pain are all important aspects that should be taken into account when evaluating different follow-up approaches.

This meta-analysis should be evaluated in light of its limitations. Few studies with long-term follow-up (i.e. ten years or more) were identified. Long-term updates from high quality follow-up studies should be pursued, as the impact of an increased curative intent treatment rate for recurrences may not be visual yet after an initial five years of follow-up. In addition, many of the studies lacked statistical power to detect survival differences between follow-up approaches, and one could argue that the same may apply to the currently performed meta-analyses.

## 5. Conclusion

This meta-analysis provides a broad perspective on the available evidence with regards to oncological follow-up after curative intent treatment for common solid cancers. It shows that little high quality data is available for tumours other than colorectal and breast cancer. Amongst the high quality studies identified, intensive follow-up approaches do not seem to prolong survival, despite resulting in high curative intent treatment rates for colorectal cancer.

### Disclosures

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### Conflict of interest interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.07.025.

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