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Assessment of cognitive function after surgery for colorectal cancer – a scoping review

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Abstract

Objective

Colorectal cancer is primarily treated with surgery. Major surgery and older age are risk factors associated with postoperative decline in cognitive function. In clinical research, a wide range of instruments have been used for the assessment of cognitive function. There are no clear criteria for the measurement of postoperative cognitive dysfunction.

This scoping review aimed to map how and when cognitive function has been assessed after surgery for colorectal cancer and the incidence of postoperative cognitive decline reported.

Design

A systematic scoping review following the JBI approach. The searches were done in Scopus and PubMed, with the last search in January, 2023.

Inclusion criteria was reports of postoperatively assessed cognitive function outcomes in adults who had colorectal cancer surgery where the first assessment was done within 1 year of surgery.

Results

In total, 50 reports were included (16 clinical trials, 33 cohort studies, and one case report). Cognitive function was assessed with patient-reported outcomes measures, clinical screening tools, neurophysiological testing and complication classification. The definition was most often related to the specific instrument, as predefined cut-off or change from baseline. Assessments were performed between 1 h and 36 months after surgery – few reports included follow-up both within and after 30 days postoperatively. Incidence of cognitive decline varied considerably (0-64%), depending on the instrument, definition criteria and time of assessment. Most studies reported a decline in cognitive function after surgery with recovery during follow-up.

Conclusions

This study showed a heterogeneity in the choice of assessment method and measurement criteria for cognitive dysfunction after colorectal cancer surgery. A more unified measurement approach in further research would be beneficial to evaluate post-operative cognitive function and understand its impact on the daily lives of patients with colorectal cancer.

Trial registration

Protocol registered at Open Science Framework, DOI:10.17605/OSF.IO/2M3DT

Strength and limitations of this study

- This review is following a systematic approach with a preregistered protocol
- Search strategy was developed, and searches conducted by experienced librarians
- This is the first review on cognitive changes after surgery with focus on patients with colorectal cancer
- There was no critical appraisal for methodological limitation or risk of bias assessment preformed for included studies

Introduction

Cognitive functions, such as memory, attention and executive functions, can decline after surgery(1). Older age is a risk factor(1, 2), but 30-40% of all adults have been reported to develop postoperative cognitive dysfunction or decline (POCD) after major non-cardiac surgery(3). Generally, it seems to be a temporary condition(2) but patients older than 60 years have an increased risk of persistent cognitive dysfunction 3 months after surgery(3). Colorectal cancer is one of the most common types of cancer worldwide and is primarily treated with surgery(4, 5). Considering the high incidence of colorectal cancer, particularly among older adults, a substantial number of patients could be at risk for developing cognitive dysfunction after colorectal surgery.

Postoperative cognitive dysfunction is a research construct and there has been no standardised definition(2, 6). In 2018, the international and multidisciplinary Nomenclature Consensus Working Group published a recommendation on cognitive changes after surgery(6). The group aimed to align the terminology of postoperative changes to that of the clinical classification of cognitive function in general. The recommended terms were *delayed neurocognitive recovery* in case of occurrence during the first 30 days after surgery and *postoperative neurocognitive disorder* for diagnosis between 31-365 days after surgery. They further recommended the use of the Diagnostic and Statistical Manual for Mental Disorders' (DSM-V) criteria for neurocognitive disorder. For diagnosis, DSM-V requires subjective complaints as well as objective testing and specifies that everyday living is hindered at least in terms of instrumental activities (e.g., taking medication, and paying bills)(7). For classification DSM-V also states that cognitive deficits are not present solely as a component of delirium.

The assessment of the patients' function after surgery is an important issue since postoperative recovery, of which cognitive function is an integrated part, is prognostic for long-term recovery and has economic implications(8). A long-term follow-up of a Danish cohort found that patients who developed postoperative cognitive dysfunction after non-cardiac surgery retired earlier from the labour market and incurred higher social transfer payments(9). It has also been found that those with postoperative cognitive dysfunction at discharge had higher mortality within 30 days and those with persistent dysfunction after 3 months had higher mortality during the first year after surgery(3). While cognitive screening is recommended in American Cancer Society's survivorship care guidelines for colorectal cancer, it is only mentioned in association with chemotherapy (10).

The objective of this review was to map how cognitive dysfunction has been defined and assessed after surgery for colorectal cancer. The aims were to identify research reports of cognitive function after

colorectal cancer surgery, explore the incidence of cognitive changes, clarifying the definitions and criteria used and describe how cognitive function has been assessed. The review questions were identified as:

- How and when was cognitive function assessed after colorectal cancer surgery?
- What definition and nomenclature were used to describe cognitive changes?
- What outcome of cognitive function was reported after surgery?

The investigative and explorative nature of the research made it suitable for using a scoping review approach. At the start of this project, we found no registered protocol for systematic reviews at PROSPERO for the assessment of cognitive dysfunction after colorectal surgery, nor any scoping review registered at Open Science Framework. No published protocols or reviews were found on the subject when searched in PubMed, Scopus, Cochrane Database of Systematic Reviews and JBI Evidence Synthesis.

Methods

The protocol based on the JBI methodology(11) containing the objectives, inclusion criteria and methods for this scoping review was registered on July 24, 2021 at Open Science Framework, DOI 10.17605/OSF.IO/2M3DT. The registration was made before the screening of results had begun.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) was followed(12). The checklist is available in Supplement I. Patients or the public were not involved in the design, conduct, or reporting of this review.

Inclusion criteria

The review included reports on primary research studies. The languages were limited to English and the Scandinavian languages (Norwegian, Swedish, and Danish). No restrictions were applied based on the year of publication.

Population was adults with colorectal cancer, the concept examined was outcomes of cognitive function within the context postoperative assessment the first year after cancer surgery.

The criterium of assessment within 1 year was added after protocol registration to align with the recommended temporal specification for postoperative cognitive changes, i.e., only in the first 12 months after surgery(6).

Search strategy

The main search was conducted by librarians at the Biomedical Library, University of Gothenburg, on April 23, 2021, in PubMed (via Medline) and Scopus databases. A subsequent search was made on January 3, 2023.

Search on Scopus:

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

In addition to database searches, bibliographic searches were conducted. Excluded review articles that contained key terms in the title (colorectal cancer or surgery, cognitive function, or effects of cancer treatments) were scanned for relevant sources. This was repeated for all reports included in the full-text examination. The complete database search strategy is available in Supplement II.

Screening and selection

After the removal of duplicates, search results were transferred to the web-based screening tool Rayyan(13). Two blinded reviewers screened titles and abstracts. Conflicts were discussed, and the senior author had the last say if a consensus was not reached. Full-text screening was performed by one researcher in EndNote(14). Exclusion criteria for all excluded reports were confirmed by another researcher.

The exclusion criteria for screening had no hierarchy, and the first relevant exclusion criterium was used for classification. Predefined reasons for exclusion in the title and abstract examination were protocol or review, not primary research, and no participants with colorectal cancer or surgery. During the screening process, the following exclusion criteria were added; metastatic surgery (including HIPEC) and focus on effects of chemotherapy on cognitive functions since it is not relevant to primary colorectal

surgery; delirium assessed only by a clinical definition (i.e., no cognitive testing); and no assessment within 1 year of surgery.

Data charting

Data was extracted by one researcher. For the initial search, the software NVivo(15) was used in qualitative and iterative process to categorise text and figures depending on content relevant to the review questions. Data were then charted in an Excel spreadsheets using Colectica(16) for metadata. For the subsequent search data was charted directly to the spreadsheet. The results were then compiled into relevant tables and charts. All charted data were controlled for accuracy by a second researcher.

Data were charted for study characteristics such as aims, methodology and study population. Data relevant to review questions were nomenclature, definitions and instruments used. The time of assessment was charted as months, days or hours as specified in each report. Cognitive outcomes were charted as frequency and if decline and recovery occurred and differences between compared groups. Since not all reports used statistical testing for within-group comparison, numerical values were compared as presented. Details of all charted variables used in this review are presented in the metadata in Supplement III.

Results

After the removal of duplicates, 1136 records were screened in title and abstract examination. There were 23 reports identified from other sources (Fig 1 (17)). Out of the 205 articles that were subjected to full-text examination, 50 were included. Supplement IV includes a summary of data relevant to the review questions from all included reports.

The included reports were published 2000-2022. There were 33 observational cohort studies, 16 reports of controlled trials, and one case report. The aim of reports was mainly to investigate cognitive function (38%), quality of life (40%) or recovery after surgery (18%). Table on characteristic for all included sources is in appendix.

Forty study populations were exclusively patients with colorectal cancer, of the remaining study populations colorectal cancer patients comprised 19-89%. Sample sizes in observational studies ranged 11-1129 and in clinical trials 40-281. Across all studies, there was a mean of 46% female participants, and the average age reported was 66 years, covering a range of 18-99 years. The study populations were mainly from Europe (48%) and Asia (42%), the remaining reports had populations from Australia, Brazil,

Canada, and USA. There was also one international online population(18). In five reports, the participants had received no other cancer treatment than surgery(19-23). Information on adjuvant treatment was given in twenty reports.

Perioperative intervention concerning anaesthesia (types of drugs or procedural aspects) was used in 81% (n=13) of the clinical trials with dexmedetomidine being used in half of those (n=6). Observational studies compared groups most frequently according to surgical method or procedure (n=8), healthy controls or the general population (n=6), patients' age (n=5) or whether postoperative cognitive decline developed or not (n=5).

Assessment of cognitive function

Cognitive function was generally assessed with questionnaires or screening tools (fig 2). The two other assessments methods were neuropsychological testing and complication classification. More than one type of assessment method and instrument could be used in the same report. See supplement V for full list of instruments. A separate assessment of postoperative delirium was made in eight reports(19, 24-30), and instrumental activities of daily living (IADLs) were reported after surgery in two sources(27, 31).

A total of six questionnaires, five previously described and one novel(18) was used for patient-reported outcomes. Answers to questionnaires were collected by in person or telephone interviews or self-administered during visits, online or at home. The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire - Core 3.0 (EORTC QLQ-C30) was the most frequently utilized instrument overall. Studies that utilized patient-reported outcomes were generally observational studies with focus on quality of life. One clinical trial used self-reported outcome of cognitive function(32).

Five different screening tools were represented with the Mini-Mental State Examination (MMSE) as the most utilized. When specified, screenings were done by trained personnel, often the same individual for all assessments, and with the assessor blinded to the patient's intervention group. Screening tools was used in all but two clinical trials. In reports with the aim to investigate cognitive function screening tools were the most frequent instrument employed (12/19).

Two reports measured cognitive dysfunction as a complication, both were observational studies reviewing patient records and grading with the Clavien-Dindo classification(33, 34). Nine reports assessed cognitive functions with neuropsychological testing employing a wide range of tests for several cognitive domains such as processing speed, attention, and verbal memory. Tests could be used either together as a battery with a composite score or as individual tests, reported separately. The time

requirement for neuropsychological testing was given in three reports, 30, 60 and 90 min. When reported, testing was done in a quiet environment and by trained personnel. There were two computerized tests, the Attention Network Test (ANT) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Neuropsychological testing was used in three clinical trials, once as the only assessment method(28) and otherwise in combination with a screening tool(25, 35). When reported separately return to preoperative values occurred later when assessed with neuropsychological testing than the screening tool(25). In one case both CANTAB and a battery of seven individual neuropsychological tests were uses in the same report(23) and the association between the neuropsychological testing methods was stated as weak-to-moderate.

Across studies, cognitive assessment was performed in the shorter term, 1-12 hours, and 1-30 days after surgery, and in the longer term, 2-36 months after surgery. Most reports had a follow-up only within 30 days (48%) or only after 30 days (40%). One clinical trial had follow-up after the first 30 days(32). Cognitive function was assessed up to 11 times, including baseline, with a mean of three assessment points. There were six cross-sectional reports.

Nomenclature and definition

Impairment was the most frequent term to describe cognitive function decrease in general, followed by dysfunction, both terms occurred in several combinations. Neurocognitive was used in combination with impairment, decline, deficit, and dysfunction. About half of the reports utilized more than one term. Two reports referred to problems with concentrating and memory without any generic term. Sixteen reports used cognitive or mental function, capacity, or ability without any term indicating a decline in function.

A narrative definition of postoperative cognitive dysfunction as a concept was absent in most reports. When present, it concerned the decline of cognitive functions such as memory, executive control, and attention. Two reports also mention decline in social ability(36, 37). Four reports included symptoms such as confusion, disorientation, anxiety, agitation, or delirium in their definition(22, 36, 38, 39). Two reports stated that no abnormalities in cognitive function should have been present preoperatively(35, 39).

A little more than half of the reports presented criteria for measurement of cognitive dysfunction. Instrument-specific criteria were most common. Both predefined cut-offs and change from baseline was used, with or without subdivisions. Instrument-specific criteria were used with screening tools and

questionnaires, for neuropsychological testing general criteria were more common (table 1). The Z-score was the most common general criteria, defined in four reports. Occurrence of specific or any symptoms of cognitive decline was also used as criteria both with questionnaires and complication classification. There was also a vague definition (i.e., the lower the score, the lower the function).

Table 1. Criteria for measurement of cognitive dysfunction

Instrument specific	Utilised with	Comment
Cut-off	MoCA, MMSE, PtDATA,	
Cut-off with subdivision	HSD-R, MMSE, SPMSQ, EORTC QLQ-C30	
Decrease from baseline	AMT, MMSE, SPMSQ	
Decrease from baseline with subdivisions	EORTC QLQ-C30	Based on EORTC's guidelines
Instrument general	Utilised with	Comment
Z-score (with cut-off)	Neuropsychological tests, MMSE	
Lowest quartile	EORTC QLQ-C30	
Global deficit score (with cut-off)	Neuropsychological tests	T-score converted to 0-5
Standard deviation(s)	Neuropsychological tests, FACT-Cog	In relation to healthy control or baseline
Other	Utilised with	Comment
Specific/any symptom	Clavien-Dindo classification, Survivorship care plan tool, EORTC QLQ-C30	
Lower score = lower function	MMSE	

MoCA - Montreal Cognitive Assessment, MMSE – Mini-Mental State Examination, PtDATA - Patient's Disease and Treatment Assessment Form—General, HDS-R - Hasegawa's Dementia Scale – Revised, SPMSQ - Short Portable Mental Status Questionnaire, EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0, AMT - Abbreviated Mental Test, FACT-Cog - Functional Assessment of Cancer Treatment – Cognitive function issues

Outcome of cognitive assessments

Of the reports that had comparable preoperative values, 86% (30/35) showed a decline at the first follow-up after surgery. The reports not showing decline had follow up at 1 month as the earliest(24, 40-43). Of the reports showing decline, one third (10/30) had first follow-up after the first 30 days. Full or partial recovery occurred in most reports (fig 3). Recovery occurred at the earliest 1 day after surgery and at the latest after 24 months. In four reports, no recovery occurred within the follow-up period (5 days-12 months)(19, 31, 35, 44). In seven reports, there was a decline of function after a previous assessment had shown recovery.

Incidence of cognitive dysfunction after surgery

The frequency of cognitive dysfunction after surgery was presented in 20 reports. Across these, the instruments for assessment, measurement criteria for dysfunction, and follow-up periods differed (table 2). Postoperative incidence ranged from 0-64%, incidence of cognitive dysfunction at baseline was reported in three reports, 8.2-28%.

Table 2. Reports with frequency of cognitive dysfunction in clinical trials

2a - Reports with frequency of cognitive dysfunction in clinical trials						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Chen, 2020	88	MMSE	Score <28	Day 1 & 3	16.3-64.4% (in total)	Dexmedetomidine intervention
Liu, T., 2021	100	MMSE	Z-score ≤ -2	1 day 2 days 3 days	10-25% 8-16% 4-10%	Transcutaneous electrical acupoint stimulation (TEAS) intervention
Zhang, J., 2019	140	MMSE	Not reported	1 day 3 days	8.8-21.7% 0-13.3%	Dexmedetomidine intervention
Bao, 2020	178	MMSE	Not reported	3 days	8.4-22.9%	Dexmedetomidine combined with ulinastatin intervention
Ding, 2022	40	Battery of 5 neuropsychological tests and HDS-R	>1 SD decline on ≥2 tests	5 days	5-25%	Dexmedetomidine intervention
Liu, Y., 2020	96	MMSE	>2 points decrease	7 days	12.5-29.2%	Dexmedetomidine combined with epidural blockade intervention
Wang, P., 2021	120	MMSE	≥3 points decrease	7 days	5.1-16.4%	Probiotics intervention 43% colorectal cancer patients in study population
Wang, Y., 2020	281	SPMSQ	>2 errors	Before surgery 30 days	16.3-17.1% 7.4-25.5%	Tailored Family-Involved Hospital Elder Life Program (t-HELP) intervention 19% colorectal cancer patients in study population
2b - Reports with frequency of cognitive dysfunction in observational studies						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Vardy, 2014	363	Battery of 7 neuropsychological tests, CANTAB FACT-COG	GDS* >0.5 >2 SD below HC on ≥1 test, or >1,5 SD on ≥2 below HC >1,5 SD below HC (≤119)	Before adjuvant treatment	30-47% 33-51% 18.5-21%	Cross-sectional Comparing localised to metastatic cancer patients Healthy controls (HC) 13-17% with neuropsychological testing, 17 % FACT-COG *GDS – Global deficit score
Lin, 2014	50	Battery of 7 neuropsychological tests	Z-score ≥1.96 on ≥2 test or	7 days	34%	46% colorectal cancer patients in study population

			composite Z-score			
Wu, 2016	110	CANTAB	Z-score <-1.96 on ≥2 test or combined Z-score <-1.96	7 days	26.4%	
Zhang, Y., 2019	77	Battery of 3 neuropsychological tests and MMSE	Z-score >1.96 or combined Z-score ≥1.96	7 days	24.7%	
Li, 2013	114	Clavien-Dindo classification	≥ grade 1	Within 30 days	1.8%	Complication defined as “Delusions requiring medical treatment” 37% colorectal cancer patients in study population
Fagard, 2017	190	Clavien-Dindo classification	≥ grade 1	Within 30 days	16.6%	Complication defined as “Neurological - including altered mental function”
Samuelsson, 2019	49	MMSE	Score <24	Before surgery 1 months 6 months 12 months	8.2% 5% 2.5% 2.7%	
Couwenberg, 2018	272	EORTC QLQ-C30	>10 points decrease (since baseline)	3 months 6 months 12 months 18 months 24 months	39.6-41.1% 35.2-41.1% 22.7-30.5% 18.5-33.3% 20.0-29.4%	Comparing abdominoperineal resection with low anterior resection
Vardy, 2021	206	Patient’s Disease and Treatment Assessment Form—General	≥4 (out of 10)	11 months 14.5 months 23 months	≈18-21% ≈14-17% ≈17-20%	Two separate symptoms “Trouble concentrating” and “Problems with memory”. 68% colorectal cancer patients in study population
Deckx, 2015	321	EORTC QLQ-C30	Score <67. (lowest quartile)	Before surgery 12 months	18-28% 26-31%	Comparing older (≥70) cancer patients to younger Older controls: 22% at both assessments 24% colorectal cancer patients in study population
Arndt, 2004	309	EORTC QLQ-C30	Any level of concern	12 months	55.9%	Cross-sectional
Frick, 2017	1129	Internet-based tool for the creation of survivorship care plans	Answer “yes,”	12 months	48.6%	Cross-sectional 89% colorectal cancer patients in study population

MMSE – Mini mental state examination, HDS-R - Revised Hasegawa's Dementia Scale, SPMSQ - Short Portable Mental Status Questionnaire , CANTAB – Cambridge Neuropsychological Test Automated Battery, FACT-COG – Functional Assessment of Cancer Therapy – Cognitive, EORTC QLQ-C30 - The European Organization for Research and Treatment of Cancer, Quality of Life of Cancer Patients

There were eight clinical trials presenting incidence, most of them had one assessment within 7 days of surgery (table 2a). The highest incidence reported was 64%, which represented a total of patients with cognitive dysfunction at postoperative day 1 and 3 in a control group(39). A 0% incidence was reported 3 days after surgery in an experimental group(22). Across all reports the incidence ranged 8.8-25% at the earliest follow up, 1 day after surgery. At 7 days after surgery an incidence of 5-29% was reported across all reports. All reports with more than one postoperative follow-up showed decreasing numbers of cognitive dysfunction over time. One study reported baseline incidence of 16-17%, at follow-up, 30 days after surgery, the incidence was lowered in the intervention group, and increased in the control group(27).

For the observational studies (table 2b) the highest incidence was 56%, reported in a cross-sectional report 12 month after diagnosis(45). The remaining reports with data for 12 months had an incidence between 2.7-49%. The lowest incidence reported was 1.8% as a total within 30 days of surgery(34). At 7 days after surgery an incidence of 25-34% was reported across all studies. In the reports with more than one postoperative assessment incidence generally decreased with time. At the latest follow-up, around 2 years after surgery, incidence ranged 20-29% across reports. One study reported incidence for older persons without cancer as 22% which was stable after 12 months, while the incidence increased for cancer patients(31). A cross-sectional report showed differences in incidence with neuropsychological testing but not with self-reported measurers when comparing cancer patient to healthy controls(23).

Discussion

The 50 reports in this review assessed cognitive function after surgery using a diversity of methods and definitions. Due to the heterogeneity across definitions and assessment methods, it was difficult to synthesize information, and reach firm conclusions regarding incidence of cognitive decline after colorectal cancer surgery. Nevertheless, decline in cognitive function was found in more than 80% of the reports with preoperative levels, regardless of the instrument and the specific definition. Collectively, the data suggests that changes in cognitive function do occur in colorectal cancer patients who received surgery.

As with all reviews, the current work has some inherent limitations. It is always the possibility that some relevant sources have been missed. However, the findings in this review are consistent with the broader literature. The EORTC-CRC Q30 was the most used instrument when measuring cognitive function after chemotherapy in a colorectal cancer population(46) and the MMSE is the mostly used screening tool for

postoperative cognitive assessment(1). Since this scoping review had an exploratory focus there was no formal rating of the quality of evidence. A general concern with the data in this review, however, is that a large portion is obtained through self-report or screening tools. Subjective complaints of cognitive function are poorly correlated with objective testing in cancer patients(23, 47). It has therefore been suggested that subjective complaints might be an indicator of anxiety and depression rather than cognitive dysfunction(47, 48). It is recommended that cognitive changes after surgery should be assessed with neuropsychological tests for specific cognitive domains rather than with screening tools(6, 49). Among the reports in this review employing objective measurements, the use of screening tools was twice as common as neurophysiological testing. Of the studies that aimed to investigate cognitive function, fewer than half used neurophysiological tests. There has been discussion on whether screening tools are appropriate or not when detecting postoperative cognitive dysfunction(2), for detecting cognitive changes after cancer treatment screening tools are however not considered sufficient(50). Another concern with the data is the potential overlap between postoperative decline of cognitive functions and postoperative delirium(6, 51). Delirium has its own diagnostic definition, and focuses on awareness and by definition, to diagnose neurocognitive disorder, cognitive deficits cannot be present solely as part of delirium(7). Only eight reports in this review performed a separate assessment of delirium making it uncertain in the other studies whether the cognitive decline reported was delirium induced or not, at least in the period directly after surgery when there is a risk of postoperative delirium(52).

Decline of cognitive function in the first 30 days after surgery is defined as *delayed neurocognitive recovery* in the recommendation on terminology of cognitive change after surgery as this period is affected by complicating factors such as delirium, immobility and analgesic medication(6). About half of the reports in this review reported only on the period within the first 30 days and with only one of the interventional studies having follow-up after 30 days it is not known if the effects of interventions persist after the recovery window. Overall, it has been questioned if postoperative cognitive dysfunction persists over time(2). A recently published study indicates that there is no cognitive impairment in the long term for colorectal cancer survivors(53). In this review recovery of cognitive function was reported in all but a few reports with preoperative values and follow-up after 30 days. Incidence in included reports decline over time. However, the incidence of cognitive dysfunction after surgery might be underestimated during long-term follow-up due to the inability of patients with the worst declines to participate in studies(54). This selection bias could also inflate reports of cognitive recovery since the

study population may have a higher mean function over time as those with lower scores cannot continue their participation.

The heterogeneity shown in this review regarding instrument and criteria of measurements are similar to a recent review on cognitive impairment after chemotherapy in colorectal cancer patient(46). How to best measure cognitive function is beyond the scope of this review. However, advocates for patient-focused care have stressed that when assessing recovery after surgery, the patient should act as their own control(8). Measurement criteria using that approach would reduce the risk that a decline in a person with normal high or low function might go unnoticed if they remain above or always was below a predefined threshold for impairment(7). There is of course the discussion of what changes should be considered significant and the point of interest is perhaps better focused on if the functional decline affects the patient's daily life or not. Assessment of instrumental activity of daily living (IADLs) are considered a good indicator of problems derived from subtle cognitive decline(6, 7). Yet only two reports in this review reported IADLs.

As there was no formal rating of the quality of evidence included in the scoping review, the overall conclusions are considered to have low evidence. Nevertheless, a majority of the reports in this review noted cognitive functional decline in the study populations with comparable preoperative levels. When it comes to colorectal cancer patients, adjuvant treatments as well as the cancer itself need to be considered as causative factors for cognitive decline(55). A holistic approach to cognitive decline for all colorectal cancer treatments and the cancer itself would surely be beneficial. Therefore, extending recommendation of cognitive screening of patients receiving chemotherapy to all colorectal cancer survivors, regardless of treatment modality, could be of value and requires further investigation, especially considering that the existing recommendation has the lowest level of evidence(10). To strengthen the evidence on cognitive decline after colorectal cancer surgery neurophysiological testing should likely be considering worth the effort in future research. Future research would also do well to considering separate assessment of delirium. Especially when assessing cognitive function soon after surgery, but it has implication also in the long run since there is an indication that those with postoperative delirium are less likely to recover from cognitive changes after surgery(51). Studies assessing both cognitive function and instrumental activities of daily living would also provide a more detailed account of how cognitive decline impacts patients' lives after colorectal cancer surgery. Randomized clinical trials with longer follow-up periods could also be a valuable contribution to provide knowledge on if a perioperative intervention would have effect on persistent cognitive decline.

Conclusion

A more unified approach when it comes to the criteria for measurement of postoperative cognitive function would be beneficial to align research and increase the quality of evidence. Longitudinal studies with follow-up both within and after 30-days, preferable with neuropsychological testing and separate assessment of delirium, would provide new knowledge on whether cognitive dysfunction persist after the recovery period. Randomised controlled trials with the same approach could also contribute with knowledge on whether interventions do reduce actual neurocognitive decline and not only delirium induced manifestation. There could also be room for more research that inform on the degree to which the postoperative cognitive function decline impacts the daily lives of colorectal cancer patients.

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Competing interest

None declared.

Author statement

Authors' contributions

CE provided concept and protocol, screened based on all examination levels, charting and summarisation of data, and writing manuscript. EA reviewed protocol, screened based on title and abstract examination, revised manuscript, and provided clinical and research expertise. RL controlled charted data and exclusion based full-text examination, and revised manuscripts. All authors read and approved the final manuscript.

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Data sharing statement

Data set available upon request, metadata available in supplement.

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Figure legend

Figure 1. PRISMA Flow chart

Figure 2. Graph of instrument for assessment of cognitive function

Figure 3. Graph of recovery within follow-up period

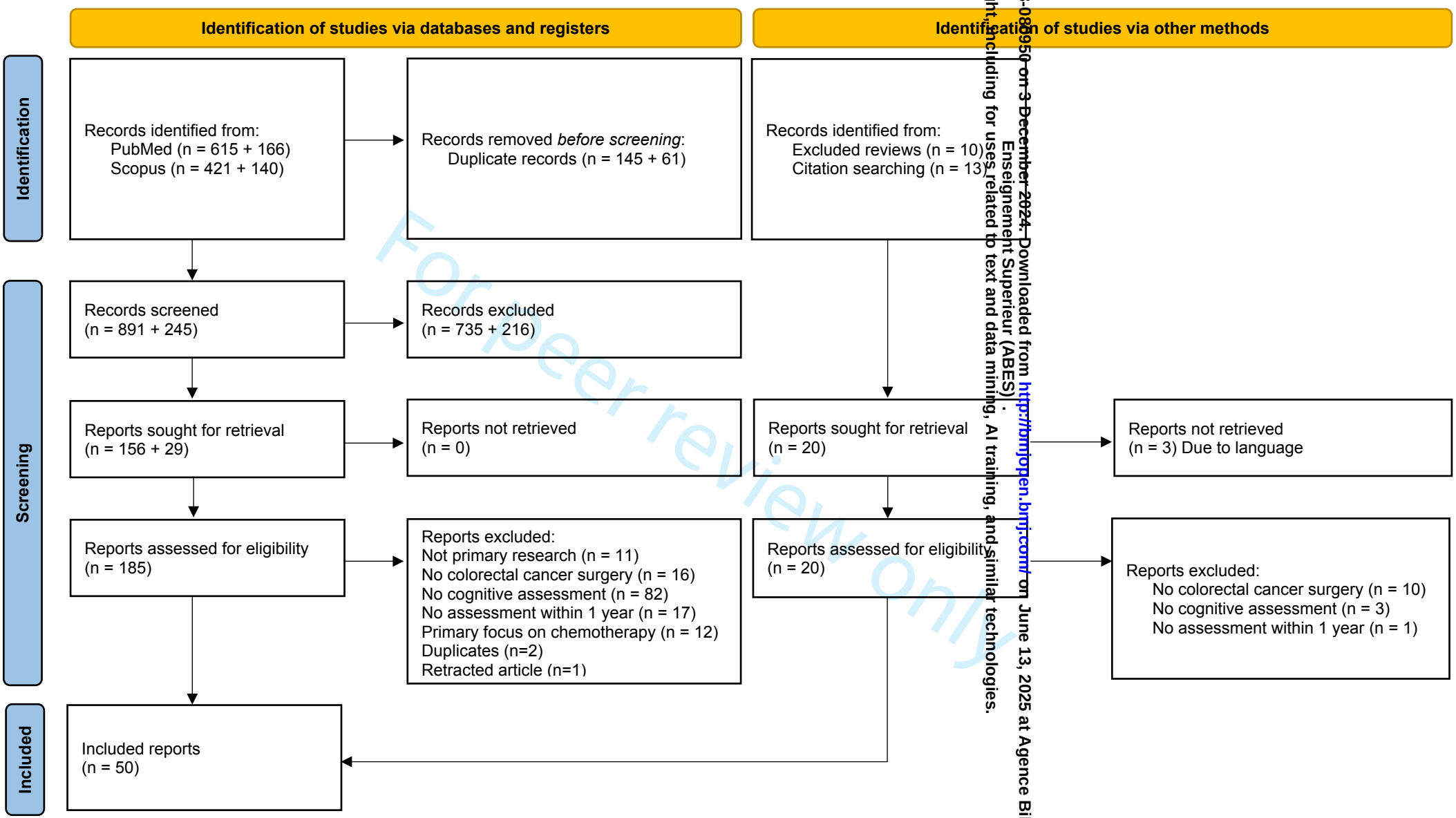
Report	Population (n, cancer, country)	End points	Summary
Arndt, 2004	309, Colorectal cancer 100%, Germany	Quality of life	Observational study comparing cancer survivors with general population
Bao, 2020	178, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical trial on comparing dexmedetomidine to ulinastatin combined with dexmedetomidine in elderly after laparoscopic surgery with no previous chemo or radiation therapy
Beaussier, 2006	52, Colorectal cancer 100%, France	Postoperative recovery including mental function	Randomised controlled trial comparing intrathecal morphine with IV PCA morphine compared to intravenous morphine alone in elderly patient undergoing major colorectal surgery.
Brown, 2014	614, Colorectal cancer 100%, United Kingdom	Quality of life	Longitudinal observational study of complications effect on long-term quality of life after colorectal cancer surgery comparing patient with 30 days complications to those with no complications.
Chen, 2020.	88, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial investigating protective effect of dexmedetomidine
Couwenberg, 2018	270, Rectal cancer 100%, the Netherlands	Quality of life	Longitudinal observational study comparing to general population to patient undergoing low anterior resection and abdominoperineal resection
Couwenberg, 2018	345, Rectal cancer 100%, the Netherlands	Postoperative complications and quality of life	Longitudinal observational study comparing older and younger patient with rectal cancer to reference population and the impact of postoperative complication in elderly
D'Ambrosia, 2019	39, Rectal cancer 100%, Italy	Quality of life	Longitudinal observational study of patient with T2-T3 rectal cancer comparing laparoscopic total mesorectal excision and endoluminal locoregional resection. Patients with adjuvant chemotherapy was excluded.
De Souza, 2018	29, Rectal cancer 100%, Brazil	Quality of life	Longitudinal observational study of patient treated with curative intent.
Deckx, L., et al., 2015	321, Colorectal cancer 24%, Belgium and the Netherlands	Cognitive function, depression, and fatigue	Longitudinal observational study comparing older and younger cancer patient to older persons without cancer.
Ding, 2022	40, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial on effects of dexmedetomidine in elderly patients after laparoscopic surgery
Fagard, 2017	190, Colon cancer 86%, Rectal cancer 14%, Belgium	Postoperative complications	Observational study of association between geriatric screening and 30 days complication after colorectal cancer surgery in older patients. Patients receiving neoadjuvant therapy where excluded.

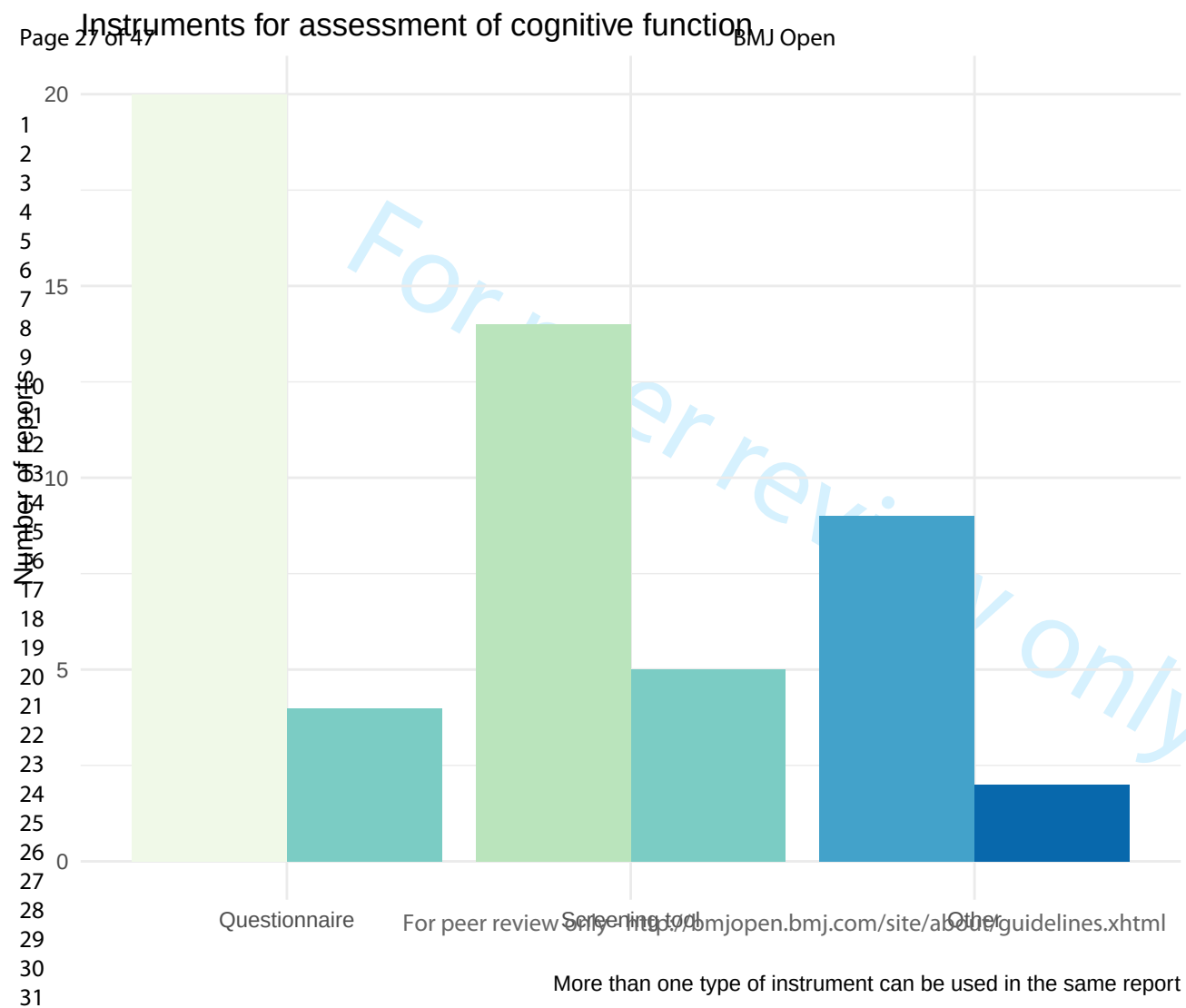
Frick, 2017	1129, Colon cancer 70%, Rectal cancer 19%, international	Sequelae in cancer survivors	Cross-sectional study of persons using an internet-based tool for creating Survivorship care plans
Gamerio, 2008	70, Colorectal cancer 100%, Germany	Postoperative cognitive function and mood	Observational study comparing laparoscopic and open colectomy
He, 2017	90, Colon cancer 100%, China	Postoperative cognitive function	Randomised clinical trial on effects of remote ischemic preconditioning in elderly
How, 2012	62, Rectal cancer 100%, United Kingdom & Germany	Quality of life	Longitudinal observational study comparing low anterior resection and abdominoperineal excision
Janssen, 2020	265, Colorectal cancer, proportion not reported, Netherlands	Quality of life, cognitive function, and depressive symptoms	Observational study on impact of postoperative delirium after elective surgery for colorectal cancer and aortic repair and in older patients
Kinoshita, 2018	120, Rectal cancer 100%, Japan	Quality of life	Longitudinal observational study of age-related factors after sphincter saving surgery comparing those older or younger than 60 years old.
León Arellano, 2020	40, Colorectal cancer 100%, Spain	Postoperative recovery and quality of life	Observational study on ERAS
Li, 2013	114, Colorectal cancer 37%, China	Postoperative complications	Observational study of relationship between blood lactate concentration and complications after 30 days in patients undergoing major elective abdominal surgery
Lidenzi, 2015	82, Colorectal cancer 100%, Lithuania.	Quality of life	Observational longitudinal study in early postoperative period
Lin, 2014	50, Colorectal cancer 46%, China	Postoperative cognitive function	Observational study on the role of HMGB1 on cognitive decline after major gastrointestinal surgery
Liu, T., 2021	100, Colon cancer 100%, China	Postoperative cognitive function	Randomised controlled trial on effects of transcutaneous electrical acupoint stimulation in elderly patients undergoing laparoscopic surgery
Liu, Y., 2020	96, Colorectal cancer 100%, China	Postoperative recovery	Randomised clinical trial comparing dexmedetomidine, epidural blockade, and combination of both in elderly after radical resection
Mann, 2000	70, Colon cancer 66%, France	Postoperative recovery	Randomised controlled trial comparing general anaesthesia with postoperative morphine (PCA) or epidural bupivacainesufentanil anaesthesia (PCEA) after major abdominal surgery in elderly patients

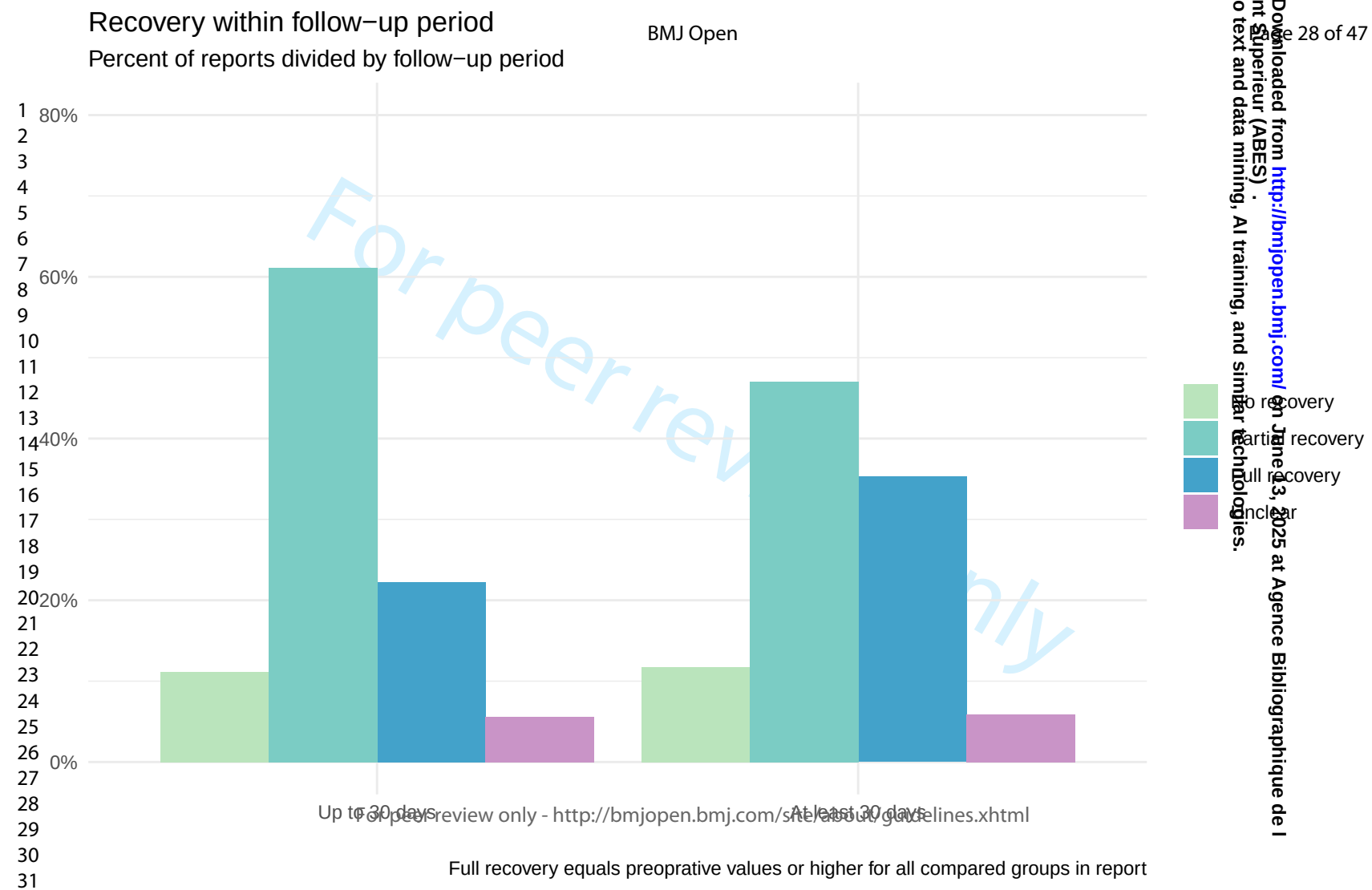
Miniotti, 2019	203, Colon cancer 71%, Rectal cancer 29%, Italy	Quality of life and psychological outcome	Cross-sectional study of supportive care needs in colorectal cancer patients compared to reference population-
Monastyrska, 2016	100, Rectal cancer 100%, Poland	Quality of life	Longitudinal observational study comparing lower anterior resection and abdominoperineal resection
Ng, 2013	74, Rectal cancer 100%, China	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery
Nolli, 2005	1, Colon cancer, Italy.	Present clinical and radiological features	Case report of a patient developing Wernicke's encephalopathy
Nusca, 2021	11, Colon cancer 73%, Rectal cancer 27%, Italy	Quality of life, function, and nutrition	Pilot study of effects of postoperative physical exercise program after laparoscopic surgery.
Olin, 2005	51, Colon cancer (proportion not reported), Sweden	Postoperative delirium	Observational study investigating occurrence and associated factors of delirium in elderly patients undergoing major abdominal surgery
Samuelsson, 2019	49, Colorectal cancer 100%, Sweden	Postoperative complications and recovery	Longitudinal observational study investigating predictive value geriatric assessment tools in patients 75 year or older
Scarpa, 2014	116, Colorectal cancer 100%, Italy	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery in patient older and younger than 70 years
Soares-Miranda, 2021	71, Colorectal cancer 100%, Portugal	Quality of life	Cross sectional study exploring association of physical fitness and health related quality of life 6 months after surgery
Tang, 2021	100, Colon cancer 62%, Rectal cancer 38%, China	Cerebral oxygenmetabolism	Randomised clinical trial on effects of dexmedetomidine assisted intravenous inhalation
van der Vlies, 2022	273, Colon cancer 71%, Rectal cancer 29%, the Netherlands	Quality of life	Longitudinal observational study of determinants for decreased health related quality of life 3 months after colorectal cancer diagnosis
Vardy, 2021	206, Colorectal cancer 68%, Australia	Quality of life and lifestyle factors	Longitudinal observational study of persons attending Sydney Cancer Survivorship Center Clinic
Vardy, 2014	363, Colorectal cancer 100%, Canada & Australia	Cognitive function and fatigue	Cross-sectional report of localised and metastatic colorectal cancer patients before adjuvant or neoadjuvant treatment compared to healthy control.
Visovatti, 2016	50, Colorectal cancer 100%, United states	Cognitive function	Cross-sectional report of colorectal cancer patients compared to healthy controls

Wang, H., 2015	117, Colon cancer 100%, China	Quality of life	Observational study comparing patients using enhanced recovery program (ERAS) and conventional perioperative management
Wang, P., 2021	120, Colorectal cancer 43%, China	Postoperative cognitive function	Randomised controlled trial investigating effect of probiotic intervention on cognitive impairment in elderly after non-cardiac surgery.
Wang, Y., 2020	281, Colorectal cancer 19%, China	Postoperative recovery and function	Randomised controlled trial investigating effectiveness of Tailored Family-Involved Hospital Elder Life Program after noncardiac surgical procedure.
Wu, 2016	110, Colon cancer 100%, China	Postoperative cognitive dysfunction	Observational study of association between miRNA-155 and cognitive function after laparoscopic surgery
Yang, 2019	130, Colon cancer 100%, China	Postoperative recovery and cognitive function	Randomised trial on effect of sevoflurane compared to isoflurane anaesthesia in elderly patients
Zhang, Y., 2019	77, Colon cancer 100%, China.	Postoperative cognitive dysfunction	Observational study to reveal risk factors for early postoperative cognitive dysfunction. No patients received preoperative chemotherapy or radiotherapy.
Zhang, C., 2020	186, Colorectal cancer 100%, China	Postoperative recovery	Randomised trial on effects of epidural blockade and combination of epidural blockade and pre intravenous injection of parecoxib in patients who didn't receive chemotherapy before surgery.
Zhang, J., 2019	140, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical study of dexmedetomidine in elderly. Patients undergoing radiotherapy or chemotherapy before surgery was excluded.
Zhang, X., 2020	159, Colorectal cancer 100%, China	Quality of Life and psychological outcome	Randomised controlled trial on effect of psychological interventions in colorectal cancer patients
Zhang, X., 2019	78, Colorectal cancer 100%, China	Postoperative cognitive function	Retrospective observational study of sevoflurane inhalation combined with epidural anaesthesia compared to propofol general anaesthesia in elderly.
Zhou, 2018	81, Colon cancer 100%, China	Postoperative cognitive function and delirium	Randomised controlled trial on effects of bispectral index monitoring in elderly patients

Fig 1: PRISMA 2020 flow diagram







Final search 2021-04-23

Database: PubMed searched on 2021-04-23

(Postoperative Cognitive Complications[mesh] OR POCD[tiab] OR PostOperative Delirium[tiab] OR postoperative decline[tiab] OR ((cognitive OR neurocognitive OR memory) AND (postoperative OR complication OR decline OR dysfunction OR disorder OR recovery OR impairment OR sequelae OR frailty)))

AND

(Colonic Neoplasms[mesh] OR Colonic Neoplasm[tiab] OR Colonic Neoplasms[tiab] OR Colon cancer[tiab] OR colonic cancer[tiab] OR colonic tumour[tiab] OR colonic tumours[tiab] OR colonic tumor[tiab] OR colonic tumors[tiab] OR Colorectal Surgery[mesh] OR Colorectal Surgery[tiab] OR Colon surgery[tiab] OR Rectal surgery[tiab] OR Colorectal Neoplasms[mesh] OR Colorectal Neoplasms[tiab] OR Colorectal Neoplasm[tiab] OR Colorectal cancer[tiab] OR colorectal tumours[tiab] OR colorectal tumour[tiab] OR colorectal tumors[tiab] OR colorectal tumor[tiab] OR rectal neoplasms[mesh] OR rectal neoplasms[tiab] OR rectal neoplasm[tiab] OR Rectal cancer[tiab] OR rectal tumours[tiab] OR rectal tumour[tiab] OR rectal tumors[tiab] OR rectal tumor[tiab])

No time restrictions
Limits English, Norweigan, Swedish, Danish 615 results

Database: Scopus searched on 2021-04-23

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

No time restrictions
Limit English, Norweigan, Swedish, Danish 421 results

PubMed 615 results
Scopus 421 results
Sum 1036 results

After de-duplication 891 results (145 articles removed)

Updated search 2022-08-08

Same as final search, same limitations except for time limit 2021-2022

PubMed results 137

Scopus results 105

Sum 242

After de-duplication 197

These 197 references are then compared with the final de-duplicated result from 2021-04-23. All duplicates were removed from 2021 and 2022.

163 references were added to Rayyan and then Carolina Ehrencrona and Eva Angenete were invited.

authors

Description	From Rayyan or EndNote

year

Description	From Rayyan or EndNote

title

Description	From Rayyan or EndNote if other sources

country - Country of study population

Type	Character

aim_category - Aim of report

Description	Derived from title and aim Cognition - if mentioned (including specific cognitive function i.e. memory or attention) not only delirium QoL - if mentioned (but not cognition) Recovery – recovery of surgery if mention, including postoperative complication (not sequalae in general from cancer (treatment))

Aim of report

1	Cognition
2	QoL
3	Recovery
4	Other

endpoints

Description	Derived from aim texts and title

size - Size of study population

Description	Included in analysis. Healthy control not included.

crc_size - Colorectal population

Description	Percent colorectal cancer patients of total study population

crc_type - Tumour location

Tumour location

1	Colon
2	Rectum
3	Colon or Rectum

Note

Description	If population is divided as Colon and Rectal separate specify. Note if characteristic has been charted for CRC only if mixed population. Other notes regarding characteristics

age_low - Lowest age of participant

Description	If actual range is missing, lowest possible age (from inclusion criteria) used Yellow if not found

age_high - Highest age of participant

Description	If actual range is missing, highest possible age (from inclusion criteria) used Yellow if not found Yellow if not found

age_central - Central tendency of age

Description	Chart mean if possible, otherwise median If divided by groups (M1*n1+M2n2...)/N

female

Description	Precent

other_treatment - Other cancer treatment than surgery

Description	Chart if radiotherapy or chemotherapy as neoadjuvant and adjuvant, if given before assessment

Other cancer treatment than surgery

0	Not reported
1	No (surgery only)
2	Yes, chemotherapy only
3	Yes, chemo- and/or radiotherapy
9	Unclear

comment

Description	On other treatment or method or compared groups

method

Description	If stated as non-randomized charted as cohort.
1	RCT
2	Cohort
3	Case report

assessment_points - Cognitive assessment points

Description	Including baseline

follow_up_period – Follow up period for cognitive assessment

Description	Baseline not included.
1	Up to 30 days
2	Both before and after 30 days
3	30 days or above
9	Uncertain

groups - Comparison of groups

Description	Predefined groups only, chart even if no comparison is made but note why Chart groups name and n for each group. Chart significant differences in cognitive assessment

POCD

Type	Code
Description	Proportion of cognitive dysfunction reported Yes of No. All definitions valid. Values charted separately in follow-up
0	No
1	Yes

instrument

Description	Note all instrument used where postoperative cognitive outcome is reported

neuro

Description	Neuropsychological/Neurocognitive test used

PROM

Description	Patient reported outcome used (questionnaires)

Screen

Description	Screening tools used

other

Description	Other instrument used

administration

Description	Note how instrument were administered to participant, if specific condition, location, personal was used

IADL

Description	Note yes if it was reported that instrumental activity of daily living was measured after surgery. Note 9 if measured but only before surgery.
0	No
1	Yes

9	Only before surgery

decline

Description	Decline in cognitive function first follow-up after surgery compared to presurgery values. Chart yes if any groups on any assessment have declined result at first follow up, need not be significant.
0	No decline of function at first follow-up
1	Decline reported on first follow up
8	Uncertain, conflicting values reported
9	No preop values to compare with

recovery - Recovery to preoperative values

Description	Chart yes to preop if any group during any follow up is above or at preop values. Chart yes not preop if no group return to or above preop values. Chart no if no group recover during follow up.

Recovery to preoperative values

0	No recovery
1	Recovery to preop levels
2	Recovery but not to preop levels
8	Unclear data
9	No preop values

recovery_timepoint

Description	Chart time for recovery to preop values and which follow up T in () and group if relevant, chart groups separately if preop values occurred at different time points. Chart last follow up if none recovered to preop values

fluctuation

Description	Chart if decline occurred after recovery for any group If no preop values chart not applicable - 9
0	No
1	Yes

9	NA

end_recovery - Recovery at end of follow-up

Description	Chart Full recovery only if all compared groups reach preoperative values or higher. Otherwise chart partial recovery unless no recovery at all.

Recovery to preoperative values

0	No recovery
1	Full recovery (of all groups)
2	Partial recovery (not all compared groups or not to preoperative values)
8	Comparable values not reported

delirium

Description	Separate assessment of delirium Also note yes if delirium was exclusion criteria
0	No
1	Yes
9	Unclear

nomenclature

Description	Chart once per term Chart longest term (i.e. postoperative cognitive dysfunction vs cognitive dysfunction) if one term includes another Only chart neutral term (i.e. cognitive function) if no term indicating decline is used

definition - Criteria of measurement

Description	Chart criteria for cognitive dysfunction. Also chart general criteria if it applied to cognitive outcome as well.

narrative

Description	Narrative description of (postoperative) cognitive dysfunction.

follow_up	
Description	Consecutive number for assessment. Chart 0 for preoperative assessment.

months	
Description	timepoint for follow up in months, if stated as years transformed to months 888 - not applicable

days	
Description	timepoint for follow up in days 888 - not applicable

hours	
Description	timepoint for follow up in hours, charted as reported (i.e. > 23 h reported as hours not days) 888 - not applicable

comment_follow_up	
Description	Specification of time point

outcome - Outcome of cognitive assessment	
Description	If POCD (or comparable) % reported If symptom % reported, if no exact number use > or < nearest scale point and assumed value in () Significant difference between groups (with values not p) If baseline values chart those Note recovery or decline (both significant and not) no numbers needed If reported as recovered to preoperative levels note when, else not if value equal or above preop

Comment_outcome	
Description	Note inconsistency, n if group change over time, other useful information regarding interpretation of outcome reported

Summary of all included reports

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Arndt, 2004	EORTC QLQ-C30	One year after diagnosis	Cognitive functioning	Any level of concern Differences of more than 10 points are clinically meaningful	55.9% with any level of concern Clinically significant different between CRC and general population under 60 years Reported as similar responses between those who underwent adjuvant therapy or surgery alone (data not shown).
Bao, 2020	MMSE	1st and 3rd day after surgery	Postoperative cognitive dysfunction (POCD)	NR	Combination group, CG, dexmedetomidine and ulinastatin, had significantly higher function through follow up than routine group, RG, (dexmedetomidine only). POCD total 8,4%(CG) and 22.89%(RG), at day 1 7.4% (CG) and 16.9% (RG) and day 3 1.05% (CG) and 6.0% (RG)
Beaussier, 2006	MMSE, Digital Symbol Substitution Test	Preoperative and daily until discharge	Mental function impairment Postoperative impairment of mental skills	NR	No significant different between groups (preoperative intrathecal morphine or saline) regarding mental functions after 24 h or return to preoperative values
Brown, 2014	EORTC QLQ-C30	Baseline, 3 months, 6 months, 18 months, and 36 months	Cognitive functioning Higher mental functions Cognitive capacity	NR	No difference in cognitive function between patient who had a complication within 30 day of surgery and those who did not.
Chen, 2020.	MMSE	Preoperative, postoperative day 1 and day 3	Neurocognitive function Postoperative cognitive dysfunction/impairment Cognitive brain dysfunction Disorder of brain function.	Score 24-27 mild, 19-23 moderate, <18 severe impairment.	Study group (dexmedetomidine) had significantly higher scores than control(saline) during follow-up. Total cognitive impairment study group 16%, control 64%.
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, after 3, 6, 12, 18, and 24 months	Cognitive functioning	Clinically relevant worsened cognitive domain scores relative to their baseline score was defined as a decrease of > 10 points (10% of the scale breadth)	Significantly lower cognitive function scores for the whole study population compared to age-match reference population at all follow-ups. Compared to baseline significant mean difference were found at 3 & 6 months for

					those with abdominoperineal resection (APR) and during the whole follow up for those with low anterior resection (LAR). Proportion of worsened cognitive domain: 3 months APR 41%, LAR 40%, 6 months APR 35%, LAR 41%, 12 months APR 23%, LAR 31%, 18 months APR 19%, LAR 33%, 24 months APR 29%, LAR 20%
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, 3, 6, 12 months	Cognitive function	NR	Older patients (≥ 70 years) had significant lower cognitive function than reference population at all follow up. Younger patients had significantly lower function at 3 and 6 months compared to baseline and lower scores at 3 months compared to older patients.
D'Ambrosia, 2019	EORTC QLQ-C30	Preoperatively. After 1, 6, 12 and 36 months.	Cognitive functioning	NR	Scores for both groups (Laparoscopic total mesorectal excision, LTME, and Endoluminal loco-regional resection, ELRR) where above preoperative levels at first follow up. At 6 months LTME declined with significant difference to ELRR that was stable. Thereafter LTME declined, at 36 months to preoperative levels, while score in ELRR improved further.
De Souza, 2018	EORTC QLQ-C30	Before, 3 months and 12 months after surgery.	Cognitive function	Score 0-25= very poor, 26-50 = poor, 51-75= good, 76-100= very good	Cognitive function changed from good before surgery to very good at both follow ups.
Decks, 2015	EORTC QLQ-C30	Baseline and one-year-follow-up	Cognitive impairment	The frequency of cognitive impairment was operationalized by using the lowest functioning quartile as cut-off, this corresponded to a score <67 in all three groups.	Frequency of impairment for younger cancer patient, YCP, (<70 years) 28% at baseline and 32% at 1 year. For older cancer patients, OCP, it was 28% at baseline and 26% at 1 year. For older patients without cancer, OPwC it was 22% at both time points.

					OCP had significantly higher cognitive function at baseline compared with OPwC. OCP had a significant decline between baseline and 1 year.
Ding, 2022	Revised Hasegawa's Dementia Scale (HDS-R). Digit span subtest, digit symbol test, trail-making test, word recall, verbal fluency test.	At 1 day before the operation, 1 day after the operation, and 5 days after the operation	Neurocognitive Dysfunction Postoperative cognitive dysfunction (POCD) Postoperative consciousness dysfunction Hippocampal-dependent cognitive function"	The postoperative test value compared with the preoperative test value. If the deviation value exceeded one standard deviation value, the function was judged as the postoperative function decline. POCD was if two or more postoperative tests showed simultaneous functional decline	Significantly decreased score on HDS-R in both Dexmedetomidine (DEX) and control group at both follow ups. Compared to control significantly higher values for DEX group at both follow up. Significantly higher incidence of POCD in control group 25% than DEX group 5% DEX at T2
Fagard, 2017	Clavien Dindo classification	Within 30 days after surgery	Cognitive impairment Altered mental function	Neurological - including altered mental function	Neurological complications total 12.6%
Frick, 2017	Internet-based tool for the creation of survivorship care plan	Median 12 months after diagnosis	Cognitive changes Neurocognitive decline	NR	Cognitive changes total population 48.6%.
Gamerio, 2008	Stroop Test, German Trail-Making Test, Wordlist power level and speed	Preoperatively and at follow-up until postoperative day 4	Early postoperative cognitive dysfunction/ changes Postoperative neuropsychological dysfunction Long-term cognitive deterioration Cognitive abilities/state/ Cognitive impairments/disturbance	NR	No significant differences between laparoscopic and conventional colectomy.
He., 2017	MoCA	One day before surgery. One, three and seven days after surgery.	Cognitive function impairment Postoperative cognitive dysfunction (POCD) Cognitive decline	Score < 26 is considered abnormal	Significantly difference between control and Remote ischemic preconditioning group one day and three days after surgery.
How, 2012	EORTC QLQ-C30	One day before surgery or before neoadjuvant therapy, 1 and 2 year postoperatively	Impaired cognitive function	NR	Significantly higher mean cognitive function score for those with abdominoperineal excision (APE) at 1 year compared to those with low anterior resection (LAR)

Janssen, 2020	MMSE	Baseline (the first outpatient clinic visit, after 6 months and after 1 year.	Cognitive decline (Persistent) postoperative cognitivie dysfuntion Cognitive impairment	A score equal to or lower than 24 indicating cognitive impairment	Significant lower score at baseline for group with delirium. Significant decline in score compared to baseline during follow up for group without delirium.
Kinoshita, 2018	EORTC QLQ-C30	Before surgery, 1 month, 6 months and 12 months after surgery	Cognitive functioning	A change of score of 5–10 points indicate a minimal change, whereas a change of more than 20 points indicates a large change	Significant change from before surgery at 1 month for age ≥60. No significant difference between age <60 and ≥60. at any time-point.
León Arellano, 2020	EORTC QLQ-C30	1-2 days before surgery, at Postoperative day 7 and 30,	Cognitive function	NR	Significant decline at both follow up.
Li, 2013	Medical record Clavien Dindo classification	Within 30 days after surgery	Postoperative cognitive dysfunction	Delusions requiring medical treatment	Postoperative cognitive dysfunction as a complication in 2 patients.
Lidenzi, 2015	EORTC QLQ-C30	One day before, second and fifth day after surgery, one and three months after surgery	Cognitive functioning	NR	Decline in cognitive function scale on second day with recovery on fifth day. Back to preoperative levels at one month and above preoperative levels at three months.
Lin, 2014	Hopkin Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Trail-Making Test; Benton Judgment of Line Orientation, Digit Span Test; Symbol-Digit Modalities Test, Index, verbal fluency test	Before surgery and after 1 week or on the day of hospital discharge if earlier than 1 week	Cognitive decline/deterioration Post-operative cognitive dysfunction (POCD) (Neuro)cognitive deficit performance deficit in cognitive/hippocampus dependent memory cognitive impairment memory dysfunction/deficit neurocognitive dysfunction	POCD was determined using Z score recommended by International Study of Postoperative Cognitive Dysfunction (ISPOCD) studies Patients were regarded as developing POCD if the Z score was ≥ 1.96 on ≥ 2 individual cognitive tests or the composite Z score was ≥ 1.96."	Incidence of POCD 34 %.

Liu, 2021	MMSE	One day before surgery, Postoperative days (POD) 1, 2, and 3	Postoperative cognitive decline (POCD) cognitive dysfunction	POCD was defined as a Z-score −2 based on a pre- and postoperative MMSE The following formula was used: [(postoperative MMSE– preoperative MMSE)-ΔX MMSE normative population]/[SD MMSE normative population]. In this current study, ΔX MMSE normative population = 0.5 and SD (ΔX MMSE normative population) = 1.5 were used to calculate Z-score	POCD for the control group was 25%, 16% and 10 % for POD1-3. For the transcutaneous electrical acupoint stimulation (TEAS) group POCD was 10%, 8% and 4% on POD1-3. There was no significant difference between group on POCD on each day. On cumulative duration TEAS group had significantly lower incidence than control group on postoperative day 2 and 3.
Liu, 2020	MMSE	Before and at 4, 12, 24, and 48 hours and 7 days after surgery	(Early) Postoperative cognitive dysfunctioning (POCD)	A mean MMSE score declin >2 points between postope and preoperative surgery	Combined group (dexmedetomidine and epidural blockade) had significantly higher scores than all other groups (dexmedtomidine only, epidural only, control) at 12 to 24 h and higher than all but dexmedetomidine only at 48 h and 7 days
Mann, 2000	Abbreviated Mental Test (AMT)	Day before surgery, day of surgery (PM), twice a day (AM, PM) day 1-5 after surgery	Mental status Postoperative cognitive dysfunction Cognitive impairment	Decrease in the AMT score of 2 or more points (as part of a delirium diagnosis)	Significant lower scores for PCA-group (general anaesthesia and postoperative morphine) compared to PCEA-group (general anaesthesia combined with epidural bupivacainesufentanil) on day 4 AM and day 5 PM.
Miniotti, 2019	EORTC QLQ-C30	Majority within 12 months of diagnosis.	Cognitive functioning problems in concentrating and remembering	NR	Significantly lower scores on cognitive function scale than reference population from EORTC reference value manual.
Monastyrska, 2016	EORTC QLQ-C30	One day prior to and 6 months following surgery	Cognitive functioning	NR	Both groups, lower anterior resection (LAR) and abdominoperineal resection (APR) significantly higher mean scores at follow up with LAR significantly higher than APR.
Ng, 2013	EORTC QLQ-C30	Before surgery and at 4, 8 and 12 months after surgery	Cognitive functioning	A difference in mean QoL score of more than 10 points was regarded as clinically significant	Significant lower scores at 8 months for those with open resection compared to laparoscopic as well as clinically significant decline since baseline.

Nolli, 2005	NR	Re-admission (after a brief domiciliary period) Discharge (after 60 days) One year follow up	Cognitive defects	NR	On discharge deficits of attention and memory. At one year suboptimal recovery of attention and dramatic fixation memory deficit (development of Wernicke-Korsakoff syndrome).
Nusca, 2021	EORTC QLQ-C30	The first post-surgical follow-up visit approximately ten days after surgery. after the end of the exercise program, 2 months and: 4 months thereafter.	cognitive impairment	NR	Significant higher cognitive function score in the group attending a 2-month-long supervised and combined exercise–training program during the postoperative period than the group which did not at the end of the exercise program.
Olin, 2005	MMSE	At 3–4 weeks before surgery, day for postoperatively and at discharge.	Cognitive impairment Cognitive status Cognitive dysfunction Mental function	Scores from 0 to 10 of a total 30 corresponded to severe cognitive impairment	Significantly lower scores at day 4 in the long postoperative delirium (≥ 3 days) group compared to the group with no delirium.
Samuelsson, 2019	MMSE	Preoperative and at follow-up 1, 3 and 12 months after surgery	Cognitive impairment Cognitive decline	Possible cognitive impairment <24	At risk for cognitive impairment 8.2% preoperative, 5% at 1 month, 2,5% at 3 months, 2,7% at 12 months. Reported as cognition was improved compared to baseline at 3 months.
Scarpa, 2014	EORTC QLQ-C30	Admission, 1 month and 6 months	Cognitive function	NR	Significant higher values on cognitive function scale in the laparoscopic group for younger (<70 years) compared to elderly at 1 and 6 months.
Soares-Miranda, 2021	EORTC QLQ-C30	Six months post-surgery.	Cognitive impairment Cognitive capacity Cognitive decline	NR	Unadjusted and adjusted (age, sex, and cancer stage) linear regression showed that better performance in 6-minute walk test was associated with higher cognitive function.
Tang, 2021	MoCA	At 6, 12, 24, and 48 h after the operation.	Cognitive dysfunction (Early) Postoperative Cognitive dysfunction (POCD)	A lower score indicated lower cognitive function, < 26 indicated abnormal.	Observation group (dexmedetomidine) had statistically significant higher cognitive function compared to control over follow up. There was also a significant change in function over time within both groups.

van der Vlies, 2022	EORTC QLQ-C30	At diagnosis and 3 months after diagnosis	cognitive impairment	NR	Participants with decreased health related quality of life (HRQL) had statistically significant more affected cognitive function than participants with preserved HRQL. The decline was lager in patients who did not undergo surgery, either due to poor performance status or personal preference. In the surgically treated patients, there was slight impairments of cognitive functioning.
Vardy, 2014	Battery of clinical neuropsychological test (Letter-Number Sequencing, Digit Span, Spatial Span, Digit symbol, Trail Making Test A&B, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised) CANTAB and modified FACT-COG	Assessment after surgery before adjuvant treatment or before any treatment if neoadjuvant treatment was planned	Cognitive impairment Cognitive decline	Global cognitive impairment was defined as Global Deficit score (GDS) of >0.5. Impairment on individual cognitive tests in 5 domains. International Cognition and Cancer Task Force (ICCTF), 1 standard deviation (SD) below the HC on at least one cognitive test, or >1.5 SD below on two or more tests A score <1.5 SD below the HC mean on the FACT-Cog was classified as perceived cognitive impairment (≤119/168)	Significant difference between localised cancer and healthy controls in cognitive impairment regardless of objective test method and definition. There was no significant difference between those evaluated pre- and post surgery in those with localised cancer. Frequency of cognitive impairment: Clinical test (GDS:ICCTF) / CANTAB (GDS:ICCTF) Localised cancer 45%:51% / 30%:39% Metastatic cancer 47%:49% / 31%:33 Healthy controls 15%:17%%/13%:17% Frequency of perceived cognitive impairment; localized cancer 21%, metastatic 18.5%, healthy controls 17%.
Vardy, 2021	Patient's Disease and Treatment Assessment Form-General	(T1) Initial visit (median 11 months after diagnosis) (T2) First follow up (median 3,6 months after T1) (T3) One year follow up	Trouble concentrating Memory impairment	Symptoms of at least moderate severity (4 or above out of 10)	Trouble concentrating : Above 20% at T1, reduced to less than 20% at T2-T3 Problems with memory: Less than 20% at T1, reduced at T2 and increased to 20% at T3.
Visovatti, 2016	Attention Network, Test (ANT),, The digit span, The Trail Making Test ,	Within six months of a new diagnosis	Cognitive impairment Cognitive changes Cognitive problems Cognitive decline	NR	Participants with cancer had significantly slower response time on ANT, lower scores at digit span forward and trail making test A and attention composite score.

	The Rey Auditory Verbal Learning Test , The Attentional Function Index, The Everyday Memory Questionnaire				
Wang, H., 2015	EORTC QLQ-C30	Preoperatively and postoperative day (POD) 3, 6, 10, 14, 21, 28	Cognitive functioning	EORTC guidelines; clinically significant changes: 10 ''little'', 10–20 ''moderately'' 20 ''very much'' better or worse	Significant less decline of cognitive function scale in ERAS-group than control POD3 and POD6. Recovery to preoperative values for ERAS-group at POD21 and control at POD28.
Wang, P., 2021	MMSE	Admission and the 7th day post-surgery	Postoperative (neuro)cognitive impairment	Postoperative cognitive impairment defined as decline in MMSE score of 3 or more points	Probiotic group (twice daily until discharge) had significantly higher MMSE score than control at 7 days after surgery. Postoperative cognitive impairment at day 7 probiotic group 5.1%, control 16.4%
Wang, Y., 2020	Short Portable Mental Status Questionnaire	Day before the surgical procedure, discharge, 30 days after discharge	Cognitive changes Cognitive impairment	Declined on SPMSQ at discharge 0 to 2 errors indicate normal mental functioning;	Significantly higher proportion of intact cognitive function in patients on tailored family-involved Hospital Elder Life Program (t-HELP) units which increased over time compared to usual care units which decreased. Significant lower with decline on SPMSQ at discharged in t-HELP units 0,8% vs usual care units 7%.
Wu, 2016	CANTAB	On the day before surgery, and at 7 days and at 3 months after the surgery	Postoperative cognitive dysfunction (POCD) Cognitive impairment Cognitive function change"	POCD was defined when the reliable change index RCI score was <–1.96 at least on 2 tests or when the combined Z score was <–1.96	POCD 26.4% at 7 days, no report for 3 months.
Yang, 2019	MMSE	Before anaesthesia and 4 h, 24 h and 48 h after anaesthesia.	Postoperative cognitive function Cognitive ability	NR	Significantly higher scores for sevoflurane group (SEV) than isoflurane group (ISO) up to second follow up (24 4h). Significantly lower scores for both groups compared to before anaesthesia at 4 h and 24 h after anaesthesia

Zhang, C., 2020	MMSE	At 1h, 6h, 24h and 48h after surgery	Cognitive functioning	NR	Significant higher scores for combination (epidural blockade and parecoxib) group compared to epidural only group and control during all follow up, as well as epidural against control.
Zhang, J., 2019	MMSE	One day before surgery and 1 day and 3 days after surgery.	Postoperative cognitive dysfunction (POCD)	28-30 normal cognition, 24-27 mild cognitive dysfunction, 19-23 moderate cognitive dysfunction and 0-18 severe cognitive dysfunction	Significant higher score in experiment group (dexmedetomidine) than control (saline) during follow-up. Significantly lower scores in both groups compared to before surgery at both follow-ups. POCD in experiment group 9 % day 1 and no day 3. In control 22% day 1 and 13 % day 3.
Zhang, X., 2020	EORTC QLQ-C30	At admission, 3 month and 6 month follow up	Cognitive function	NR	No significant difference in cognitive function between control group and group which received psychological intervention.
Zhang, X., 2019	MMSE	Before anaesthesia, 1 day, 3 days and 5 days after operation	Postoperative perceptual function Postoperative cognitive impairment/dysfunction"	NR	Observation group (sevoflurane inhalation combined with epidural anaesthesia) had significantly higher scores at day 1 and 3 compared to control group (propofol general anaesthesia). Significant lower for both groups day 1 and 3 compared to baseline. Significant recovery day 3 compared to day 1 as well as day 5 compared to day 3 and day 1.
Zhang, Y., 2019	MMSE, visual verbal learning test, digital span test, digital symbol test	One day before surgery Seven days after surgery	Postoperative cognitive dysfunction (POCD)	POCD was diagnosed when the Z score was greater than 1.96 or the combined Z score was ≥1.96.	POCD 24.7%.
Zhou, 2018	Attention Network Test (ANT)	Pre-operatively and at day 1 and day 5	Postoperative attention network dysfunction Cognitive changes Postoperative cognitive impairment	NR	Significant difference between bispectral index monitoring group (BIS) and non-BIS (control) group on alerting and orientation on day 5.

			Postoperative cognitive dysfunction (POCD)		Significant change for both groups in all domains (alerting, orientation, and executive control) at day 1 compared to baseline. At day 5 significant change in executive control for BIS and all domains for non-BIS group. Age was significantly correlated with pre-operative alerting function in the BIS and non-BIS group. Propofol (general anaesthesia) was significantly correlated with alerting, orientation, and executive control at postoperative day 1 and 5.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0

MMSE – Mini mental state examination

MoCA – Montreal Cognitive Assessment

CANTAB - Cambridge Neuropsychological Test Automated Battery

FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Questionnaires

Attentional Function Index (AFI)

Everyday Memory Questionnaire (EMQ)

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0 (EORTC QLQ-C30)

Functional Assessment of Cancer Treatment – Cognitive function issues (FACT-Cog)

Patient's Disease and Treatment Assessment Form—General (PtDATA)

Screening tools

Abbreviated Mental Test (AMT)

Hasegawa's Dementia Scale - Revised (HDS-R)

Mini-Mental State Examination (MMSE)

Montreal Cognitive Assessment (MoCA)

Short Portable Mental Status Questionnaire (SPMSQ)

Neuropsychological test

Attention Network Test (ANT)

Benton Judgment of Line Orientation (JLO)

Brief Visuospatial Memory Test-Revised (BVMT-R)

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Digit Span Test

Digit Symbol Substitution Test (DSST)

Hopkin Verbal Learning Test-Revised (HVLT-R)

Letter-Number Sequencing

Rey Auditory Verbal Learning Test (RAVLT),

Stroop Test

Symbol-Digit Modalities Test (SDMT)

Trail-Making Test, (TMT)

Visual verbal learning test (VVLT)

Verbal fluency test

Word recall

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Assessment of cognitive function after surgery for colorectal cancer – a scoping review

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Keywords: Cognitive Dysfunction, Colorectal Neoplasms, Colorectal Surgery, Neuropsychological Tests, Patient Outcome Assessment, Postoperative Cognitive Complications

Abstract

Objective

Colorectal cancer is primarily treated with surgery. Major surgery and older age are risk factors associated with postoperative decline in cognitive function. In clinical research, a wide range of instruments have been used to assess cognitive function. There are no clear criteria for the measurement of postoperative cognitive dysfunction.

This scoping review aimed to map how and when cognitive function has been assessed after surgery for colorectal cancer and the incidence of postoperative cognitive decline reported.

Design

Systematic scoping review following the JBI approach.

Data sources

Scopus and PubMed. Last search January 2023.

Eligibility Criteria

Reports with outcomes of postoperatively assessed cognitive function in colorectal cancer patients with first assessment within 1 year of surgery was included.

Data extraction and synthesis

Data was extracted by one researcher and controlled for accuracy by a second researcher. Data was summarized in tables and charts.

Results

In total, 50 reports were included (16 clinical trials, 33 cohort studies, and one case report). Cognitive function was assessed with patient-reported outcomes measures, clinical screening tools, neurophysiological testing and complication classification. The definition was most often related to the specific instrument, as predefined cut-off or change from baseline. Assessments were performed between 1 h and 36 months after surgery – few reports included follow-up both within and after 30 days postoperatively. Incidence of cognitive decline varied considerably (0-64%), depending on the instrument, definition criteria and time of assessment. Most studies reported a decline in cognitive function after surgery with recovery during follow-up.

Conclusions

This study showed a heterogeneity in the choice of assessment method and measurement criteria for cognitive dysfunction after colorectal cancer surgery. A more unified measurement approach in further research would be beneficial to evaluate post-operative cognitive function and understand its impact on the daily lives of patients with colorectal cancer.

Trial registration

Protocol registered at Open Science Framework, DOI:10.17605/OSF.IO/2M3DT

Strength and limitations of this study

- This review is following a systematic approach with a preregistered protocol
- Search strategy was developed, and searches conducted by experienced librarians
- There was no critical appraisal for methodological limitation or risk of bias assessment preformed for included studies

Introduction

Cognitive functions, such as memory, attention and executive functions, can decline after surgery[1]. The pathogenesis is not entirely known but most probably it is multifactorial. This can incorporate patient-related factors, including genetic predisposition, the anaesthetic and surgical procedure, and the systemic inflammatory response that surgery give rise to[2]. Older age is a risk factor[1, 2], but 30-40% of all adults have been reported to develop postoperative cognitive dysfunction or decline (POCD) after major non-cardiac surgery[3]. Generally, it seems to be a temporary condition[2] but patients older than 60 years have an increased risk of persistent cognitive dysfunction 3 months after surgery[3]. Colorectal cancer is one of the most common types of cancer worldwide and is primarily treated with surgery[4, 5]. Considering the high incidence of colorectal cancer, particularly among older adults, a substantial number of patients could be at risk for developing cognitive dysfunction after colorectal surgery.

Postoperative cognitive dysfunction is a research construct and there has been no standardised definition[2, 6]. In 2018, the international and multidisciplinary Nomenclature Consensus Working Group published a recommendation on cognitive changes after surgery[6]. The group aimed to align the terminology of postoperative changes to that of the clinical classification of cognitive function in general. The recommended terms were *delayed neurocognitive recovery* in case of occurrence during the first 30 days after surgery and *postoperative neurocognitive disorder* for diagnosis between 31-365 days after surgery. They further recommended the use of the Diagnostic and Statistical Manual for Mental Disorders' (DSM-V) criteria for neurocognitive disorder. For diagnosis, DSM-V requires subjective complaints as well as objective testing and specifies that everyday living is hindered at least in terms of instrumental activities (e.g., taking medication, and paying bills)[7]. For classification DSM-V also states that cognitive deficits are not present solely as a component of delirium.

The assessment of the patients' function after surgery is an important issue since postoperative recovery, of which cognitive function is an integrated part, is prognostic for long-term recovery and has economic implications[8]. A long-term follow-up of a Danish cohort found that patients who developed postoperative cognitive dysfunction after non-cardiac surgery retired earlier from the labour market and

incurred higher social transfer payments[9]. It has also been found that those with postoperative cognitive dysfunction at discharge had higher mortality within 30 days and those with persistent dysfunction after 3 months had higher mortality during the first year after surgery[3]. While cognitive screening is recommended in American Cancer Society's survivorship care guidelines for colorectal cancer, it is only mentioned in association with chemotherapy [10]. As cognitive decline is associated with major surgery in general, it is reasonable to expect that cognitive decline can occur in patients with colorectal cancer undergoing surgery even if chemotherapy is not part of the treatment regime.

The objective of this review was to map how cognitive dysfunction has been defined and assessed after surgery for colorectal cancer. The aims were to identify research reports of cognitive function after colorectal cancer surgery, explore the incidence of cognitive changes, clarifying the definitions and criteria used and describe how cognitive function has been assessed. The review questions were identified as:

- How and when was cognitive function assessed after colorectal cancer surgery?
- What definition and nomenclature were used to describe cognitive changes?
- What outcome of cognitive function was reported after surgery?

The investigative and explorative nature of the research made it suitable for using a scoping review approach. At the start of this project, we found no registered protocol for systematic reviews at PROSPERO for the assessment of cognitive dysfunction after colorectal surgery, nor any scoping review registered at Open Science Framework. No published protocols or reviews were found on the subject when searched in PubMed, Scopus, Cochrane Database of Systematic Reviews and JBI Evidence Synthesis.

Methods

The protocol based on the JBI methodology[11] containing the objectives, inclusion criteria and methods for this scoping review was registered on July 24, 2021 at Open Science Framework, DOI 10.17605/OSF.IO/2M3DT. The registration was made before the screening of results had begun.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) was followed[12]. The checklist is available in Supplement I. Patients, or the public were not involved in the design, conduct, or reporting of this review.

Inclusion criteria

The review included reports on primary research studies. The languages were limited to English and the Scandinavian languages (Norwegian, Swedish, and Danish). No restrictions were applied based on the year of publication.

Population was adults with colorectal cancer, the concept examined was outcomes of cognitive function within the context postoperative assessment the first year after cancer surgery.

The criterium of assessment within 1 year was added after protocol registration to align with the recommended temporal specification for postoperative cognitive changes, i.e., only in the first 12 months after surgery[6].

Search strategy

The main search was conducted by librarians at the Biomedical Library, University of Gothenburg, on April 23, 2021, in PubMed (via Medline) and Scopus databases. A subsequent search was made on January 3, 2023.

Search on Scopus:

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

In addition to database searches, bibliographic searches were conducted. Excluded review articles that contained key terms in the title (colorectal cancer or surgery, cognitive function, or effects of cancer treatments) were scanned for relevant sources. This was repeated for all reports included in the full-text examination. The complete database search strategy is available in Supplement II.

Screening and selection

After the removal of duplicates, search results were transferred to the web-based screening tool Rayyan[13]. Two blinded reviewers screened titles and abstracts. Conflicts were discussed, and the senior author had the last say if a consensus was not reached. Full-text screening was performed by one researcher in EndNote[14]. Exclusion criteria for all excluded reports were confirmed by another researcher.

The exclusion criteria for screening had no hierarchy, and the first relevant exclusion criterium was used for classification. Predefined reasons for exclusion in the title and abstract examination were protocol or review, not primary research, and no participants with colorectal cancer or surgery. During the screening process, the following exclusion criteria were added; metastatic surgery (including HIPEC) and focus on effects of chemotherapy on cognitive functions since it is not relevant to primary colorectal surgery; delirium assessed only by a clinical definition (i.e., no cognitive testing); and no assessment within 1 year of surgery.

Data charting

Data was extracted by one researcher. For the initial search, the software NVivo[15] was used in qualitative and iterative process to categorise text and figures depending on content relevant to the review questions. Data were then charted in an Excel spreadsheets using Colectica[16] for metadata. For the subsequent search data was charted directly to the spreadsheet. The results were then compiled into relevant tables and charts. All charted data were controlled for accuracy by a second researcher.

Data were charted for study characteristics such as aims, methodology and study population. Data relevant to review questions were nomenclature, definitions and instruments used. The time of assessment was charted as months, days or hours as specified in each report. Cognitive outcomes were charted as frequency and if decline and recovery occurred and differences between compared groups. Since not all reports used statistical testing for within-group comparison, numerical values were compared as presented. Details of all charted variables used in this review are presented in the metadata in Supplement III.

Results

After the removal of duplicates, 1136 records were screened in title and abstract examination. There were 23 reports identified from other sources (Fig 1[17]). Out of the 205 articles that were subjected to

full-text examination, 50 were included. Supplement IV includes a summary of data relevant to the review questions from all included reports.

The included reports were published 2000-2022. There were 33 observational cohort studies, 16 reports of controlled trials, and one case report. The aim of reports was mainly to investigate cognitive function (38%), quality of life (40%) or recovery after surgery (18%). Table on characteristic for all included sources is in Supplement V.

Forty study populations were exclusively patients with colorectal cancer, of the remaining study populations colorectal cancer patients comprised 19-89%. Sample sizes in observational studies ranged 11-1129 and in clinical trials 40-281. Across all studies, there was a mean of 46% female participants, and the average age reported was 66 years, covering a range of 18-99 years. The study populations were mainly from Europe (48%) and Asia (42%), the remaining reports had populations from Australia, Brazil, Canada, and USA. There was also one international online population[18]. In five reports, the participants had received no other cancer treatment than surgery[19-23]. Information on adjuvant treatment was given in twenty reports.

Perioperative intervention concerning anaesthesia (types of drugs or procedural aspects) was used in 81% (n=13) of the clinical trials with dexmedetomidine being used in half of those (n=6). Observational studies compared groups most frequently according to surgical method or procedure (n=8), healthy controls or the general population (n=6), patients' age (n=5) or whether postoperative cognitive decline developed or not (n=5).

Assessment of cognitive function

Cognitive function was generally assessed with questionnaires or screening tools (fig 2). The two other assessments methods were neuropsychological testing and complication classification. More than one type of assessment method and instrument could be used in the same report. See Supplement VI for full list of instruments. A separate assessment of postoperative delirium was made in eight reports[19, 24-30], and instrumental activities of daily living (IADLs) were reported after surgery in two sources[27, 31].

A total of six questionnaires, five previously described and one novel[18] was used for patient-reported outcomes. Answers to questionnaires were collected by in person or telephone interviews or self-administered during visits, online or at home. The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire - Core 3.0 (EORTC QLQ-C30) was the most frequently utilized

instrument overall. Studies that utilized patient-reported outcomes were generally observational studies with focus on quality of life. One clinical trial used self-reported outcome of cognitive function[32].

Five different screening tools were represented with the Mini-Mental State Examination (MMSE) as the most utilized. When specified, screenings were done by trained personnel, often the same individual for all assessments, and with the assessor blinded to the patient's intervention group. Screening tools was used in all but two clinical trials. In reports with the aim to investigate cognitive function screening tools were the most frequent instrument employed (12/19).

Two reports measured cognitive dysfunction as a complication, both were observational studies reviewing patient records and grading with the Clavien-Dindo classification[33, 34]. Nine reports assessed cognitive functions with neuropsychological testing employing a wide range of tests for several cognitive domains such as processing speed, attention, and verbal memory. Tests could be used either together as a battery with a composite score or as individual tests, reported separately. The time requirement for neuropsychological testing was given in three reports, 30, 60 and 90 min. When reported, testing was done in a quiet environment and by trained personnel. There were two computerized tests, the Attention Network Test (ANT) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Neuropsychological testing was used in three clinical trials, once as the only assessment method[28] and otherwise in combination with a screening tool[25, 35]. When reported separately return to preoperative values occurred later when assessed with neuropsychological testing than the screening tool[25]. In one case both CANTAB and a battery of seven individual neuropsychological tests were uses in the same report[23] and the association between the neuropsychological testing methods was stated as weak-to-moderate.

Across studies, cognitive assessment was performed in the shorter term, 1-12 hours, and 1-30 days after surgery, and in the longer term, 2-36 months after surgery. Most reports had a follow-up only within 30 days (48%) or only after 30 days (40%). One clinical trial had follow-up after the first 30 days[32]. Cognitive function was assessed up to 11 times, including baseline, with a mean of three assessment points. There were six cross-sectional reports.

Nomenclature and definition

Impairment was the most frequent term to describe cognitive function decrease in general, followed by dysfunction, both terms occurred in several combinations. Neurocognitive was used in combination with impairment, decline, deficit, and dysfunction. About half of the reports utilized more than one term.

Two reports referred to problems with concentrating and memory without any generic term. Sixteen reports used cognitive or mental function, capacity, or ability without any term indicating a decline in function.

A narrative definition of postoperative cognitive dysfunction as a concept was absent in most reports. When present, it concerned the decline of cognitive functions such as memory, executive control, and attention. Two reports also mention decline in social ability[36, 37]. Four reports included symptoms such as confusion, disorientation, anxiety, agitation, or delirium in their definition[22, 36, 38, 39]. Two reports stated that no abnormalities in cognitive function should have been present preoperatively[35, 39].

A little more than half of the reports presented criteria for measurement of cognitive dysfunction. Instrument-specific criteria were most common. Both predefined cut-offs and change from baseline was used, with or without subdivisions. Instrument-specific criteria were used with screening tools and questionnaires, for neuropsychological testing general criteria were more common (table 1). The Z-score was the most common general criteria, defined in four reports. Occurrence of specific or any symptoms of cognitive decline was also used as criteria both with questionnaires and complication classification. There was also a vague definition (i.e., the lower the score, the lower the function).

Table 1. Criteria for measurement of cognitive dysfunction

Instrument specific	Utilised with	Comment
Cut-off	MoCA, MMSE, PtDATA,	
Cut-off with subdivision	HSD-R, MMSE, SPMSQ, EORTC QLQ-C30	
Decrease from baseline	AMT, MMSE, SPMSQ	
Decrease from baseline with subdivisions	EORTC QLQ-C30	Based on EORTC's guidelines
Instrument general	Utilised with	Comment
Z-score (with cut-off)	Neuropsychological tests, MMSE	
Lowest quartile	EORTC QLQ-C30	
Global deficit score (with cut-off)	Neuropsychological tests	T-score converted to 0-5
Standard deviation(s)	Neuropsychological tests, FACT-Cog	In relation to healthy control or baseline
Other	Utilised with	Comment
Specific/any symptom	Clavien-Dindo classification, Survivorship care plan tool, EORTC QLQ-C30	
Lower score = lower function	MMSE	

MoCA - Montreal Cognitive Assessment, MMSE – Mini-Mental State Examination, PtDATA - Patient's Disease and Treatment Assessment Form—General, HDS-R - Hasegawa's Dementia Scale – Revised, SPMSQ - Short Portable Mental Status Questionnaire, EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0, AMT - Abbreviated Mental Test, FACT-Cog - Functional Assessment of Cancer Treatment – Cognitive function issues

Outcome of cognitive assessments

Of the reports that had comparable preoperative values, 86% (30/35) showed a decline at the first follow-up after surgery. The reports not showing decline had follow up at 1 month as the earliest[24, 40-43]. Of the reports showing decline, one third (10/30) had first follow-up after the first 30 days. Full or partial recovery occurred in most reports (fig 3). Recovery occurred at the earliest 1 day after surgery and at the latest after 24 months. In four reports, no recovery occurred within the follow-up period (5 days-12 months)[19, 31, 35, 44]. In seven reports, there was a decline of function after a previous assessment had shown recovery.

Incidence of cognitive dysfunction after surgery

The frequency of cognitive dysfunction after surgery was presented in 20 reports. Across these, the instruments for assessment, measurement criteria for dysfunction, and follow-up periods differed (table 2). Postoperative incidence ranged from 0-64%, incidence of cognitive dysfunction at baseline was reported in three reports, 8.2-28%.

Table 2. Reports with frequency of cognitive dysfunction in clinical trials

2a - Reports with frequency of cognitive dysfunction in clinical trials						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Chen, 2020	88	MMSE	Score <28	Day 1 & 3	16.3-64.4% (in total)	Dexmedetomidine intervention
Liu, T., 2021	100	MMSE	Z-score ≤ -2	1 day 2 days 3 days	10-25% 8-16% 4-10%	Transcutaneous electrical acupoint stimulation (TEAS) intervention
Zhang, J., 2019	140	MMSE	Not reported	1 day 3 days	8.8-21.7% 0-13.3%	Dexmedetomidine intervention No patients with neoadjuvant chemo- or radiotherapy
Bao, 2020	178	MMSE	Not reported	3 days	8.4-22.9%	Dexmedetomidine combined with ulinastatin intervention No patients with neoadjuvant chemo- or radiotherapy
Ding, 2022	40	Battery of 5 neuropsychological tests and HDS-R	>1 SD decline on ≥2 tests	5 days	5-25%	Dexmedetomidine intervention
Liu, Y., 2020	96	MMSE	>2 points decrease	7 days	12.5-29.2%	Dexmedetomidine combined with epidural blockade intervention
Wang, P., 2021	120	MMSE	≥3 points decrease	7 days	5.1-16.4%	Probiotics intervention 43% colorectal cancer patients in study population
Wang, Y., 2020	281	SPMSQ	>2 errors	Before surgery 30 days	16.3-17.1% 7.4-25.5%	Tailored Family-Involved Hospital Elder Life Program (t-HELP) intervention 19% colorectal cancer patients in study population
2b - Reports with frequency of cognitive dysfunction in observational studies						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Vardy, 2014	363	Battery of 7 neuropsychological tests, CANTAB FACT-COG	GDS* >0.5 >2 SD below HC on ≥1 test, or >1,5 SD on ≥2 below HC >1,5 SD below HC (≤119)	After surgery and before adjuvant treatment, or before neoadjuvant treatment.	30-47% 33-51% 18.5-21%	Cross-sectional Comparing localised to metastatic cancer patients Healthy controls (HC) 13-17% with neuropsychological testing, 17 % FACT-COG No patients with neoadjuvant chemo- or radiotherapy *GDS – Global deficit score
Lin, 2014	50	Battery of 7 neuropsychological tests	Z-score ≥1.96 on ≥2 test or	7 days	34%	46% colorectal cancer patients in study population

			composite Z-score			
Wu, 2016	110	CANTAB	Z-score <-1.96 on ≥2 test or combined Z-score <-1.96	7 days	26.4%	
Zhang, Y., 2019	77	Battery of 3 neuropsychological tests and MMSE	Z-score >1.96 or combined Z-score ≥1.96	7 days	24.7%	No patients with neoadjuvant chemo- or radiotherapy
Li, 2013	114	Clavien-Dindo classification	≥ grade 1	Within 30 days	1.8%	Complication defined as "Delusions requiring medical treatment" 37% colorectal cancer patients in study population
Fagard, 2017	190	Clavien-Dindo classification	≥ grade 1	Within 30 days	16.6%	Complication defined as "Neurological - including altered mental function" No patients with neoadjuvant chemo- or radiotherapy
Samuelsson, 2019	49	MMSE	Score <24	Before surgery 1 months 6 months 12 months	8.2% 5% 2.5% 2.7%	
Couwenberg, 2018	272	EORTC QLQ-C30	>10 points decrease (since baseline)	3 months 6 months 12 months 18 months 24 months	39.6-41.1% 35.2-41.1% 22.7-30.5% 18.5-33.3% 20.0-29.4%	Comparing abdominoperineal resection with low anterior resection 99.6 % had neoadjuvant chemo- or radiotherapy
Vardy, 2021	206	Patient's Disease and Treatment Assessment Form—General	≥4 (out of 10)	11 months 14.5 months 23 months	≈18-21% ≈14-17% ≈17-20%	Two separate symptoms "Trouble concentrating" and "Problems with memory". 68% colorectal cancer patients in study population 83% had chemotherapy, 21% radiotherapy
Deckx, 2015	321	EORTC QLQ-C30	Score <67. (lowest quartile)	Before surgery 12 months	18-28% 26-31%	Comparing older (≥70) cancer patients to younger Older controls 22% at both assessments 24% colorectal cancer patients in study population 26-54% had (neo)adjuvant therapy
Arndt, 2004	309	EORTC QLQ-C30	Any level of concern	12 months	55.9%	Cross-sectional 49.2% had adjuvant chemo- or radiotherapy
Frick, 2017	1129	Internet-based tool for the creation of survivorship care plans	Answer "yes,"	12 months	48.6%	Cross-sectional 89% colorectal cancer patients in study population 13% (colon), 6% (rectal) had surgery as only treatment

MMSE – Mini mental state examination, HDS-R - Revised Hasegawa's Dementia Scale, SPMSQ - Short Portable Mental Status Questionnaire , CANTAB – Cambridge Neuropsychological Test Automated Battery, FACT-COG – Functional Assessment of Cancer Therapy – Cognitive, EORTC QLQ-C30 - The European Organization for Research and Treatment of Cancer, Quality of Life of Cancer Patients

There were eight clinical trials presenting incidence, most of them had one assessment within 7 days of surgery (table 2a). The highest incidence reported was 64%, which represented a total of patients with cognitive dysfunction at postoperative day 1 and 3 in a control group[39]. A 0% incidence was reported 3 days after surgery in an experimental group[22]. Across all reports the incidence ranged 8.8-25% at the earliest follow up, 1 day after surgery. At 7 days after surgery an incidence of 5-29% was reported across all reports. All reports with more than one postoperative follow-up showed decreasing numbers of cognitive dysfunction over time. One study reported baseline incidence of 16-17%, at follow-up, 30 days after surgery, the incidence was lowered in the intervention group, and increased in the control group[27].

For the observational studies (table 2b) the highest incidence was 56%, reported in a cross-sectional report 12 month after diagnosis[45]. The remaining reports with data for 12 months had an incidence between 2.7-49%. The lowest incidence reported was 1.8% as a total within 30 days of surgery[34]. At 7 days after surgery an incidence of 25-34% was reported across all studies. In the reports with more than one postoperative assessment incidence generally decreased with time. At the latest follow-up, around 2 years after surgery, incidence ranged 20-29% across reports. One study reported incidence for older persons without cancer as 22% which was stable after 12 months, while the incidence increased for cancer patients[31]. A cross-sectional report showed differences in incidence with neuropsychological testing but not with self-reported measurers when comparing cancer patient to healthy controls[23].

Discussion

The 50 reports in this review assessed cognitive function after surgery using a diversity of methods and definitions. Due to the heterogeneity across definitions and assessment methods, it was difficult to synthesize information, and reach firm conclusions regarding incidence of cognitive decline after colorectal cancer surgery. Nevertheless, decline in cognitive function was found in more than 80% of the reports with preoperative levels, regardless of the instrument and the specific definition. Collectively, the data suggests that changes in cognitive function do occur in colorectal cancer patients who received surgery.

A limitation of this study, as inherent with all reviews, is the possibility that some relevant sources have been missed. However, the findings in this review are consistent with the broader literature. For example the EORTC-CRC Q30 was the most used instrument when measuring cognitive function after chemotherapy in a colorectal cancer population[46] and the MMSE is the mostly used screening tool for postoperative cognitive assessment[1]. Since this scoping review had an exploratory focus, we did no

formal rating of the quality of evidence and therefore any conclusions drawn based on the results of included studies must be made with caution.

A general concern with the data in this review is that a large portion is obtained through self-report or screening tools. Subjective complaints of cognitive function are poorly correlated with objective testing in cancer patients[23, 47]. It has therefore been suggested that subjective complaints might be an indicator of anxiety and depression rather than cognitive dysfunction[47, 48]. It is recommended that cognitive changes after surgery should be assessed with neuropsychological tests for specific cognitive domains rather than with screening tools[6, 49]. Among the reports in this review employing objective measurements, the use of screening tools was twice as common as neurophysiological testing. Of the studies that aimed to investigate cognitive function, fewer than half used neurophysiological tests. There has been discussion on whether screening tools are appropriate or not when detecting postoperative cognitive dysfunction[2], for detecting cognitive changes after cancer treatment screening tools are however not considered sufficient[50]. Another concern with the data is the potential overlap between postoperative decline of cognitive functions and postoperative delirium[6, 51]. Delirium has its own diagnostic definition, and focuses on awareness and by definition, to diagnose neurocognitive disorder, cognitive deficits cannot be present solely as part of delirium[7]. Only eight reports in this review performed a separate assessment of delirium making it uncertain in the other studies whether the cognitive decline reported was delirium induced or not, at least in the period directly after surgery when there is a risk of postoperative delirium[52].

Decline of cognitive function in the first 30 days after surgery is defined as *delayed neurocognitive recovery* in the recommendation on terminology of cognitive change after surgery as this period is affected by complicating factors such as delirium, immobility and analgesic medication[6]. About half of the reports in this review reported only on the period within the first 30 days and with only one of the interventional studies having follow-up after 30 days it is not known if the effects of interventions persist after the recovery window. Overall, it has been questioned if postoperative cognitive dysfunction persists over time[2]. A recently published study indicates that there is no cognitive impairment in the long term for colorectal cancer survivors[53]. It has been suggested that postoperative cognitive function should not be assessed later than 6-9 months after surgery[54] but in the recommendation of terminology *postoperative cognitive dysfunction* apply to new occurrence or deterioration of pre-existed impairment up to 12 months after surgery[6]. In this review recovery of cognitive function was reported in all but a few reports with preoperative values and follow-up after 30 days. Incidence in included reports decline

over time. However, the incidence of cognitive dysfunction after surgery might be underestimated during long-term follow-up due to the inability of patients with the worst declines to participate in studies[55]. This selection bias could also inflate reports of cognitive recovery since the study population may have a higher mean function over time as those with lower scores cannot continue their participation.

The heterogeneity shown in this review regarding instrument and criteria of measurements are similar to a recent review on cognitive impairment after chemotherapy in colorectal cancer patient[46] and has also been shown previously with assessment of postoperative cognitive dysfunction[1, 2, 54]. How to best measure cognitive function is beyond the scope of this review. However, advocates for patient-focused care have stressed that when assessing recovery after surgery, the patient should act as their own control[8]. Measurement criteria using that approach would reduce the risk that a decline in a person with normal high or low function might go unnoticed if they remain above or always was below a predefined threshold for impairment[7]. There is of course the discussion of what changes should be considered significant and the point of interest is perhaps better focused on if the functional decline affects the patient's daily life or not. Assessment of instrumental activity of daily living (IADLs) are considered a good indicator of problems derived from subtle cognitive decline[6, 7]. Yet only two reports in this review reported IADLs.

As there was no formal rating of the quality of evidence included in the scoping review, the overall conclusions are considered to have low evidence. Nevertheless, a majority of the reports in this review noted cognitive functional decline in the study populations with comparable preoperative levels. When it comes to colorectal cancer patients, adjuvant treatments as well as the cancer itself need to be considered as causative factors for cognitive decline[56]. A holistic approach to cognitive decline for all colorectal cancer treatments and the cancer itself would surely be beneficial. Therefore, extending recommendation of cognitive screening of patients receiving chemotherapy to all colorectal cancer survivors, regardless of treatment modality, could be of value and requires further investigation, especially considering that the existing recommendation has the lowest level of evidence[10]. To strengthen the evidence on cognitive decline after colorectal cancer surgery neurophysiological testing should likely be considering worth the effort in future research. Future research would also do well to considering separate assessment of delirium. Especially when assessing cognitive function soon after surgery, but it has implication also in the long run since there is an indication that those with postoperative delirium are less likely to recover from cognitive changes after surgery[51]. Studies assessing

both cognitive function and instrumental activities of daily living would also provide a more detailed account of how cognitive decline impacts patients' lives after colorectal cancer surgery. Randomized clinical trials with longer follow-up periods could also be a valuable contribution to provide knowledge on if a perioperative intervention would have effect on persistent cognitive decline.

Conclusion

A more unified approach when it comes to the criteria for measurement of postoperative cognitive function would be beneficial to align research and increase the quality of evidence. Longitudinal studies with follow-up both within and after 30-days, preferable with neuropsychological testing and separate assessment of delirium, would provide new knowledge on whether cognitive dysfunction persist after the recovery period. Randomised controlled trials with the same approach could also contribute with knowledge on whether interventions do reduce actual neurocognitive decline and not only delirium induced manifestation. There could also be room for more research that inform on the degree to which the postoperative cognitive function decline impacts the daily lives of colorectal cancer patients.

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Competing interest

None declared.

Author statement

Authors' contributions

CE are responsible for the overall content as gurantor and provided concept and protocol, screened based on all examination levels, charted and summarised data, and wrote the manuscript. EA reviewed protocol, screened based on title and abstract examination, revised manuscript, and provided clinical and research expertise. RL controlled charted data and exclusion based on full-text examination, and revised manuscripts. All authors read and approved the final manuscript.

Non-authors' contributions

Eva Hessman and Linda Hammarbäck, Biomedical Library, Gothenburg University Library, University of Gothenburg, Gothenburg, Sweden, advised on search strategy, conducted searches and retrieved full texts. Andreas Samuelsson, Scandinavian Surgical Outcomes Research Group - SSORG, screened based on title and abstract examination for subsequent search.

Patient and Public Involvement

Patients, or the public were not involved in the design, conduct, or reporting of this review.

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Data sharing statement

Data set available upon request, metadata available in supplement.

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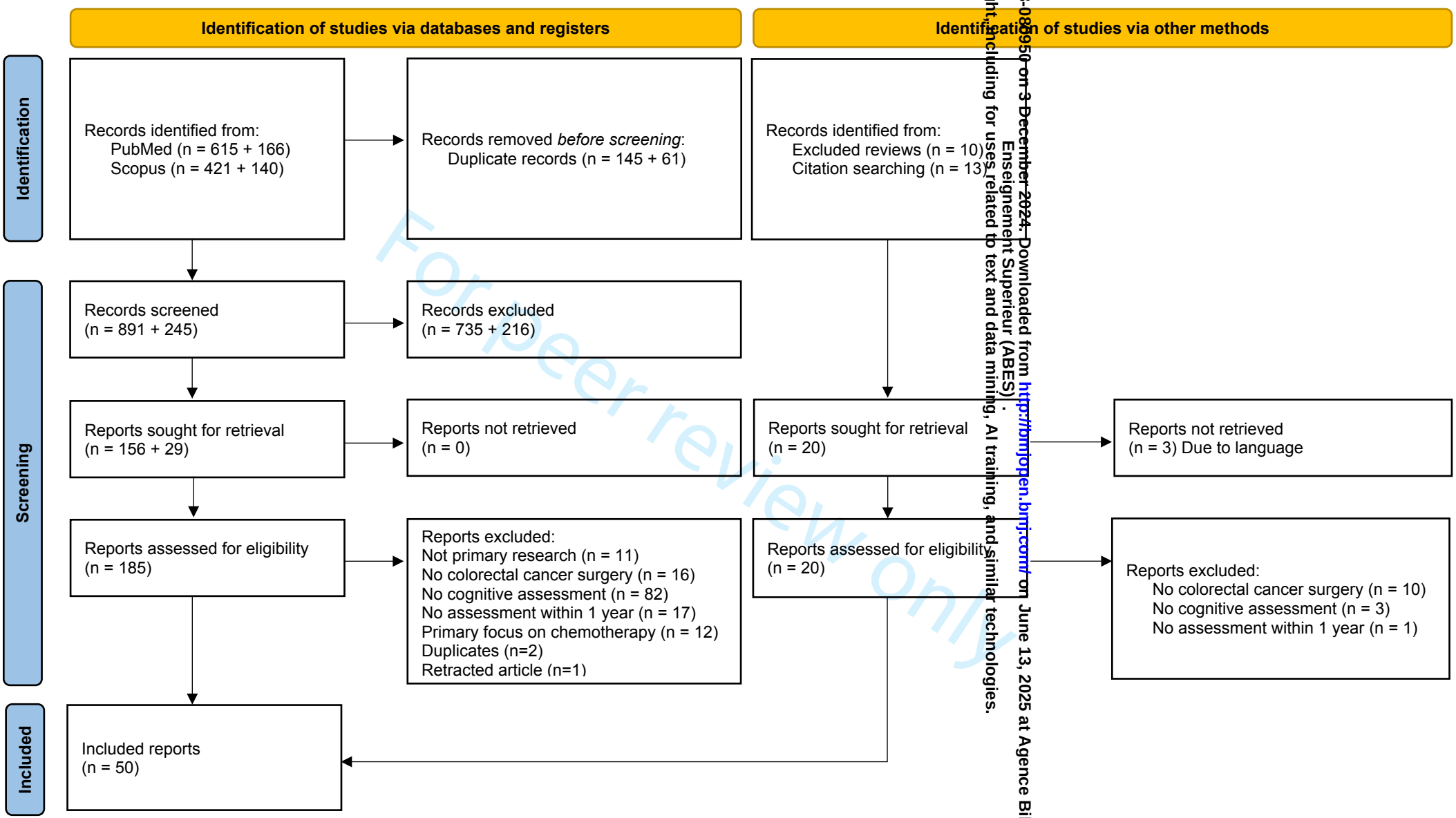
Figure legend

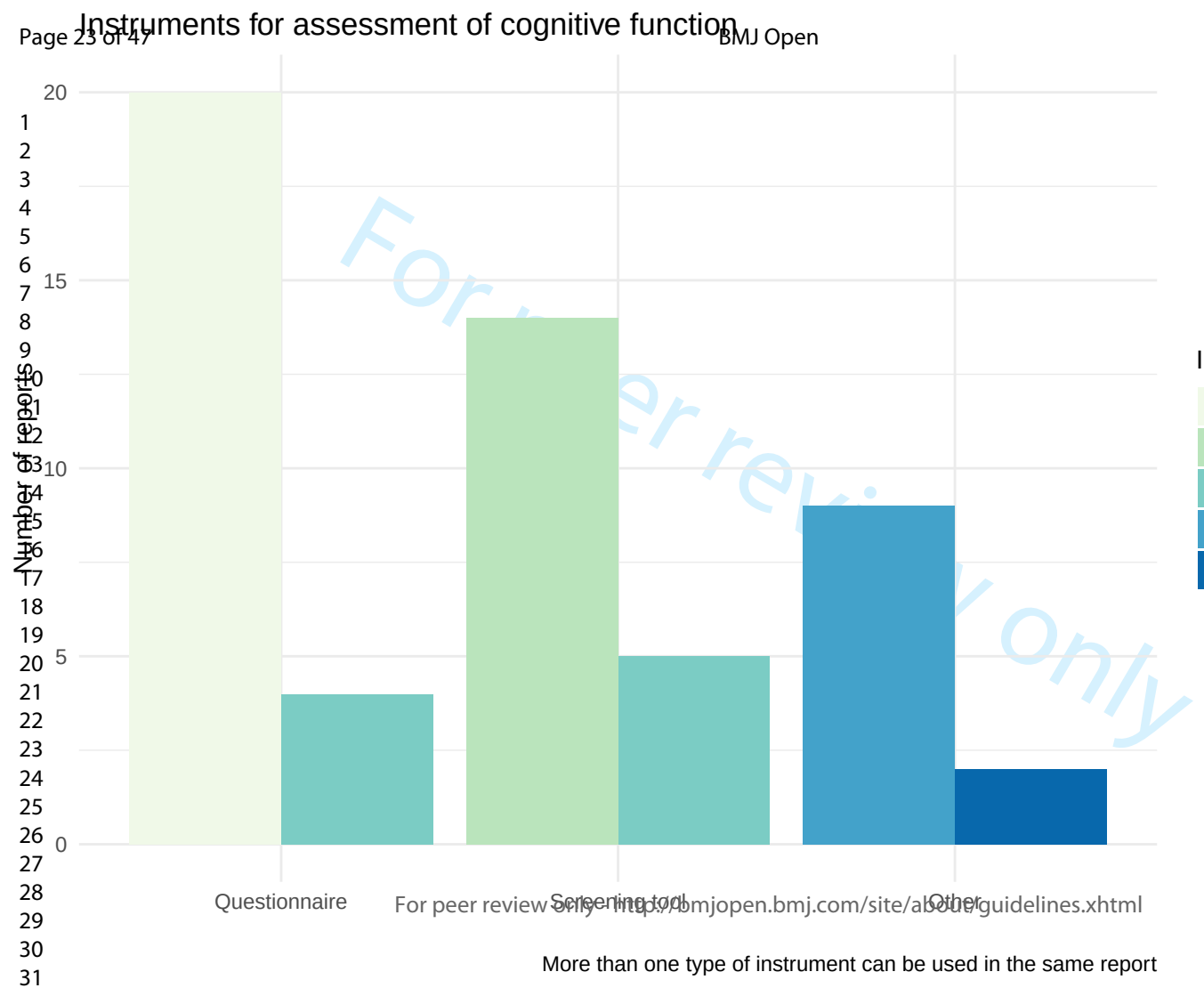
Figure 1. PRISMA Flow chart

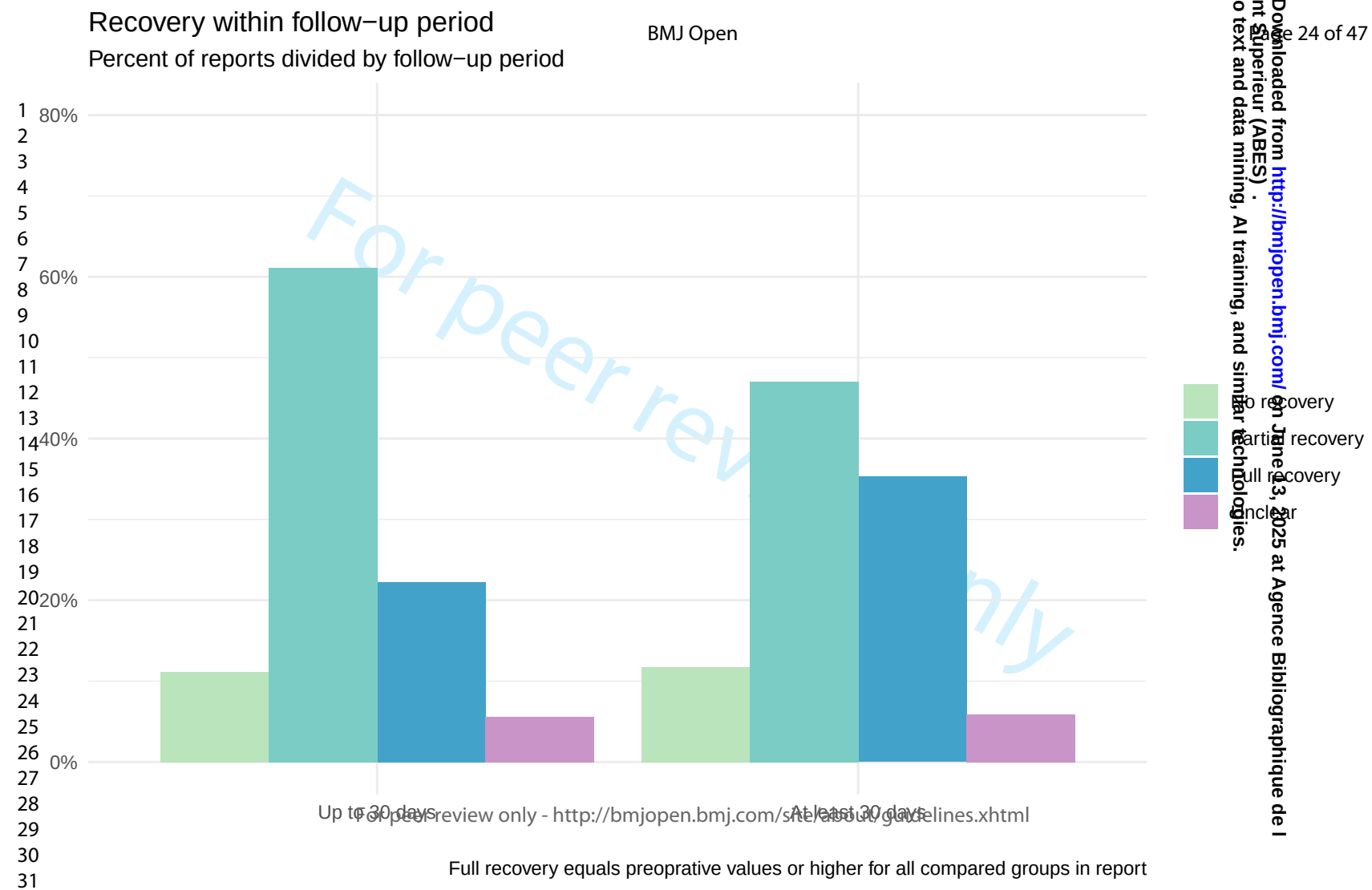
Figure 2. Graph of instrument for assessment of cognitive function

Figure 3. Graph of recovery within follow-up period

Fig 1: PRISMA 2020 flow diagram







Final search 2021-04-23

Database: PubMed searched on 2021-04-23

(Postoperative Cognitive Complications[mesh] OR POCD[tiab] OR PostOperative Delirium[tiab] OR postoperative decline[tiab] OR ((cognitive OR neurocognitive OR memory) AND (postoperative OR complication OR decline OR dysfunction OR disorder OR recovery OR impairment OR sequelae OR frailty)))

AND

(Colonic Neoplasms[mesh] OR Colonic Neoplasm[tiab] OR Colonic Neoplasms[tiab] OR Colon cancer[tiab] OR colonic cancer[tiab] OR colonic tumour[tiab] OR colonic tumours[tiab] OR colonic tumor[tiab] OR colonic tumors[tiab] OR Colorectal Surgery[mesh] OR Colorectal Surgery[tiab] OR Colon surgery[tiab] OR Rectal surgery[tiab] OR Colorectal Neoplasms[mesh] OR Colorectal Neoplasms[tiab] OR Colorectal Neoplasm[tiab] OR Colorectal cancer[tiab] OR colorectal tumours[tiab] OR colorectal tumour[tiab] OR colorectal tumors[tiab] OR colorectal tumor[tiab] OR rectal neoplasms[mesh] OR rectal neoplasms[tiab] OR rectal neoplasm[tiab] OR Rectal cancer[tiab] OR rectal tumours[tiab] OR rectal tumour[tiab] OR rectal tumors[tiab] OR rectal tumor[tiab])

No time restrictions
Limits English, Norweigan, Swedish, Danish 615 results

Database: Scopus searched on 2021-04-23

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

No time restrictions
Limit English, Norweigan, Swedish, Danish 421 results

PubMed 615 results
Scopus 421 results
Sum 1036 results

After de-duplication 891 results (145 articles removed)

Updated search 2023-01-02

Same as final search, same limitations except for time limit 2021-2023

PubMed results 166

Scopus results 140

Sum 306

After de-duplication 249

These 249 references are then compared with the final de-duplicated result from 2021-04-23. All duplicates (n=4) were removed so only the unique reports still remained from 2021 and 2022.

245 references were added to Rayyan and then Carolina Ehrencrona and Eva Angenete were invited.

Edit: 2023-02-08 Andreas Samuelsson was invited to Rayyan.

authors

Description	From Rayyan or EndNote

year

Description	From Rayyan or EndNote

title

Description	From Rayyan or EndNote if other sources

country - Country of study population

Type	Character

aim_category - Aim of report

Description	Derived from title and aim Cognition - if mentioned (including specific cognitive function i.e. memory or attention) not only delirium QoL - if mentioned (but not cognition) Recovery – recovery of surgery if mention, including postoperative complication (not sequalae in general from cancer (treatment))

Aim of report

1	Cognition
2	QoL
3	Recovery
4	Other

endpoints

Description	Derived from aim texts and title

size - Size of study population

Description	Included in analysis. Healthy control not included.

crc_size - Colorectal population

Description	Percent colorectal cancer patients of total study population

crc_type - Tumour location

Tumour location

1	Colon
2	Rectum
3	Colon or Rectum

Note

Description	If population is divided as Colon and Rectal separate specify. Note if characteristic has been charted for CRC only if mixed population. Other notes regarding characteristics

age_low - Lowest age of participant

Description	If actual range is missing, lowest possible age (from inclusion criteria) used Yellow if not found

age_high - Highest age of participant

Description	If actual range is missing, highest possible age (from inclusion criteria) used Yellow if not found Yellow if not found

age_central - Central tendency of age

Description	Chart mean if possible, otherwise median If divided by groups (M1*n1+M2n2...)/N

female

Description	Precent

other_treatment - Other cancer treatment than surgery

Description	Chart if radiotherapy or chemotherapy as neoadjuvant and adjuvant, if given before assessment

Other cancer treatment than surgery

0	Not reported
1	No (surgery only)
2	Yes, chemotherapy only
3	Yes, chemo- and/or radiotherapy
9	Unclear

comment

Description	On other treatment or method or compared groups

method

Description	If stated as non-randomized charted as cohort.
1	RCT
2	Cohort
3	Case report

assessment_points - Cognitive assessment points

Description	Including baseline

follow_up_period – Follow up period for cognitive assessment

Description	Baseline not included.
1	Up to 30 days
2	Both before and after 30 days
3	30 days or above
9	Uncertain

groups - Comparison of groups

Description	Predefined groups only, chart even if no comparison is made but note why Chart groups name and n for each group. Chart significant differences in cognitive assessment

POCD

Type	Code
Description	Proportion of cognitive dysfunction reported Yes of No. All definitions valid. Values charted separately in follow-up
0	No
1	Yes

instrument

Description	Note all instrument used where postoperative cognitive outcome is reported

neuro

Description	Neuropsychological/Neurocognitive test used

PROM

Description	Patient reported outcome used (questionnaires)

Screen

Description	Screening tools used

other

Description	Other instrument used

administration

Description	Note how instrument were administered to participant, if specific condition, location, personal was used

IADL

Description	Note yes if it was reported that instrumental activity of daily living was measured after surgery. Note 9 if measured but only before surgery.
0	No
1	Yes

9	Only before surgery

decline

Description	Decline in cognitive function first follow-up after surgery compared to presurgery values. Chart yes if any groups on any assessment have declined result at first follow up, need not be significant.
0	No decline of function at first follow-up
1	Decline reported on first follow up
8	Uncertain, conflicting values reported
9	No preop values to compare with

recovery - Recovery to preoperative values

Description	Chart yes to preop if any group during any follow up is above or at preop values. Chart yes not preop if no group return to or above preop values. Chart no if no group recover during follow up.

Recovery to preoperative values

0	No recovery
1	Recovery to preop levels
2	Recovery but not to preop levels
8	Unclear data
9	No preop values

recovery_timepoint

Description	Chart time for recovery to preop values and which follow up T in () and group if relevant, chart groups separately if preop values occurred at different time points. Chart last follow up if none recovered to preop values

fluctuation

Description	Chart if decline occurred after recovery for any group If no preop values chart not applicable - 9
0	No
1	Yes

9	NA

end_recovery - Recovery at end of follow-up

Description	Chart Full recovery only if all compared groups reach preoperative values or higher. Otherwise chart partial recovery unless no recovery at all.

Recovery to preoperative values

0	No recovery
1	Full recovery (of all groups)
2	Partial recovery (not all compared groups or not to preoperative values)
8	Comparable values not reported

delirium

Description	Separate assessment of delirium Also note yes if delirium was exclusion criteria
0	No
1	Yes
9	Unclear

nomenclature

Description	Chart once per term Chart longest term (i.e. postoperative cognitive dysfunction vs cognitive dysfunction) if one term includes another Only chart neutral term (i.e. cognitive function) if no term indicating decline is used

definition - Criteria of measurement

Description	Chart criteria for cognitive dysfunction. Also chart general criteria if it applied to cognitive outcome as well.

narrative

Description	Narrative description of (postoperative) cognitive dysfunction.

follow_up	
Description	Consecutive number for assessment. Chart 0 for preoperative assessment.

months	
Description	timepoint for follow up in months, if stated as years transformed to months 888 - not applicable

days	
Description	timepoint for follow up in days 888 - not applicable

hours	
Description	timepoint for follow up in hours, charted as reported (i.e. > 23 h reported as hours not days) 888 - not applicable

comment_follow_up	
Description	Specification of time point

outcome - Outcome of cognitive assessment	
Description	If POCD (or comparable) % reported If symptom % reported, if no exact number use > or < nearest scale point and assumed value in () Significant difference between groups (with values not p) If baseline values chart those Note recovery or decline (both significant and not) no numbers needed If reported as recovered to preoperative levels note when, else not if value equal or above preop

Comment_outcome	
Description	Note inconsistency, n if group change over time, other useful information regarding interpretation of outcome reported

Summary of all included reports

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Arndt, 2004	EORTC QLQ-C30	One year after diagnosis	Cognitive functioning	Any level of concern Differences of more than 10 points are clinically meaningful	55.9% with any level of concern Clinically significant different between CRC and general population under 60 years Reported as similar responses between those who underwent adjuvant therapy or surgery alone (data not shown).
Bao, 2020	MMSE	1st and 3rd day after surgery	Postoperative cognitive dysfunction (POCD)	NR	Combination group, CG, dexmedetomidine and ulinastatin, had significantly higher function through follow up than routine group, RG, (dexmedetomidine only). POCD total 8,4%(CG) and 22.89%(RG), at day 1 7.4% (CG) and 16.9% (RG) and day 3 1.05% (CG) and 6.0% (RG)
Beaussier, 2006	MMSE, Digital Symbol Substitution Test	Preoperative and daily until discharge	Mental function impairment Postoperative impairment of mental skills	NR	No significant different between groups (preoperative intrathecal morphine or saline) regarding mental functions after 24 h or return to preoperative values
Brown, 2014	EORTC QLQ-C30	Baseline, 3 months, 6 months, 18 months, and 36 months	Cognitive functioning Higher mental functions Cognitive capacity	NR	No difference in cognitive function between patient who had a complication within 30 day of surgery and those who did not.
Chen, 2020.	MMSE	Preoperative, postoperative day 1 and day 3	Neurocognitive function Postoperative cognitive dysfunction/impairment Cognitive brain dysfunction Disorder of brain function.	Score 24-27 mild, 19-23 moderate, <18 severe impairment.	Study group (dexmedetomidine) had significantly higher scores than control(saline) during follow-up. Total cognitive impairment study group 16%, control 64%.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, after 3, 6, 12, 18, and 24 months	Cognitive functioning	Clinically relevant worsened cognitive domain scores relative to their baseline score was defined as a decrease of > 10 points (10% of the scale breadth)	Significantly lower cognitive function scores for the whole study population compared to age-match reference population at all follow-ups. Compared to baseline significant mean difference were found at 3 & 6 months for those with abdominoperineal resection (APR) and during the whole follow up for those with low anterior resection (LAR). Proportion of worsened cognitive domain: 3 months APR 41%, LAR 40%, 6 months APR 35%, LAR 41%, 12 months APR 23%, LAR 31%, 18 months APR 19%, LAR 33%, 24 months APR 29%, LAR 20%
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, 3, 6, 12 months	Cognitive function	NR	Older patients (≥ 70 years) had significant lower cognitive function than reference population at all follow up. Younger patients had significantly lower function at 3 and 6 months compared to baseline and lower scores at 3 months compared to older patients.
D'Ambrosia, 2019	EORTC QLQ-C30	Preoperatively. After 1, 6, 12 and 36 months.	Cognitive functioning	NR	Scores for both groups (Laparoscopic total mesorectal excision, LTME, and Endoluminal loco-regional resection, ELRR) where above preoperative levels at first follow up. At 6 months LTME declined with significant difference to ELRR that was stable. Thereafter LTME declined, at 36 months to preoperative levels, while score in ELRR improved further.
De Souza, 2018	EORTC QLQ-C30	Before, 3 months and 12 months after surgery.	Cognitive function	Score 0-25= very poor, 26-50 = poor, 51-75= good, 76-100= very good	Cognitive function changed from good before surgery to very good at both follow ups.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Decks, 2015	EORTC QLQ-C30	Baseline and one-year-follow-up	Cognitive impairment	The frequency of cognitive impairment was operationalized by using the lowest functioning quartile as cut-off, this corresponded to a score <67 in all three groups.	Frequency of impairment for younger cancer patient, YCP, (<70 years) 28% at baseline and 32% at 1 year. For older cancer patients, OCP, it was 28% at baseline and 26% at 1 year. For older patients without cancer, OPwC it was 22% at both time points. OCP had significantly higher cognitive function at baseline compared with OPwC. OCP had a significant decline between baseline and 1 year.
Ding, 2022	Revised Hasegawa's Dementia Scale (HDS-R). Digit span subtest, digit symbol test, trail-making test, word recall, verbal fluency test.	At 1 day before the operation, 1 day after the operation, and 5 days after the operation	Neurocognitive Dysfunction Postoperative cognitive dysfunction (POCD) Postoperative consciousness dysfunction Hippocampal-dependent cognitive function"	The postoperative test value was compared with the preoperative test value. If the deviation value exceeded one standard deviation value, the function was judged as the postoperative function decline. POCD was if two or more postoperative tests showed a simultaneous functional decline.	Significantly decreased score on HDS-R in both Dexmedetomidine (DEX) and control group at both follow ups. Compared to control significantly higher values for DEX group at both follow up. Significantly higher incidence of POCD in control group 25% than DEX group 5% DEX at T2
Fagard, 2017	Clavien Dindo classification	Within 30 days after surgery	Cognitive impairment Altered mental function	Neurological - including altered mental function	Neurological complications total 12.6%
Frick, 2017	Internet-based tool for the creation of survivorship care plan	Median 12 months after diagnosis	Cognitive changes Neurocognitive decline	NR	Cognitive changes total population 48.6%.
Gamerio, 2008	Stroop Test, German Trail-Making Test, Wordlist power level and speed	Preoperatively and at follow-up until postoperative day 4	Early postoperative cognitive dysfunction/ changes Postoperative neuropsychological dysfunction Long-term cognitive deterioration Cognitive abilities/state/ Cognitive impairments/disturbance	NR	No significant differences between laparoscopic and conventional colectomy.
He., 2017	MoCA	One day before surgery. One, three and seven days after surgery.	Cognitive function impairment Postoperative cognitive dysfunction (POCD) Cognitive decline	Score < 26 is considered abnormal	Significantly difference between control and Remote ischemic preconditioning group one day and three days after surgery.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
How, 2012	EORTC QLQ-C30	One day before surgery or before neoadjuvant therapy, 1 and 2 year postoperatively	Impaired cognitive function	NR	Significantly higher mean cognitive function score for those with abdominoperineal excision (APE) at 1 year compared to those with low anterior resection (LAR)
Janssen, 2020	MMSE	Baseline (the first outpatient clinic visit, after 6 months and after 1 year.	Cognitive decline (Persistent) postoperative cognitivie dysfuntion Cognitive impairment	A score equal to or lower than 24 indicating cognitive impairment	Significant lower score at baseline for group with delirium. Significant decline in score compared to baseline during follow up for group without delirium.
Kinoshita, 2018	EORTC QLQ-C30	Before surgery, 1 month, 6 months and 12 months after surgery	Cognitive functioning	A change of score of 5–10 points indicate a minimal change, while a change of more than 20 points indicates a large change	Significant change from before surgery at 1 month for age ≥60. No significant difference between age <60 and ≥60. at any time-point.
León Arellano, 2020	EORTC QLQ-C30	1-2 days before surgery, at Postoperative day 7 and 30,	Cognitive function	NR	Significant decline at both follow up.
Li, 2013	Medical record Clavien Dindo classification	Within 30 days after surgery	Postoperative cognitive dysfunction	Delusions requiring medical treatment	Postoperative cognitive dysfunction as a complication in 2 patients.
Lidenzi, 2015	EORTC QLQ-C30	One day before, second and fifth day after surgery, one and three months after surgery	Cognitive functioning	NR	Decline in cognitive function scale on second day with recovery on fifth day. Back to preoperative levels at one month and above preoperative levels at three months.
Lin, 2014	Hopkin Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Trail-Making Test; Benton Judgment of Line Orientation, Digit Span Test; Symbol-Digit Modalities Test, Index, verbal fluency test	Before surgery and after 1 week or on the day of hospital discharge if earlier than 1 week	Cognitive decline/deterioration Post-operative cognitive dysfunction (POCD) (Neuro)cognitive deficit performance deficit in cognitive/hippocampus dependent memory cognitive impairment memory dysfunction/deficit neurocognitive dysfunction	POCD was determined using Z score recommended by International Study of Postoperative Cognitive Dysfunction (ISPOCD) studies Patients were regarded as developing POCD if the Z score was ≥ 1.96 on ≥ 2 individual cognitive tests or the composite Z score was ≥ 1.96."	Incidence of POCD 34 %.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Liu, 2021	MMSE	One day before surgery, Postoperative days (POD) 1, 2, and 3	Postoperative cognitive decline (POCD) cognitive dysfunction	POCD was defined as a Z-score −2 based on a pre- and postoperative MMSE The following formula was used: [(postoperative MMSE–preoperative MMSE)-ΔX MMSE normative population]/[SD ΔX MMSE normative population]. In this current study, ΔX MMSE normative population = 0.5 and SD (ΔX MMSE normative population) = 1.5 were used to calculate Z-score	POCD for the control group was 25%, 16% and 10 % for POD1-3. For the transcutaneous electrical acupoint stimulation (TEAS) group POCD was 10%, 8% and 4% on POD1-3. There was no significant difference between group on POCD on each day. On cumulative duration TEAS group had significantly lower incidence than control group on postoperative day 2 and 3.
Liu, 2020	MMSE	Before and at 4, 12, 24, and 48 hours and 7 days after surgery	(Early) Postoperative cognitive dysfunctioning (POCD)	A mean MMSE score decline >2 points between postoperative and preoperative surgery	Combined group (dexmedetomidine and epidural blockade) had significantly higher scores than all other groups (dexmedtomidine only, epidural only, control) at 12 to 24 h and higher than all but dexmedetomidine only at 48 h and 7 days
Mann, 2000	Abbreviated Mental Test (AMT)	Day before surgery, day of surgery (PM), twice a day (AM, PM) day 1-5 after surgery	Mental status Postoperative cognitive dysfunction Cognitive impairment	Decrease in the AMT score of 2 or more points (as part of a delirium diagnosis)	Significant lower scores for PCA-group (general anaesthesia and postoperative morphine) compared to PCEA-group (general anaesthesia combined with epidural bupivacainesufentanil) on day 4 AM and day 5 PM.
Miniotti, 2019	EORTC QLQ-C30	Majority within 12 months of diagnosis.	Cognitive functioning problems in concentrating and remembering	NR	Significantly lower scores on cognitive function scale than reference population from EORTC reference value manual.
Monastyrska, 2016	EORTC QLQ-C30	One day prior to and 6 months following surgery	Cognitive functioning	NR	Both groups, lower anterior resection (LAR) and abdominoperineal resection (APR) significantly higher mean scores at follow up with LAR significantly higher than APR.
Ng, 2013	EORTC QLQ-C30	Before surgery and at 4, 8 and 12 months after surgery	Cognitive functioning	A difference in mean QoL scores of more than 10 points was regarded as clinically significant	Significant lower scores at 8 months for those with open resection compared to laparoscopic as well as clinically significant decline since baseline.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Nolli, 2005	NR	Re-admission (after a brief domiciliary period) Discharge (after 60 days) One year follow up	Cognitive defects	NR	On discharge deficits of attention and memory. At one year suboptimal recovery of attention and dramatic fixation memory deficit (development of Wernicke-Korsakoff syndrome).
Nusca, 2021	EORTC QLQ-C30	The first post-surgical follow-up visit approximately ten days after surgery. after the end of the exercise program, 2 months and: 4 months thereafter.	cognitive impairment	NR	Significant higher cognitive function score in the group attending a 2-month-long supervised and combined exercise–training program during the postoperative period than the group which did not at the end of the exercise program.
Olin, 2005	MMSE	At 3–4 weeks before surgery, day for postoperatively and at discharge.	Cognitive impairment Cognitive status Cognitive dysfunction Mental function	Scores from 0 to 10 of a total 30 corresponded to severe cognitive impairment	Significantly lower scores at day 4 in the long postoperative delirium (≥ 3 days) group compared to the group with no delirium.
Samuelsson, 2019	MMSE	Preoperative and at follow-up 1, 3 and 12 months after surgery	Cognitive impairment Cognitive decline	Possible cognitive impairment <24	At risk for cognitive impairment 8.2% preoperative, 5% at 1 month, 2,5% at 3 months, 2,7% at 12 months. Reported as cognition was improved compared to baseline at 3 months.
Scarpa, 2014	EORTC QLQ-C30	Admission, 1 month and 6 months	Cognitive function	NR	Significant higher values on cognitive function scale in the laparoscopic group for younger (<70 years) compared to elderly at 1 and 6 months.
Soares-Miranda, 2021	EORTC QLQ-C30	Six months post-surgery.	Cognitive impairment Cognitive capacity Cognitive decline	NR	Unadjusted and adjusted (age, sex, and cancer stage) linear regression showed that better performance in 6-minute walk test was associated with higher cognitive function.
Tang, 2021	MoCA	At 6, 12, 24, and 48 h after the operation.	Cognitive dysfunction (Early) Postoperative Cognitive dysfunction (POCD)	A lower score indicated lower cognitive function, < 26 indicated abnormal.	Observation group (dexmedetomidine) had statistically significant higher cognitive function compared to control over follow up. There was also a significant change in function over time within both groups.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
van der Vlies, 2022	EORTC QLQ-C30	At diagnosis and 3 months after diagnosis	cognitive impairment	NR	Participants with decreased health related quality of life (HRQL) had statistically significant more affected cognitive function than participants with preserved HRQL. The decline was lager in patients who did not undergo surgery, either due to poor performance status or personal preference. In the surgically treated patients, there was slight impairments of cognitive functioning.
Vardy, 2014	Battery of clinical neuropsychological test (Letter-Number Sequencing, Digit Span, Spatial Span, Digit symbol, Trail Making Test A&B, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised) CANTAB and modified FACT-COG	Assessment after surgery before adjuvant treatment or before any treatment if neoadjuvant treatment was planned	Cognitive impairment Cognitive decline	Global cognitive impairment defined as Global Deficit score (GDS) of >0.5. Impairment on individual cognitive tests in five domains. International Cognition and Cancer Task Force (ICCTF), ≥1 standard deviation (SD) below the HC on at least one cognitive test, or >1.5 SD below on two or more tests A score <1.5 SD below the HC mean on the FACT-Cog was classified as perceived cognitive impairment (≤119/168)	Significant difference between localised cancer and healthy controls in cognitive impairment regardless of objective test method and definition. There was no significant difference between those evaluated pre- and post surgery in those with localised cancer. Frequency of cognitive impairment: Clinical test (GDS:ICCTF) / CANTAB (GDS:ICCTF) Localised cancer 45%:51% / 30%:39% Metastatic cancer 47%:49% / 31%:33 Healthy controls 15%:17%%/13%:17% Frequency of perceived cognitive impairment; localized cancer 21%, metastatic 18.5%, healthy controls 17%.
Vardy, 2021	Patient's Disease and Treatment Assessment Form-General	(T1) Initial visit (median 11 months after diagnosis) (T2) First follow up (median 3,6 months after T1) (T3) One year follow up	Trouble concentrating Memory impairment	Symptoms of at least moderate severity (4 or above out of 10)	Trouble concentrating : Above 20% at T1, reduced to less than 20% at T2-T3 Problems with memory: Less than 20% at T1, reduced at T2 and increased to 20% at T3.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Visovatti, 2016	Attention Network, Test (ANT),, The digit span, The Trail Making Test , The Rey Auditory Verbal Learning Test , The Attentional Function Index, The Everyday Memory Questionnaire	Within six months of a new diagnosis	Cognitive impairment Cognitive changes Cognitive problems Cognitive decline	NR	Participants with cancer had significantly slower response time on ANT, lower scores at digit span forward and trail making test A and attention composite score.
Wang, H., 2015	EORTC QLQ-C30	Preoperatively and postoperative day (POD) 3, 6, 10, 14, 21, 28	Cognitive functioning	EORTC guidelines; clinically significant change: 10 ‘‘little”, 10–20 ‘‘moderately” 20 ‘‘very much” better or worse	Significant less decline of cognitive function scale in ERAS-group than control POD3 and POD6. Recovery to preoperative values for ERAS-group at POD21 and control at POD28.
Wang, P., 2021	MMSE	Admission and the 7th day post-surgery	Postoperative (neuro)cognitive impairment	Postoperative cognitive impairment defined as decline in MMSE score of 3 or more points	Probiotic group (twice daily until discharge) had significantly higher MMSE score than control at 7 days after surgery. Postoperative cognitive impairment at day 7 probiotic group 5.1%, control 16.4%
Wang, Y., 2020	Short Portable Mental Status Questionnaire	Day before the surgical procedure, discharge, 30 days after discharge	Cognitive changes Cognitive impairment	Declined on SPMSQ at discharge; 0 to 2 errors indicate normal mental functioning;	Significantly higher proportion of intact cognitive function in patients on tailored family-involved Hospital Elder Life Program (t-HELP) units which increased over time compared to usual care units which decreased. Significant lower with decline on SPMSQ at discharged in t-HELP units 0,8% vs usual care units 7%.
Wu, 2016	CANTAB	On the day before surgery, and at 7 days and at 3 months after the surgery	Postoperative cognitive dysfunction (POCD) Cognitive impairment Cognitive function change"	POCD was defined when the reliable change index RCI score was <–1.96 at least on 2 tests or when the combined Z score was <–1.96	POCD 26.4% at 7 days, no report for 3 months.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Yang, 2019	MMSE	Before anaesthesia and 4 h, 24 h and 48 h after anaesthesia.	Postoperative cognitive function Cognitive ability	NR	Significantly higher scores for sevoflurane group (SEV) than isoflurane group (ISO) up to second follow up (24 4h). Significantly lower scores for both groups compared to before anaesthesia at 4 h and 24 h after anaesthesia
Zhang, C., 2020	MMSE	At 1h, 6h, 24h and 48h after surgery	Cognitive functioning	NR	Significant higher scores for combination (epidural blockade and parecoxib) group compared to epidural only group and control during all follow up, as well as epidural against control.
Zhang, J., 2019	MMSE	One day before surgery and 1 day and 3 days after surgery.	Postoperative cognitive dysfunction (POCD)	28-30 normal cognition, 24-27 mild cognitive dysfunction, 19-23 moderate cognitive dysfunction and 0-18 severe cognitive dysfunction	Significant higher score in experiment group (dexmedetomidine) than control (saline) during follow-up. Significantly lower scores in both groups compared to before surgery at both follow-ups. POCD in experiment group 9 % day 1 and no day 3. In control 22% day 1 and 13 % day 3.
Zhang, X., 2020	EORTC QLQ-C30	At admission, 3 month and 6 month follow up	Cognitive function	NR	No significant difference in cognitive function between control group and group which received psychological intervention.
Zhang, X., 2019	MMSE	Before anaesthesia, 1 day, 3 days and 5 days after operation	Postoperative perceptual function Postoperative cognitive impairment/dysfunction"	NR	Observation group (sevoflurane inhalation combined with epidural anaesthesia) had significantly higher scores at day 1 and 3 compared to control group (propofol general anaesthesia). Significant lower for both groups day 1 and 3 compared to baseline. Significant recovery day 3 compared to day 1 as well as day 5 compared to day 3 and day 1.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Zhang, Y., 2019	MMSE, visual verbal learning test, digital span test, digital symbol test	One day before surgery Seven days after surgery	Postoperative cognitive dysfunction (POCD)	POCD was diagnosed when the score was greater than 1.96 or the combined Z score was ≥1.96	POCD 24.7%.
Zhou, 2018	Attention Network Test (ANT)	Pre-operatively and at day 1 and day 5	Postoperative attention network dysfunction Cognitive changes Postoperative cognitive impairment Postoperative cognitive dysfunction (POCD)	NR	Significant difference between bispectral index monitoring group (BIS) and non-BIS (control) group on alerting and orientation on day 5. Significant change for both groups in all domains (alerting, orientation, and executive control) at day 1 compared to baseline. At day 5 significant change in executive control for BIS and all domains for non-BIS group. Age was significantly correlated with pre-operative alerting function in the BIS and non-BIS group. Propofol (general anaesthesia) was significantly correlated with alerting, orientation, and executive control at postoperative day 1 and 5.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Table of study characteristic

Report	Population (n, cancer, country)	End points	Summary
Arndt, 2004	309, Colorectal cancer 100%, Germany	Quality of life	Observational study comparing cancer survivors with general population
Bao, 2020	178, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical trial on comparing dexmedetomidine to ulinastatin combined with dexmedetomidine in elderly after laparoscopic surgery with no previous chemo or radiation therapy
Beaussier, 2006	52, Colorectal cancer 100%, France	Postoperative recovery including mental function	Randomised controlled trial comparing intrathecal morphine with IV PCA morphine compared to intravenous morphine alone in elderly patient undergoing major colorectal surgery.
Brown, 2014	614, Colorectal cancer 100%, United Kingdom	Quality of life	Longitudinal observational study of complications effect on long-term quality of life after colorectal cancer surgery comparing patient with 30 days complications to those with no complications.
Chen, 2020.	88, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial investigating protective effect of dexmedetomidine
Couwenberg, 2018	270, Rectal cancer 100%, the Netherlands	Quality of life	Longitudinal observational study comparing to general population to patient undergoing low anterior resection and abdominoperineal resection
Couwenberg, 2018	345, Rectal cancer 100%, the Netherlands	Postoperative complications and quality of life	Longitudinal observational study comparing older and younger patient with rectal cancer to reference population and the impact of postoperative complication in elderly
D'Ambrosia, 2019	39, Rectal cancer 100%, Italy	Quality of life	Longitudinal observational study of patient with T2-T3 rectal cancer comparing laparoscopic total mesorectal excision and endoluminal locoregional resection. Patients with adjuvant chemotherapy was excluded.
De Souza, 2018	29, Rectal cancer 100%, Brazil	Quality of life	Longitudinal observational study of patient treated with curative intent.
Deckx, L., et al., 2015	321, Colorectal cancer 24%, Belgium and the Netherlands	Cognitive function, depression, and fatigue	Longitudinal observational study comparing older and younger cancer patient to older persons without cancer.
Ding, 2022	40, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial on effects of dexmedetomidine in elderly patients after laparoscopic surgery
Fagard, 2017	190, Colon cancer 86%, Rectal cancer 14%, Belgium	Postoperative complications	Observational study of association between geriatric screening and 30 days complication after colorectal cancer surgery in older patients. Patients receiving neoadjuvant therapy where excluded.

Report	Population (n, cancer, country)	End points	Summary
Frick, 2017	1129, Colon cancer 70%, Rectal cancer 19%, international	Sequelae in cancer survivors	Cross-sectional study of persons using an internet-based tool for creating Survivorship care plans
Gamerio, 2008	70, Colorectal cancer 100%, Germany	Postoperative cognitive function and mood	Observational study comparing laparoscopic and open colectomy
He, 2017	90, Colon cancer 100%, China	Postoperative cognitive function	Randomised clinical trial on effects of remote ischemic preconditioning in elderly
How, 2012	62, Rectal cancer 100%, United Kingdom & Germany	Quality of life	Longitudinal observational study comparing low anterior resection and abdominoperineal excision
Janssen, 2020	265, Colorectal cancer, proportion not reported, Netherlands	Quality of life, cognitive function, and depressive symptoms	Observational study on impact of postoperative delirium after elective surgery for colorectal cancer and aortic repair and in older patients
Kinoshita, 2018	120, Rectal cancer 100%, Japan	Quality of life	Longitudinal observational study of age-related factors after sphincter saving surgery comparing those older or younger than 60 years old.
León Arellano, 2020	40, Colorectal cancer 100%, Spain	Postoperative recovery and quality of life	Observational study on ERAS
Li, 2013	114, Colorectal cancer 37%, China	Postoperative complications	Observational study of relationship between blood lactate concentration and complications after 30 days in patients undergoing major elective abdominal surgery
Lidenzi, 2015	82, Colorectal cancer 100%, Lithuania.	Quality of life	Observational longitudinal study in early postoperative period
Lin, 2014	50, Colorectal cancer 46%, China	Postoperative cognitive function	Observational study on the role of HMGB1 on cognitive decline after major gastrointestinal surgery
Liu, T., 2021	100, Colon cancer 100%, China	Postoperative cognitive function	Randomised controlled trial on effects of transcutaneous electrical acupoint stimulation in elderly patients undergoing laparoscopic surgery
Liu, Y., 2020	96, Colorectal cancer 100%, China	Postoperative recovery	Randomised clinical trial comparing dexmedetomidine, epidural blockade, and combination of both in elderly after radical resection
Mann, 2000	70, Colon cancer 66%, France	Postoperative recovery	Randomised controlled trial comparing general anaesthesia with postoperative morphine (PCA) or epidural bupivacainesufentanil anaesthesia (PCEA) after major abdominal surgery in elderly patients

Report	Population (n, cancer, country)	End points	Summary
Miniotti, 2019	203, Colon cancer 71%, Rectal cancer 29%, Italy	Quality of life and psychological outcome	Cross-sectional study of supportive care needs in colorectal cancer patients compared to reference population-
Monastyrska, 2016	100, Rectal cancer 100%, Poland	Quality of life	Longitudinal observational study comparing lower anterior resection and abdominoperineal resection
Ng, 2013	74, Rectal cancer 100%, China	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery
Nolli, 2005	1, Colon cancer, Italy.	Present clinical and radiological features	Case report of a patient developing Wernicke's encephalopathy
Nusca, 2021	11, Colon cancer 73%, Rectal cancer 27%, Italy	Quality of life, function, and nutrition	Pilot study of effects of postoperative physical exercise program after laparoscopic surgery.
Olin, 2005	51, Colon cancer (proportion not reported), Sweden	Postoperative delirium	Observational study investigating occurrence and associated factors of delirium in elderly patients undergoing major abdominal surgery
Samuelsson, 2019	49, Colorectal cancer 100%, Sweden	Postoperative complications and recovery	Longitudinal observational study investigating predictive value geriatric assessment tools in patients 75 year or older
Scarpa, 2014	116, Colorectal cancer 100%, Italy	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery in patient older and younger than 70 years
Soares-Miranda, 2021	71, Colorectal cancer 100%, Portugal	Quality of life	Cross sectional study exploring association of physical fitness and health related quality of life 6 months after surgery
Tang, 2021	100, Colon cancer 62%, Rectal cancer 38%, China	Cerebral oxygenmetabolism	Randomised clinical trial on effects of dexmedetomidine assisted intravenous inhalation
van der Vlies, 2022	273, Colon cancer 71%, Rectal cancer 29%, the Netherlands	Quality of life	Longitudinal observational study of determinants for decreased health related quality of life 3 months after colorectal cancer diagnosis
Vardy, 2021	206, Colorectal cancer 68%, Australia	Quality of life and lifestyle factors	Longitudinal observational study of persons attending Sydney Cancer Survivorship Center Clinic
Vardy, 2014	363, Colorectal cancer 100%, Canada & Australia	Cognitive function and fatigue	Cross-sectional report of localised and metastatic colorectal cancer patients before adjuvant or neoadjuvant treatment compared to healthy control.
Visovatti, 2016	50, Colorectal cancer 100%, United states	Cognitive function	Cross-sectional report of colorectal cancer patients compared to healthy controls

Report	Population (n, cancer, country)	End points	Summary
Wang, H., 2015	117, Colon cancer 100%, China	Quality of life	Observational study comparing patients using enhanced recovery program (ERAS) and conventional perioperative management
Wang, P., 2021	120, Colorectal cancer 43%, China	Postoperative cognitive function	Randomised controlled trial investigating effect of probiotic intervention on cognitive impairment in elderly after non-cardiac surgery.
Wang, Y., 2020	281, Colorectal cancer 19%, China	Postoperative recovery and function	Randomised controlled trial investigating effectiveness of Tailored Family-Involved Hospital Elder Life Program after noncardiac surgical procedure.
Wu, 2016	110, Colon cancer 100%, China	Postoperative cognitive dysfunction	Observational study of association between miRNA-155 and cognitive function after laparoscopic surgery
Yang, 2019	130, Colon cancer 100%, China	Postoperative recovery and cognitive function	Randomised trial on effect of sevoflurane compared to isoflurane anaesthesia in elderly patients
Zhang, Y., 2019	77, Colon cancer 100%, China.	Postoperative cognitive dysfunction	Observational study to reveal risk factors for early postoperative cognitive dysfunction. No patients received preoperative chemotherapy or radiotherapy.
Zhang, C., 2020	186, Colorectal cancer 100%, China	Postoperative recovery	Randomised trial on effects of epidural blockade and combination of epidural blockade and pre intravenous injection of parecoxib in patients who didn't receive chemotherapy before surgery.
Zhang, J., 2019	140, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical study of dexmedetomidine in elderly. Patients undergoing radiotherapy or chemotherapy before surgery was excluded.
Zhang, X., 2020	159, Colorectal cancer 100%, China	Quality of Life and psychological outcome	Randomised controlled trial on effect of psychological interventions in colorectal cancer patients
Zhang, X., 2019	78, Colorectal cancer 100%, China	Postoperative cognitive function	Retrospective observational study of sevoflurane inhalation combined with epidural anaesthesia compared to propofol general anaesthesia in elderly.
Zhou, 2018	81, Colon cancer 100%, China	Postoperative cognitive function and delirium	Randomised controlled trial on effects of bispectral index monitoring in elderly patients

Questionnaires

Attentional Function Index (AFI)

Everyday Memory Questionnaire (EMQ)

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0 (EORTC QLQ-C30)

Functional Assessment of Cancer Treatment – Cognitive function issues (FACT-Cog)

Patient's Disease and Treatment Assessment Form—General (PtDATA)

Screening tools

Abbreviated Mental Test (AMT)

Hasegawa's Dementia Scale - Revised (HDS-R)

Mini-Mental State Examination (MMSE)

Montreal Cognitive Assessment (MoCA)

Short Portable Mental Status Questionnaire (SPMSQ)

Neuropsychological test

Attention Network Test (ANT)

Benton Judgment of Line Orientation (JLO)

Brief Visuospatial Memory Test-Revised (BVMT-R)

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Digit Span Test

Digit Symbol Substitution Test (DSST)

Hopkin Verbal Learning Test-Revised (HVLT-R)

Letter-Number Sequencing

Rey Auditory Verbal Learning Test (RAVLT),

Stroop Test

Symbol-Digit Modalities Test (SDMT)

Trail-Making Test, (TMT)

Visual verbal learning test (VVLT)

Verbal fluency test

Word recall

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Assessment of cognitive function after surgery for colorectal cancer – a scoping review

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Assessment of cognitive function after surgery for colorectal cancer – a scoping review

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Abstract

Objective

Colorectal cancer is primarily treated with surgery. Major surgery and older age are risk factors associated with postoperative decline in cognitive function. In clinical research, a wide range of instruments have been used to assess cognitive function. There are no clear criteria for the measurement of postoperative cognitive dysfunction.

This scoping review aimed to map how and when cognitive function has been assessed after surgery for colorectal cancer and the incidence of postoperative cognitive decline reported.

Design

Systematic scoping review following the JBI approach.

Data sources

Scopus and PubMed. Last search January 2023.

Eligibility Criteria

Reports with outcomes of postoperatively assessed cognitive function in colorectal cancer patients with first assessment within 1 year of surgery was included.

Data extraction and synthesis

Data was extracted by one researcher and controlled for accuracy by a second researcher. Data was summarized in tables and charts.

Results

In total, 49 reports were included (16 clinical trials, 33 cohort studies). Cognitive function was assessed with patient-reported outcomes measures, clinical screening tools, neurophysiological testing and complication classification. The definition was most often related to the specific instrument, as predefined cut-off or change from baseline. Assessments were performed between 1 h and 36 months after surgery – few reports included follow-up both within and after 30 days postoperatively. Incidence of cognitive decline varied considerably (0-64%), depending on the instrument, definition criteria and time of assessment. Most studies reported a decline in cognitive function after surgery with recovery during follow-up.

Conclusions

This study showed a heterogeneity in the choice of assessment method and measurement criteria for cognitive dysfunction after colorectal cancer surgery. A more unified measurement approach in further research would be beneficial to evaluate post-operative cognitive function and understand its impact on the daily lives of patients with colorectal cancer.

Trial registration

Protocol registered at Open Science Framework, DOI:10.17605/OSF.IO/2M3DT

Strength and limitations of this study

- This review is following a systematic approach with a preregistered protocol
- Search strategy was developed, and searches conducted by experienced librarians
- There was no critical appraisal for methodological limitation or risk of bias assessment preformed for included studies

Introduction

Cognitive functions, such as memory, attention and executive functions, can decline after surgery[1]. The pathogenesis is not entirely known but most probably it is multifactorial. This can incorporate patient-related factors, including genetic predisposition, the anaesthetic and surgical procedure, and the systemic inflammatory response that surgery give rise to[2]. Older age is a risk factor[1, 2], but 30-40% of all adults have been reported to develop postoperative cognitive dysfunction or decline (POCD) after major non-cardiac surgery[3]. Generally, it seems to be a temporary condition[2] but patients older than 60 years have an increased risk of persistent cognitive dysfunction 3 months after surgery[3]. Colorectal cancer is one of the most common types of cancer worldwide and is primarily treated with surgery[4, 5]. Considering the high incidence of colorectal cancer, particularly among older adults, a substantial number of patients could be at risk for developing cognitive dysfunction after surgery.

Postoperative cognitive dysfunction is a research construct and there has been no standardised definition[2, 6]. In 2018, the international and multidisciplinary Nomenclature Consensus Working Group published a recommendation on cognitive changes after surgery[6]. The group aimed to align the terminology of postoperative changes to that of clinical classification of cognitive function in general. The recommended terms were *delayed neurocognitive recovery* in case of occurrence during the first 30 days after surgery and between 31-365 days after surgery *postoperative neurocognitive disorder*. They further recommended the use of the Diagnostic and Statistical Manual for Mental Disorders' (DSM-V) criteria for neurocognitive disorder. For diagnosis, DSM-V requires subjective complaints as well as objective testing and specifies that everyday living is hindered at least in terms of instrumental activities (e.g., taking medication, and paying bills)[7]. For classification DSM-V also states that cognitive deficits are not present solely as a component of delirium.

The assessment of the patients' function after surgery is an important issue since postoperative recovery, of which cognitive function is an integrated part, is prognostic for long-term recovery and has economic implications[8]. A long-term follow-up of a Danish cohort found that patients who developed postoperative cognitive dysfunction after non-cardiac surgery retired earlier from the labour market and

incurred higher social transfer payments[9]. It has also been found that those with postoperative cognitive dysfunction at discharge had higher mortality within 30 days and those with persistent dysfunction after 3 months had higher mortality during the first year after surgery[3]. While cognitive screening is recommended in American Cancer Society's survivorship care guidelines for colorectal cancer, it is only mentioned in association with chemotherapy [10]. As cognitive decline is associated with major surgery in general, it is reasonable to expect that cognitive decline can occur in patients with colorectal cancer undergoing surgery even if chemotherapy is not part of the treatment regime.

The objective of this review was to map how cognitive dysfunction has been defined and assessed after surgery for colorectal cancer. The aims were to identify research reports of cognitive function after colorectal cancer surgery, explore the incidence of cognitive changes, clarifying the definitions and criteria used and describe how cognitive function has been assessed. The review questions were identified as:

- How and when was cognitive function assessed after colorectal cancer surgery?
- What definition and nomenclature were used to describe cognitive changes?
- What outcome of cognitive function was reported after surgery?

The investigative and explorative nature of the research made it suitable for using a scoping review approach. At the start of this project, we found no registered protocol for systematic reviews at PROSPERO for the assessment of cognitive dysfunction after colorectal surgery, nor any scoping review registered at Open Science Framework. No published protocols or reviews were found on the subject when searched in PubMed, Scopus, Cochrane Database of Systematic Reviews and JBI Evidence Synthesis.

Methods

The protocol based on the JBI methodology[11] containing the objectives, inclusion criteria and methods for this scoping review was registered on July 24, 2021 at Open Science Framework, DOI 10.17605/OSF.IO/2M3DT. The registration was made before the screening of results had begun.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) was followed[12]. The checklist is available in Supplement I. Patients, or the public were not involved in the design, conduct, or reporting of this review.

Inclusion criteria

The review included reports on primary research studies. The languages were limited to English and the Scandinavian languages (Norwegian, Swedish, and Danish). No restrictions were applied based on the year of publication.

Population was adults with colorectal cancer, the concept examined was outcomes of cognitive function within the context postoperative assessment the first year after cancer surgery.

The criterium of assessment within 1 year was added after protocol registration to align with the recommended temporal specification for postoperative cognitive changes, i.e., only in the first 12 months after surgery[6].

Search strategy

The main search was conducted by librarians at the Biomedical Library, University of Gothenburg, on April 23, 2021, in PubMed (via Medline) and Scopus databases. A subsequent search was made on January 3, 2023.

Search on Scopus:

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

In addition to database searches, bibliographic searches were conducted. Excluded review articles that contained key terms in the title (colorectal cancer or surgery, cognitive function, or effects of cancer treatments) were scanned for relevant sources. This was repeated for all reports included in the full-text examination. The complete database search strategy is available in Supplement II.

Screening and selection

After the removal of duplicates, search results were transferred to the web-based screening tool Rayyan[13]. Two blinded reviewers screened titles and abstracts. Conflicts were discussed, and the senior author had the last say if a consensus was not reached. Full-text screening was performed by one researcher in EndNote[14]. Exclusion criteria for all excluded reports were confirmed by another researcher.

The exclusion criteria for screening had no hierarchy, and the first relevant exclusion criterium was used for classification. Predefined reasons for exclusion in the title and abstract examination were protocol or review, not primary research, and no participants with colorectal cancer or surgery. During the screening process, the following exclusion criteria were added; metastatic surgery (including HIPEC) and focus on effects of chemotherapy on cognitive functions since it is not relevant to primary colorectal surgery; delirium assessed only by a clinical definition (i.e., no cognitive testing); and no assessment within 1 year of surgery. Case-reports were excluded.

Data charting

Data was extracted by one researcher. For the initial search, the software NVivo[15] was used in qualitative and iterative process to categorise text and figures depending on content relevant to the review questions. Data were then charted in an Excel spreadsheets using Colectica[16] for metadata. For the subsequent search data was charted directly to the spreadsheet. The results were then compiled into relevant tables and charts. All charted data were controlled for accuracy by a second researcher.

Data were charted for study characteristics such as aims, methodology and study population. Data relevant to review questions were nomenclature, definitions and instruments used. The time of assessment was charted as months, days or hours as specified in each report. Cognitive outcomes were charted as frequency and if decline and recovery occurred and differences between compared groups. Since not all reports used statistical testing for within-group comparison, numerical values were compared as presented. Details of all charted variables used in this review are presented in the metadata in Supplement III.

Results

After the removal of duplicates, 1136 records were screened in title and abstract examination. There were 23 reports identified from other sources (Fig 1[17]). Out of the 205 articles that were subjected to

full-text examination, 49 were included. Supplement IV includes a summary of data relevant to the review questions from all included reports.

The included reports were published 2000-2022. There were 33 observational cohort studies and 16 reports of controlled trials. The aim of reports was mainly to investigate cognitive function (39%), quality of life (41%) or recovery after surgery (14%). Table on characteristic for all included sources is in Supplement V.

Thirty-nine study populations were exclusively patients with colorectal cancer, in the remaining study populations colorectal cancer patients comprised 19-89%. Sample sizes in observational studies ranged 11-1129 and in clinical trials 40-281. Across all studies, there was a mean of 46% female participants, and the average age reported was 66 years, covering a range of 18-99 years. The study populations were mainly from Europe (47%) and Asia (43%), the remaining reports had populations from Australia, Brazil, Canada, and USA. There was also one international online population[18]. In five reports, the participants had received no other cancer treatment than surgery[19-23]. Information on adjuvant treatment was given in twenty reports.

Perioperative intervention concerning anaesthesia (types of drugs or procedural aspects) was used in 81% (n=13) of the clinical trials with dexmedetomidine being used in half of those (n=6). Observational studies compared groups most frequently according to surgical method or procedure (n=8), healthy controls or the general population (n=6), patients' age (n=5) or whether postoperative cognitive decline developed or not (n=5).

Assessment of cognitive function

Cognitive function was generally assessed with questionnaires or screening tools (fig 2). The two other assessments methods were neuropsychological testing and complication classification. More than one type of assessment method and instrument could be used in the same report. See Supplement VI for full list of instruments. A separate assessment of postoperative delirium was made in eight reports[19, 24-30], and instrumental activities of daily living (IADLs) were reported after surgery in two sources[27, 31].

A total of six questionnaires, five previously described and one novel[18] was used for patient-reported outcomes. Answers to questionnaires were collected by in person or telephone interviews or self-administered during visits, online or at home. The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire - Core 3.0 (EORTC QLQ-C30) was the most frequently utilized

instrument overall. Studies that utilized patient-reported outcomes were generally observational studies with focus on quality of life. One clinical trial used self-reported outcome of cognitive function[32].

Five different screening tools were represented with the Mini-Mental State Examination (MMSE) as the most utilized. When specified, screenings were done by trained personnel, often the same individual for all assessments, and with the assessor blinded to the patient's intervention group. Screening tools was used in all but two clinical trials. In reports with the aim to investigate cognitive function screening tools were the most frequent instrument employed (12/19).

Two reports measured cognitive dysfunction as a complication, both were observational studies reviewing patient records and grading with the Clavien-Dindo classification[33, 34]. Nine reports assessed cognitive functions with neuropsychological testing employing a wide range of tests for several cognitive domains such as processing speed, attention, and verbal memory. Tests could be used either together as a battery with a composite score or as individual tests, reported separately. The time requirement for neuropsychological testing was given in three reports, 30, 60 and 90 min. When reported, testing was done in a quiet environment and by trained personnel. There were two computerized tests, the Attention Network Test (ANT) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Neuropsychological testing was used in three clinical trials, once as the only assessment method[28] and otherwise in combination with a screening tool[25, 35]. When reported separately return to preoperative values occurred later when assessed with neuropsychological testing than with screening tool[25]. In one case both CANTAB and a battery of seven individual neuropsychological tests were uses in the same report[23] and the association between the neuropsychological testing methods was stated as weak-to-moderate.

Across studies, cognitive assessment was performed in the shorter term, 1-12 hours, and 1-30 days after surgery, and in the longer term, 2-36 months after surgery. Most reports had a follow-up only within 30 days (49%) or only after 30 days (41%). One clinical trial had follow-up after the first 30 days[32]. Cognitive function was assessed up to 11 times, including baseline, with a mean of three assessment points. There were six cross-sectional reports.

Nomenclature and definition

Impairment was the most frequent term to describe cognitive function decrease in general, followed by dysfunction, both terms occurred in several combinations. Neurocognitive was used in combination with impairment, decline, deficit, and dysfunction. About half of the reports utilized more than one term.

Two reports referred to problems with concentrating and memory without any generic term. Sixteen reports used cognitive or mental function, capacity, or ability without any term indicating a decline in function.

A narrative definition of postoperative cognitive dysfunction as a concept was absent in most reports. When present, it concerned the decline of cognitive functions such as memory, executive control, and attention. Two reports also mention decline in social ability[36, 37]. Four reports included symptoms such as confusion, disorientation, anxiety, agitation, or delirium in their definition[22, 36, 38, 39]. Two reports stated that no abnormalities in cognitive function should have been present preoperatively[35, 39].

A little more than half of the reports presented criteria for measurement of cognitive dysfunction. Instrument-specific criteria were most common. Both predefined cut-offs and change from baseline was used, with or without subdivisions. Instrument-specific criteria were used with screening tools and questionnaires, for neuropsychological testing general criteria were more common (table 1). The Z-score was the most common general criteria, defined in four reports. Occurrence of specific or any symptoms of cognitive decline was also used as criteria both with questionnaires and complication classification. There was also a vague definition (i.e., the lower the score, the lower the function).

Table 1. Criteria for measurement of cognitive dysfunction

Instrument specific	Utilised with	Comment
Cut-off	MoCA, MMSE, PtDATA,	
Cut-off with subdivision	HSD-R, MMSE, SPMSQ, EORTC QLQ-C30	
Decrease from baseline	AMT, MMSE, SPMSQ	
Decrease from baseline with subdivisions	EORTC QLQ-C30	Based on EORTC's guidelines
Instrument general	Utilised with	Comment
Z-score (with cut-off)	Neuropsychological tests, MMSE	
Lowest quartile	EORTC QLQ-C30	
Global deficit score (with cut-off)	Neuropsychological tests	T-score converted to 0-5
Standard deviation(s)	Neuropsychological tests, FACT-Cog	In relation to healthy control or baseline
Other	Utilised with	Comment
Specific/any symptom	Clavien-Dindo classification, Survivorship care plan tool, EORTC QLQ-C30	
Lower score = lower function	MMSE	

MoCA - Montreal Cognitive Assessment, MMSE – Mini-Mental State Examination, PtDATA - Patient's Disease and Treatment Assessment Form—General, HDS-R - Hasegawa's Dementia Scale – Revised, SPMSQ - Short Portable Mental Status Questionnaire, EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0, AMT - Abbreviated Mental Test, FACT-Cog - Functional Assessment of Cancer Treatment – Cognitive function issues

Outcome of cognitive assessments

Of the reports that had comparable preoperative values, 86% (30/35) showed a decline at the first follow-up after surgery. The reports not showing decline had follow up at 1 month as the earliest[24, 40-43]. Of the reports showing decline, one third (10/30) had first follow-up after the first 30 days. Full or partial recovery occurred in most reports (fig 3). Recovery occurred at the earliest 1 day after surgery and at the latest after 24 months. In four reports, no recovery occurred within the follow-up period (5 days-12 months)[19, 31, 35, 44]. In seven reports, there was a decline of function after a previous assessment had shown recovery.

Incidence of cognitive dysfunction after surgery

The frequency of cognitive dysfunction after surgery was presented in 20 reports. Across these, the instruments for assessment, measurement criteria for dysfunction, and follow-up periods differed (table 2). Postoperative incidence ranged from 0-64%, incidence of cognitive dysfunction at baseline was reported in three reports, 8.2-28%.

Table 2. Reports with frequency of cognitive dysfunction

2a - Reports with frequency of cognitive dysfunction in clinical trials						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Chen, 2020	88	MMSE	Score <28	Day 1 & 3	16.3-64.4% (in total)	Dexmedetomidine intervention
Liu, T., 2021	100	MMSE	Z-score ≤ -2	1 day 2 days 3 days	10-25% 8-16% 4-10%	Transcutaneous electrical acupoint stimulation (TEAS) intervention
Zhang, J., 2019	140	MMSE	Not reported	1 day 3 days	8.8-21.7% 0-13.3%	Dexmedetomidine intervention No patients with neoadjuvant chemo- or radiotherapy
Bao, 2020	178	MMSE	Not reported	3 days	8.4-22.9%	Dexmedetomidine combined with ulinastatin intervention No patients with neoadjuvant chemo- or radiotherapy
Ding, 2022	40	Battery of 5 neuropsychological tests and HDS-R	>1 SD decline on ≥2 tests	5 days	5-25%	Dexmedetomidine intervention
Liu, Y., 2020	96	MMSE	>2 points decrease	7 days	12.5-29.2%	Dexmedetomidine combined with epidural blockade intervention
Wang, P., 2021	120	MMSE	≥3 points decrease	7 days	5.1-16.4%	Probiotics intervention 43% colorectal cancer patients in study population
Wang, Y., 2020	281	SPMSQ	>2 errors	Before surgery 30 days	16.3-17.1% 7.4-25.5%	Tailored Family-Involved Hospital Elder Life Program (t-HELP) intervention 19% colorectal cancer patients in study population
2b - Reports with frequency of cognitive dysfunction in observational studies						
Report	**n**	**Instrument**	**Criteria**	**Time of assessment**	**Cognitive dysfunction**	**Additional information**
Vardy, 2014	363	Battery of 7 neuropsychological tests, CANTAB FACT-COG	GDS* >0.5 >2 SD below HC on ≥1 test, or >1,5 SD on ≥2 below HC >1,5 SD below HC (≤119)	After surgery and before adjuvant treatment, or before neoadjuvant treatment.	30-47% 33-51% 18.5-21%	Cross-sectional Comparing localised to metastatic cancer patients Healthy controls (HC) 13-17% with neuropsychological testing, 17 % FACT-COG No patients with neoadjuvant chemo- or radiotherapy *GDS – Global deficit score
Lin, 2014	50	Battery of 7 neuropsychological tests	Z-score ≥1.96 on ≥2 test or	7 days	34%	46% colorectal cancer patients in study population

			composite Z-score			
Wu, 2016	110	CANTAB	Z-score <-1.96 on ≥2 test or combined Z-score <-1.96	7 days	26.4%	
Zhang, Y., 2019	77	Battery of 3 neuropsychological tests and MMSE	Z-score >1.96 or combined Z-score ≥1.96	7 days	24.7%	No patients with neoadjuvant chemo- or radiotherapy
Li, 2013	114	Clavien-Dindo classification	≥ grade 1	Within 30 days	1.8%	Complication defined as "Delusions requiring medical treatment" 37% colorectal cancer patients in study population
Fagard, 2017	190	Clavien-Dindo classification	≥ grade 1	Within 30 days	16.6%	Complication defined as "Neurological - including altered mental function" No patients with neoadjuvant chemo- or radiotherapy
Samuelsson, 2019	49	MMSE	Score <24	Before surgery 1 months 6 months 12 months	8.2% 5% 2.5% 2.7%	
Couwenberg, 2018	272	EORTC QLQ-C30	>10 points decrease (since baseline)	3 months 6 months 12 months 18 months 24 months	39.6-41.1% 35.2-41.1% 22.7-30.5% 18.5-33.3% 20.0-29.4%	Comparing abdominoperineal resection with low anterior resection 99.6 % had neoadjuvant chemo- or radiotherapy
Vardy, 2021	206	Patient's Disease and Treatment Assessment Form—General	≥4 (out of 10)	11 months 14.5 months 23 months	≈18-21% ≈14-17% ≈17-20%	Two separate symptoms "Trouble concentrating" and "Problems with memory" 68% colorectal cancer patients in study population 83% had chemotherapy, 21% radiotherapy
Deckx, 2015	321	EORTC QLQ-C30	Score <67. (lowest quartile)	Before surgery 12 months	18-28% 26-31%	Comparing older (≥70) cancer patients to younger Older controls 22% at both assessments 24% colorectal cancer patients in study population 26-54% had (neo)adjuvant therapy
Arndt, 2004	309	EORTC QLQ-C30	Any level of concern	12 months	55.9%	Cross-sectional 49.2% had adjuvant chemo- or radiotherapy
Frick, 2017	1129	Internet-based tool for the creation of survivorship care plans	Answer "yes,"	12 months	48.6%	Cross-sectional 89% colorectal cancer patients in study population 13% (colon), 6% (rectal) had surgery as only treatment

MMSE – Mini mental state examination, HDS-R - Revised Hasegawa's Dementia Scale, SPMSQ - Short Portable Mental Status Questionnaire , CANTAB – Cambridge Neuropsychological Test Automated Battery, FACT-COG – Functional Assessment of Cancer Therapy – Cognitive, EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0

There were eight clinical trials presenting incidence, most of them had one assessment within 7 days of surgery (table 2a). The highest incidence reported was 64%, which represented a total of patients with cognitive dysfunction at postoperative day 1 and 3 in a control group[39]. A 0% incidence was reported 3 days after surgery in an experimental group[22]. Across all reports the incidence ranged 8.8-25% at the earliest follow up, 1 day after surgery. At 7 days after surgery an incidence of 5-29% was reported across all reports. All reports with more than one postoperative follow-up showed decreasing numbers of cognitive dysfunction over time. One study reported baseline incidence of 16-17%, at follow-up, 30 days after surgery, the incidence was lowered in the intervention group, and increased in the control group[27].

For the observational studies (table 2b) the highest incidence was 56%, reported in a cross-sectional report 12 month after diagnosis[45]. The remaining reports with data for 12 months had an incidence between 2.7-49%. The lowest incidence reported was 1.8% as a total within 30 days of surgery[34]. At 7 days after surgery an incidence of 25-34% was reported across all studies. In the reports with more than one postoperative assessment incidence generally decreased with time. At the latest follow-up, around 2 years after surgery, incidence ranged 20-29% across reports. One study reported incidence for older persons without cancer as 22% which was stable after 12 months, while the incidence increased for cancer patients[31]. A cross-sectional report showed differences in incidence with neuropsychological testing but not with self-reported measurers when comparing cancer patient to healthy controls[23].

Discussion

The 49 reports in this review assessed cognitive function after surgery using a diversity of methods and definitions. Due to the heterogeneity across definitions and assessment methods, it is difficult to synthesize information, and reach firm conclusions regarding incidence of cognitive decline after colorectal cancer surgery. Nevertheless, decline in cognitive function was found in more than 80% of the reports with preoperative levels, regardless of the instrument and the specific definition. Collectively, the data suggests that changes in cognitive function do occur in colorectal cancer patients who received surgery.

A limitation of this study, as inherent with all reviews, is the possibility that some relevant sources have been missed. However, the findings in this review are consistent with the broader literature. For example the EORTC-CRC Q30 was the most used instrument when measuring cognitive function after chemotherapy in a colorectal cancer population[46] and the MMSE is the mostly used screening tool for postoperative cognitive assessment[1]. Since this scoping review had an exploratory focus, we did no

formal rating of the quality of evidence and therefore any conclusions drawn based on the results of included studies must be made with caution.

A general concern with the data in this review is that a large portion is obtained through self-report or screening tools. Subjective complaints of cognitive function are poorly correlated with objective testing in cancer patients[23, 47]. It has therefore been suggested that subjective complaints might be an indicator of anxiety and depression rather than cognitive dysfunction[47, 48]. It is recommended that cognitive changes after surgery should be assessed with neuropsychological tests for specific cognitive domains rather than with screening tools[6, 49]. Among the reports in this review employing objective measurements, the use of screening tools was twice as common as neurophysiological testing. Of the studies that aimed to investigate cognitive function, fewer than half used neurophysiological tests. There has been discussion on whether screening tools are appropriate or not when detecting postoperative cognitive dysfunction[2], for detecting cognitive changes after cancer treatment screening tools are however not considered sufficient[50]. Another concern with the data is the potential overlap between postoperative decline of cognitive functions and postoperative delirium[6, 51]. Delirium has its own diagnostic definition, and focuses on awareness and by definition, to diagnose neurocognitive disorder, cognitive deficits cannot be present solely as part of delirium[7]. Only eight reports in this review performed a separate assessment of delirium making it uncertain in the other studies whether the cognitive decline reported was delirium induced or not, at least in the period directly after surgery when there is a risk of postoperative delirium[52].

Decline of cognitive function in the first 30 days after surgery is defined as *delayed neurocognitive recovery* in the recommendation on terminology of cognitive change after surgery[6]. This period is affected by complicating factors such as delirium, immobility and analgesic medication, such as opioids, which also could give rise to cognitive dysfunction. Patients receiving intensive care have a high risk of developing cognitive dysfunction[53]. The need for intensive care after surgery might therefor be related to postoperative cognitive decline soon after surgery. About half of the reports in this review reported only on the period within the first 30 days and with only one of the interventional studies having follow-up after 30 days it is not known if the effects of interventions persist after the recovery window. Overall, it has been questioned if postoperative cognitive dysfunction persists over time[2]. A recently published study indicates that there is no cognitive impairment in the long term for colorectal cancer survivors[54]. It has been suggested that postoperative cognitive function should not be assessed later than 6-9 months after surgery[55] but in the recommendation of terminology *postoperative cognitive dysfunction* apply to

new occurrence or deterioration of pre-existed impairment up to 12 months after surgery[6]. In this review recovery of cognitive function was reported in all but a few reports with preoperative values and follow-up after 30 days. Incidence in included reports decline over time. However, the incidence of cognitive dysfunction after surgery might be underestimated during long-term follow-up due to the inability of patients with the worst declines to participate in studies[56]. This selection bias could also inflate reports of cognitive recovery since the study population may have a higher mean function over time as those with lower scores cannot continue their participation.

The heterogeneity shown in this review regarding instrument and criteria of measurements are similar to a recent review on cognitive impairment after chemotherapy in colorectal cancer patient[46] and has also been shown previously with assessment of postoperative cognitive dysfunction[1, 2, 55]. To adhere to a common criterion would be beneficial to synthesise results and to explore what effects postoperative cognitive decline has for patients and in the clinic. How to best measure cognitive function is beyond the scope of this review. However, advocates for patient-focused care have stressed that when assessing recovery after surgery, the patient should act as their own control[8]. Measurement criteria using that approach would reduce the risk that a decline in a person with normal high or low function might go unnoticed if they remain above or always was below a predefined threshold for impairment[7]. There is of course the discussion of what changes should be considered significant and the point of interest is perhaps better focused on if the functional decline affects the patient's daily life or not. Assessment of instrumental activity of daily living (IADLs) are considered a good indicator of problems derived from subtle cognitive decline[6, 7]. Yet only two reports in this review reported IADLs.

As there was no formal rating of the quality of evidence included in the scoping review, the overall conclusions are considered to have low evidence. Nevertheless, a majority of the reports in this review noted cognitive functional decline in the study populations with comparable preoperative levels. When it comes to colorectal cancer patients, adjuvant treatments as well as the cancer itself need to be considered as causative factors for cognitive decline[57]. A holistic approach to cognitive decline for all colorectal cancer treatments and the cancer itself would surely be beneficial. Therefore, extending recommendation of cognitive screening of patients receiving chemotherapy to all colorectal cancer survivors, regardless of treatment modality, could be of value and requires further investigation, especially considering that the existing recommendation has the lowest level of evidence[10].

To strengthen the evidence on cognitive decline after colorectal cancer surgery neurophysiological testing should likely be considering worth the effort in future research. Future research would also do

well to considering separate assessment of delirium. Especially when assessing cognitive function soon after surgery, but it has implication also in the long run since there is an indication that those with postoperative delirium are less likely to recover from cognitive changes after surgery[51]. Studies assessing both cognitive function and instrumental activities of daily living would also provide a more detailed account of how cognitive decline impacts patients' lives after colorectal cancer surgery. Randomized clinical trials with longer follow-up periods could also be a valuable contribution to provide knowledge on if a perioperative intervention would have effect on persistent cognitive decline.

Conclusion

A more unified approach when it comes to the criteria for measurement of postoperative cognitive function would be beneficial to align research and increase the quality of evidence. Longitudinal studies with follow-up both within and after 30-days, preferable with neuropsychological testing and separate assessment of delirium, would provide new knowledge on whether cognitive dysfunction persist after the recovery period. Randomised controlled trials with the same approach could also contribute with knowledge on whether interventions do reduce actual neurocognitive decline and not only delirium induced manifestation. There could also be room for more research that inform on the degree to which the postoperative cognitive function decline impacts the daily lives of colorectal cancer patients.

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Competing interest

None declared.

Author statement

Authors' contributions

CE are responsible for the overall content as gurantor and provided concept and protocol, screened based on all examination levels, charted and summarised data, and wrote the manuscript. EA reviewed protocol, screened based on title and abstract examination, revised manuscript, and provided clinical and research expertise. RL controlled charted data and exclusion based on full-text examination, and revised manuscripts. All authors read and approved the final manuscript.

Non-authors' contributions

Eva Hessman and Linda Hammarbäck, Biomedical Library, Gothenburg University Library, University of Gothenburg, Gothenburg, Sweden, advised on search strategy, conducted searches and retrieved full

texts. Andreas Samuelsson, Scandinavian Surgical Outcomes Research Group - SSORG, screened based on title and abstract examination for subsequent search.

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Data sharing statement

Data set available upon request, metadata available in supplement.

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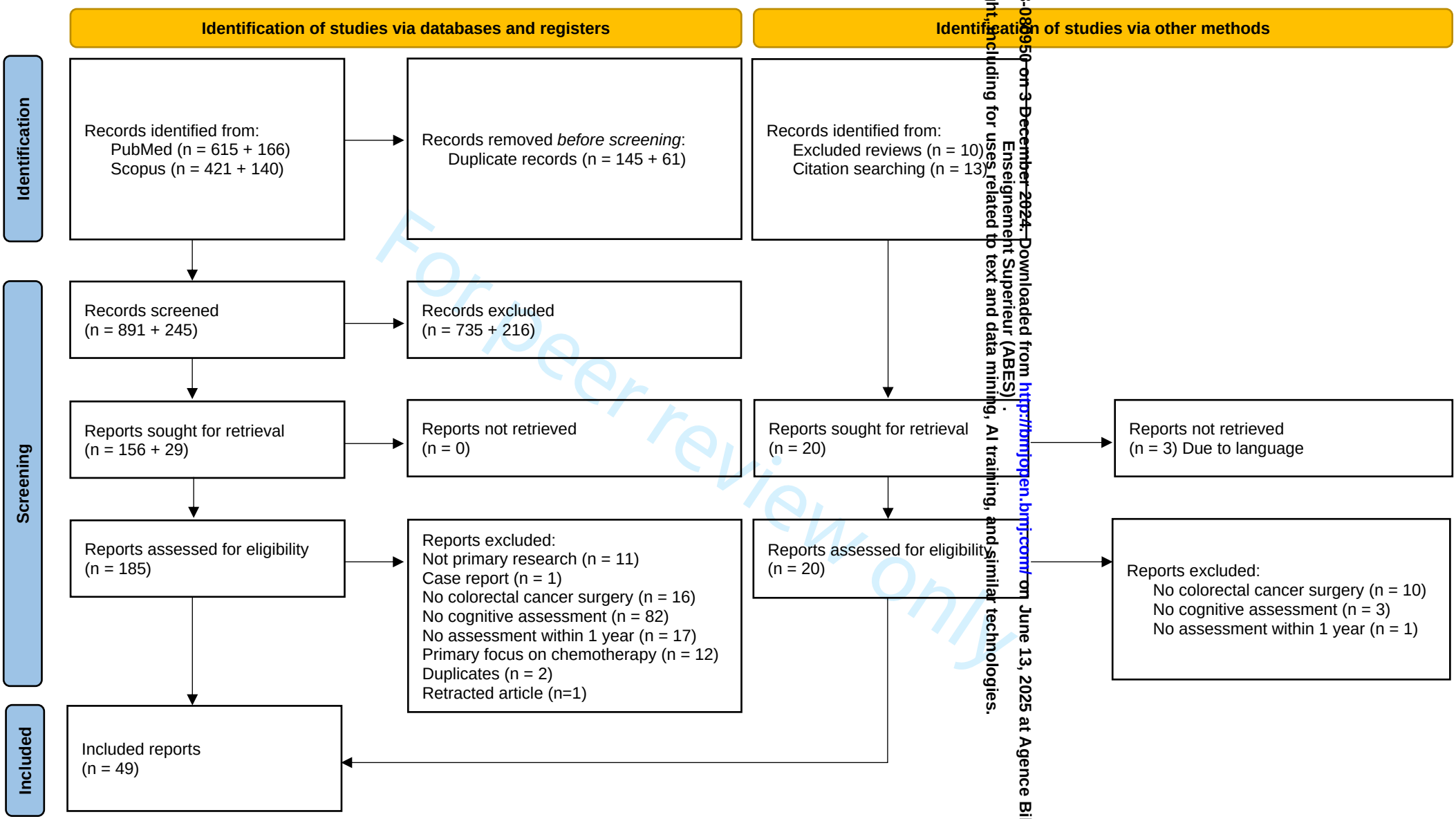
Figure legend

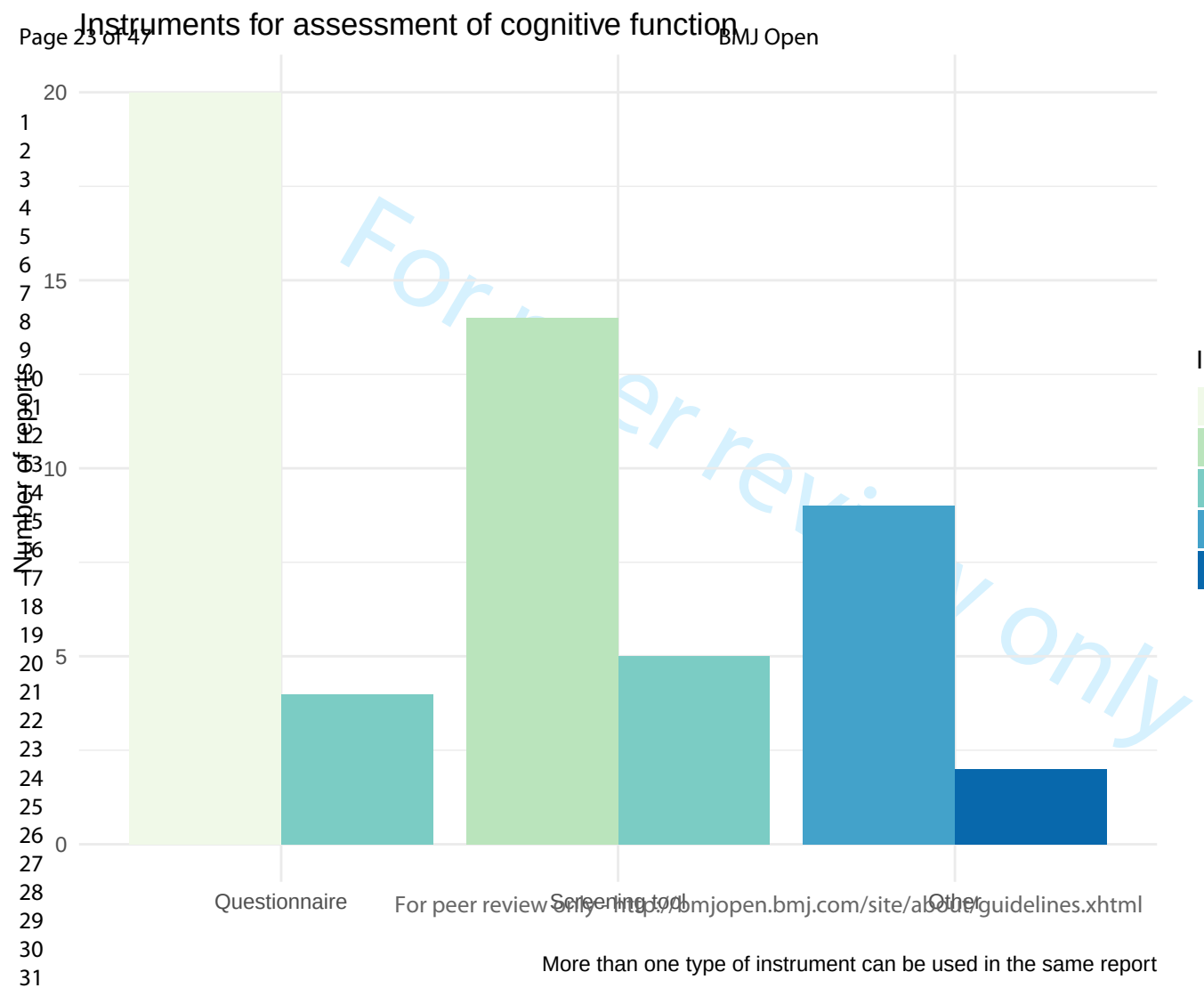
Figure 1. PRISMA Flow chart

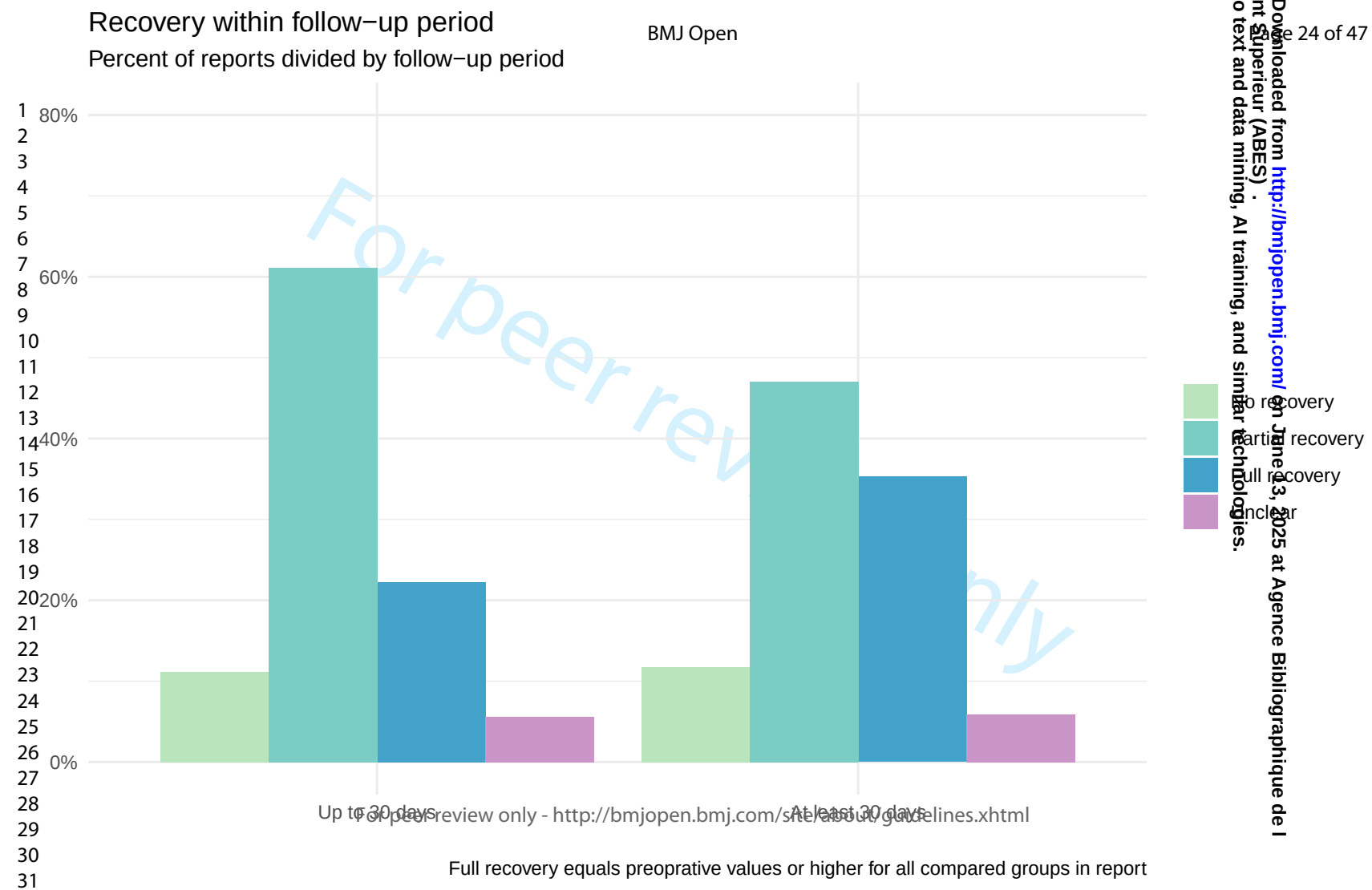
Figure 2. Graph of instrument for assessment of cognitive function

Figure 3. Graph of recovery within follow-up period

Fig 1: PRISMA 2020 flow diagram







Final search 2021-04-23

Database: PubMed searched on 2021-04-23

(Postoperative Cognitive Complications[mesh] OR POCD[tiab] OR PostOperative Delirium[tiab] OR postoperative decline[tiab] OR ((cognitive OR neurocognitive OR memory) AND (postoperative OR complication OR decline OR dysfunction OR disorder OR recovery OR impairment OR sequelae OR frailty)))

AND

(Colonic Neoplasms[mesh] OR Colonic Neoplasm[tiab] OR Colonic Neoplasms[tiab] OR Colon cancer[tiab] OR colonic cancer[tiab] OR colonic tumour[tiab] OR colonic tumours[tiab] OR colonic tumor[tiab] OR colonic tumors[tiab] OR Colorectal Surgery[mesh] OR Colorectal Surgery[tiab] OR Colon surgery[tiab] OR Rectal surgery[tiab] OR Colorectal Neoplasms[mesh] OR Colorectal Neoplasms[tiab] OR Colorectal Neoplasm[tiab] OR Colorectal cancer[tiab] OR colorectal tumours[tiab] OR colorectal tumour[tiab] OR colorectal tumors[tiab] OR colorectal tumor[tiab] OR rectal neoplasms[mesh] OR rectal neoplasms[tiab] OR rectal neoplasm[tiab] OR Rectal cancer[tiab] OR rectal tumours[tiab] OR rectal tumour[tiab] OR rectal tumors[tiab] OR rectal tumor[tiab])

No time restrictions
Limits English, Norweigan, Swedish, Danish 615 results

Database: Scopus searched on 2021-04-23

TITLE-ABS-KEY (pocd OR "PostOperative Delirium" OR "postoperative decline" OR ((cognitive OR neurocognitive OR memory) W/3 (postoperative OR complication* OR decline OR dysfunction OR disorder* OR recovery OR impairment OR sequelae OR frailty)))

AND

TITLE-ABS-KEY((colonic OR colon OR colorectal OR rectal) W/3 (neoplasm* OR cancer* OR tumour* OR tumor* OR surgery))

No time restrictions
Limit English, Norweigan, Swedish, Danish 421 results

PubMed 615 results
Scopus 421 results
Sum 1036 results

After de-duplication 891 results (145 articles removed)

Updated search 2023-01-02

Same as final search, same limitations except for time limit 2021-2023

PubMed results 166

Scopus results 140

Sum 306

After de-duplication 249

These 249 references are then compared with the final de-duplicated result from 2021-04-23. All duplicates (n=4) were removed so only the unique reports still remained from 2021 and 2022.

245 references were added to Rayyan and then Carolina Ehrencrona and Eva Angenete were invited.

Edit: 2023-02-08 Andreas Samuelsson was invited to Rayyan.

authors

Description	From Rayyan or EndNote

year

Description	From Rayyan or EndNote

title

Description	From Rayyan or EndNote if other sources

country - Country of study population

Type	Character

aim_category - Aim of report

Description	Derived from title and aim Cognition - if mentioned (including specific cognitive function i.e. memory or attention) not only delirium QoL - if mentioned (but not cognition) Recovery – recovery of surgery if mention, including postoperative complication (not sequalae in general from cancer (treatment))

Aim of report

1	Cognition
2	QoL
3	Recovery
4	Other

endpoints

Description	Derived from aim texts and title

size - Size of study population

Description	Included in analysis. Healthy control not included.

crc_size - Colorectal population

Description	Percent colorectal cancer patients of total study population

crc_type - Tumour location

Tumour location

1	Colon
2	Rectum
3	Colon or Rectum

Note

Description	If population is divided as Colon and Rectal separate specify. Note if characteristic has been charted for CRC only if mixed population. Other notes regarding characteristics

age_low - Lowest age of participant

Description	If actual range is missing, lowest possible age (from inclusion criteria) used Yellow if not found

age_high - Highest age of participant

Description	If actual range is missing, highest possible age (from inclusion criteria) used Yellow if not found Yellow if not found

age_central - Central tendency of age

Description	Chart mean if possible, otherwise median If divided by groups (M1*n1+M2n2...)/N

female

Description	Precent

other_treatment - Other cancer treatment than surgery

Description	Chart if radiotherapy or chemotherapy as neoadjuvant and adjuvant, if given before assessment

Other cancer treatment than surgery

0	Not reported
1	No (surgery only)
2	Yes, chemotherapy only
3	Yes, chemo- and/or radiotherapy
9	Unclear

comment

Description	On other treatment or method or compared groups

method

Description	If stated as non-randomized charted as cohort.
1	RCT
2	Cohort
3	Case report

assessment_points - Cognitive assessment points

Description	Including baseline

follow_up_period – Follow up period for cognitive assessment

Description	Baseline not included.
1	Up to 30 days
2	Both before and after 30 days
3	30 days or above
9	Uncertain

groups - Comparison of groups

Description	Predefined groups only, chart even if no comparison is made but note why Chart groups name and n for each group. Chart significant differences in cognitive assessment

POCD

Type	Code
Description	Proportion of cognitive dysfunction reported Yes of No. All definitions valid. Values charted separately in follow-up
0	No
1	Yes

instrument

Description	Note all instrument used where postoperative cognitive outcome is reported

neuro

Description	Neuropsychological/Neurocognitive test used

PROM

Description	Patient reported outcome used (questionnaires)

Screen

Description	Screening tools used

other

Description	Other instrument used

administration

Description	Note how instrument were administered to participant, if specific condition, location, personal was used

IADL

Description	Note yes if it was reported that instrumental activity of daily living was measured after surgery. Note 9 if measured but only before surgery.
0	No
1	Yes

9	Only before surgery

decline

Description	Decline in cognitive function first follow-up after surgery compared to presurgery values. Chart yes if any groups on any assessment have declined result at first follow up, need not be significant.
0	No decline of function at first follow-up
1	Decline reported on first follow up
8	Uncertain, conflicting values reported
9	No preop values to compare with

recovery - Recovery to preoperative values

Description	Chart yes to preop if any group during any follow up is above or at preop values. Chart yes not preop if no group return to or above preop values. Chart no if no group recover during follow up.

Recovery to preoperative values

0	No recovery
1	Recovery to preop levels
2	Recovery but not to preop levels
8	Unclear data
9	No preop values

recovery_timepoint

Description	Chart time for recovery to preop values and which follow up T in () and group if relevant, chart groups separately if preop values occurred at different time points. Chart last follow up if none recovered to preop values

fluctuation

Description	Chart if decline occurred after recovery for any group If no preop values chart not applicable - 9
0	No
1	Yes

9	NA

end_recovery - Recovery at end of follow-up

Description	Chart Full recovery only if all compared groups reach preoperative values or higher. Otherwise chart partial recovery unless no recovery at all.

Recovery to preoperative values

0	No recovery
1	Full recovery (of all groups)
2	Partial recovery (not all compared groups or not to preoperative values)
8	Comparable values not reported

delirium

Description	Separate assessment of delirium Also note yes if delirium was exclusion criteria
0	No
1	Yes
9	Unclear

nomenclature

Description	Chart once per term Chart longest term (i.e. postoperative cognitive dysfunction vs cognitive dysfunction) if one term includes another Only chart neutral term (i.e. cognitive function) if no term indicating decline is used

definition - Criteria of measurement

Description	Chart criteria for cognitive dysfunction. Also chart general criteria if it applied to cognitive outcome as well.

narrative

Description	Narrative description of (postoperative) cognitive dysfunction.

follow_up	
Description	Consecutive number for assessment. Chart 0 for preoperative assessment.

months	
Description	timepoint for follow up in months, if stated as years transformed to months 888 - not applicable

days	
Description	timepoint for follow up in days 888 - not applicable

hours	
Description	timepoint for follow up in hours, charted as reported (i.e. > 23 h reported as hours not days) 888 - not applicable

comment_follow_up	
Description	Specification of time point

outcome - Outcome of cognitive assessment	
Description	If POCD (or comparable) % reported If symptom % reported, if no exact number use > or < nearest scale point and assumed value in () Significant difference between groups (with values not p) If baseline values chart those Note recovery or decline (both significant and not) no numbers needed If reported as recovered to preoperative levels note when, else not if value equal or above preop

Comment_outcome	
Description	Note inconsistency, n if group change over time, other useful information regarding interpretation of outcome reported

Summary of all included reports

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Arndt, 2004	EORTC QLQ-C30	One year after diagnosis	Cognitive functioning	Any level of concern Differences of more than 10 points are clinically meaningful	55.9% with any level of concern Clinically significant different between CRC and general population under 60 years Reported as similar responses between those who underwent adjuvant therapy or surgery alone (data not shown).
Bao, 2020	MMSE	1st and 3rd day after surgery	Postoperative cognitive dysfunction (POCD)	NR	Combination group, CG, dexmedetomidine and ulinastatin, had significantly higher function through follow up than routine group, RG, (dexmedetomidine only). POCD total 8,4%(CG) and 22.89%(RG), at day 1 7.4% (CG) and 16.9% (RG) and day 3 1.05% (CG) and 6.0% (RG)
Beaussier, 2006	MMSE, Digital Symbol Substitution Test	Preoperative and daily until discharge	Mental function impairment Postoperative impairment of mental skills	NR	No significant different between groups (preoperative intrathecal morphine or saline) regarding mental functions after 24 h or return to preoperative values
Brown, 2014	EORTC QLQ-C30	Baseline, 3 months, 6 months, 18 months, and 36 months	Cognitive functioning Higher mental functions Cognitive capacity	NR	No difference in cognitive function between patient who had a complication within 30 day of surgery and those who did not.
Chen, 2020.	MMSE	Preoperative, postoperative day 1 and day 3	Neurocognitive function Postoperative cognitive dysfunction/impairment Cognitive brain dysfunction Disorder of brain function.	Score 24-27 mild, 19-23 moderate, <18 severe impairment.	Study group (dexmedetomidine) had significantly higher scores than control(saline) during follow-up. Total cognitive impairment study group 16%, control 64%.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, after 3, 6, 12, 18, and 24 months	Cognitive functioning	Clinically relevant worsened cognitive domain scores relative to their baseline score was defined as a decrease of > 10 points (10% of the scale breadth)	Significantly lower cognitive function scores for the whole study population compared to age-match reference population at all follow-ups. Compared to baseline significant mean difference were found at 3 & 6 months for those with abdominoperineal resection (APR) and during the whole follow up for those with low anterior resection (LAR). Proportion of worsened cognitive domain: 3 months APR 41%, LAR 40%, 6 months APR 35%, LAR 41%, 12 months APR 23%, LAR 31%, 18 months APR 19%, LAR 33%, 24 months APR 29%, LAR 20%
Couwenberg, 2018	EORTC QLQ-C30	Before neoadjuvant therapy, 3, 6, 12 months	Cognitive function	NR	Older patients (≥ 70 years) had significant lower cognitive function than reference population at all follow up. Younger patients had significantly lower function at 3 and 6 months compared to baseline and lower scores at 3 months compared to older patients.
D'Ambrosia, 2019	EORTC QLQ-C30	Preoperatively. After 1, 6, 12 and 36 months.	Cognitive functioning	NR	Scores for both groups (Laparoscopic total mesorectal excision, LTME, and Endoluminal loco-regional resection, ELRR) where above preoperative levels at first follow up. At 6 months LTME declined with significant difference to ELRR that was stable. Thereafter LTME declined, at 36 months to preoperative levels, while score in ELRR improved further.
De Souza, 2018	EORTC QLQ-C30	Before, 3 months and 12 months after surgery.	Cognitive function	Score 0-25= very poor, 26-50 = poor, 51-75= good, 76-100= very good	Cognitive function changed from good before surgery to very good at both follow ups.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Decks, 2015	EORTC QLQ-C30	Baseline and one-year-follow-up	Cognitive impairment	The frequency of cognitive impairment was operationalized by using the lowest functioning quartile as cut-off, this corresponded to a score <67 in all three groups.	Frequency of impairment for younger cancer patient, YCP, (<70 years) 28% at baseline and 32% at 1 year. For older cancer patients, OCP, it was 28% at baseline and 26% at 1 year. For older patients without cancer, OPwC it was 22% at both time points. OCP had significantly higher cognitive function at baseline compared with OPwC. OCP had a significant decline between baseline and 1 year.
Ding, 2022	Revised Hasegawa's Dementia Scale (HDS-R). Digit span subtest, digit symbol test, trail-making test, word recall, verbal fluency test.	At 1 day before the operation, 1 day after the operation, and 5 days after the operation	Neurocognitive Dysfunction Postoperative cognitive dysfunction (POCD) Postoperative consciousness dysfunction Hippocampal-dependent cognitive function"	The postoperative test value was compared with the preoperative test value. If the deviation value exceeded one standard deviation value, the function was judged as the postoperative function decline. POCD was if two or more postoperative tests showed a simultaneous functional decline.	Significantly decreased score on HDS-R in both Dexmedetomidine (DEX) and control group at both follow ups. Compared to control significantly higher values for DEX group at both follow up. Significantly higher incidence of POCD in control group 25% than DEX group 5% DEX at T2
Fagard, 2017	Clavien Dindo classification	Within 30 days after surgery	Cognitive impairment Altered mental function	Neurological - including altered mental function	Neurological complications total 12.6%
Frick, 2017	Internet-based tool for the creation of survivorship care plan	Median 12 months after diagnosis	Cognitive changes Neurocognitive decline	NR	Cognitive changes total population 48.6%.
Gamerio, 2008	Stroop Test, German Trail-Making Test, Wordlist power level and speed	Preoperatively and at follow-up until postoperative day 4	Early postoperative cognitive dysfunction/ changes Postoperative neuropsychological dysfunction Long-term cognitive deterioration Cognitive abilities/state/ Cognitive impairments/disturbance	NR	No significant differences between laparoscopic and conventional colectomy.
He., 2017	MoCA	One day before surgery. One, three and seven days after surgery.	Cognitive function impairment Postoperative cognitive dysfunction (POCD) Cognitive decline	Score < 26 is considered abnormal	Significantly difference between control and Remote ischemic preconditioning group one day and three days after surgery.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
How, 2012	EORTC QLQ-C30	One day before surgery or before neoadjuvant therapy, 1 and 2 year postoperatively	Impaired cognitive function	NR	Significantly higher mean cognitive function score for those with abdominoperineal excision (APE) at 1 year compared to those with low anterior resection (LAR)
Janssen, 2020	MMSE	Baseline (the first outpatient clinic visit, after 6 months and after 1 year.	Cognitive decline (Persistent) postoperative cognitivie dysfuntion Cognitive impairment	A score equal to or lower than 24 indicating cognitive impairment	Significant lower score at baseline for group with delirium. Significant decline in score compared to baseline during follow up for group without delirium.
Kinoshita, 2018	EORTC QLQ-C30	Before surgery, 1 month, 6 months and 12 months after surgery	Cognitive functioning	A change of score of 5–10 points indicate a minimal change, while a change of more than 20 points indicates a large change	Significant change from before surgery at 1 month for age ≥60. No significant difference between age <60 and ≥60. at any time-point.
León Arellano, 2020	EORTC QLQ-C30	1-2 days before surgery, at Postoperative day 7 and 30,	Cognitive function	NR	Significant decline at both follow up.
Li, 2013	Medical record Clavien Dindo classification	Within 30 days after surgery	Postoperative cognitive dysfunction	Delusions requiring medical treatment	Postoperative cognitive dysfunction as a complication in 2 patients.
Lidenzi, 2015	EORTC QLQ-C30	One day before, second and fifth day after surgery, one and three months after surgery	Cognitive functioning	NR	Decline in cognitive function scale on second day with recovery on fifth day. Back to preoperative levels at one month and above preoperative levels at three months.
Lin, 2014	Hopkin Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Trail-Making Test; Benton Judgment of Line Orientation, Digit Span Test; Symbol-Digit Modalities Test, Index, verbal fluency test	Before surgery and after 1 week or on the day of hospital discharge if earlier than 1 week	Cognitive decline/deterioration Post-operative cognitive dysfunction (POCD) (Neuro)cognitive deficit performance deficit in cognitive/hippocampus dependent memory cognitive impairment memory dysfunction/deficit neurocognitive dysfunction	POCD was determined using Z score recommended by International Study of Postoperative Cognitive Dysfunction (ISPOCD) studies Patients were regarded as developing POCD if the Z score was ≥ 1.96 on ≥ 2 individual cognitive tests or the composite Z score was ≥ 1.96."	Incidence of POCD 34 %.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Liu, 2021	MMSE	One day before surgery, Postoperative days (POD) 1, 2, and 3	Postoperative cognitive decline (POCD) Cognitive dysfunction	POCD was defined as a Z-score −2 based on a pre- and postoperative MMSE The following formula was used: [(postoperative MMSE–preoperative MMSE)-ΔX MMSE normative population]/[SD ΔX MMSE normative population]. In this current study, ΔX MMSE normative population = 0.5 and SD (ΔX MMSE normative population) = 1.5 were used to calculate Z-score	POCD for the control group was 25%, 16% and 10 % for POD1-3. For the transcutaneous electrical acupoint stimulation (TEAS) group POCD was 10%, 8% and 4% on POD1-3. There was no significant difference between group on POCD on each day. On cumulative duration TEAS group had significantly lower incidence than control group on postoperative day 2 and 3.
Liu, 2020	MMSE	Before and at 4, 12, 24, and 48 hours and 7 days after surgery	(Early) Postoperative cognitive dysfunctioning (POCD)	A mean MMSE score decline >2 points between postoperative and preoperative surgery	Combined group (dexmedetomidine and epidural blockade) had significantly higher scores than all other groups (dexmedtomidine only, epidural only, control) at 12 to 24 h and higher than all but dexmedetomidine only at 48 h and 7 days
Mann, 2000	Abbreviated Mental Test (AMT)	Day before surgery, day of surgery (PM), twice a day (AM, PM) day 1-5 after surgery	Mental status Postoperative cognitive dysfunction Cognitive impairment	Decrease in the AMT score of 2 or more points (as part of a delirium diagnosis)	Significant lower scores for PCA-group (general anaesthesia and postoperative morphine) compared to PCEA-group (general anaesthesia combined with epidural bupivacainesufentanil) on day 4 AM and day 5 PM.
Miniotti, 2019	EORTC QLQ-C30	Majority within 12 months of diagnosis.	Cognitive functioning Problems in concentrating and remembering	NR	Significantly lower scores on cognitive function scale than reference population from EORTC reference value manual.
Monastyrska, 2016	EORTC QLQ-C30	One day prior to and 6 months following surgery	Cognitive functioning	NR	Both groups, lower anterior resection (LAR) and abdominoperineal resection (APR) significantly higher mean scores at follow up with LAR significantly higher than APR.
Ng, 2013	EORTC QLQ-C30	Before surgery and at 4, 8 and 12 months after surgery	Cognitive functioning	A difference in mean QoL scores of more than 10 points was regarded as clinically significant	Significant lower scores at 8 months for those with open resection compared to laparoscopic as well as clinically significant decline since baseline.

NR – Not reported

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 3.0, MMSE – Mini mental state examination, MoCA – Montreal Cognitive Assessment, CANTAB - Cambridge Neuropsychological Test Automated Battery, FACT-COG - Functional Assessment of Cancer Therapy - Cognitive Function

Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Nusca, 2021	EORTC QLQ-C30	The first post-surgical follow-up visit approximately ten days after surgery. after the end of the exercise program, 2 months and: 4 months thereafter.	Cognitive impairment	NR	Significant higher cognitive function score in the group attending a 2-month-long supervised and combined exercise–training program during the postoperative period than the group which did not at the end of the exercise program.
Olin, 2005	MMSE	At 3–4 weeks before surgery, day for postoperatively and at discharge.	Cognitive impairment Cognitive status Cognitive dysfunction Mental function	Scores from 0 to 10 of a total 30 corresponded to severe cognitive impairment	Significantly lower scores at day 4 in the long postoperative delirium (≥ 3 days) group compared to the group with no delirium.
Samuelsson, 2019	MMSE	Preoperative and at follow-up 1, 3 and 12 months after surgery	Cognitive impairment Cognitive decline	Possible cognitive impairment <24	At risk for cognitive impairment 8.2% preoperative, 5% at 1 month, 2,5% at 3 months, 2,7% at 12 months. Reported as cognition was improved compared to baseline at 3 months.
Scarpa, 2014	EORTC QLQ-C30	Admission, 1 month and 6 months	Cognitive function	NR	Significant higher values on cognitive function scale in the laparoscopic group for younger (<70 years) compared to elderly at 1 and 6 months.
Soares-Miranda, 2021	EORTC QLQ-C30	Six months post-surgery.	Cognitive impairment Cognitive capacity Cognitive decline	NR	Unadjusted and adjusted (age, sex, and cancer stage) linear regression showed that better performance in 6-minute walk test was associated with higher cognitive function.
Tang, 2021	MoCA	At 6, 12, 24, and 48 h after the operation.	Cognitive dysfunction (Early) Postoperative cognitive dysfunction (POCD)	A lower score indicated lower cognitive function, < 26 indicated abnormal.	Observation group (dexmedetomidine) had statistically significant higher cognitive function compared to control over follow up. There was also a significant change in function over time within both groups.

NR – Not reported

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Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
van der Vlies, 2022	EORTC QLQ-C30	At diagnosis and 3 months after diagnosis	Cognitive impairment	NR	Participants with decreased health related quality of life (HRQL) had statistically significant more affected cognitive function than participants with preserved HRQL. The decline was lager in patients who did not undergo surgery, either due to poor performance status or personal preference. In the surgically treated patients, there was slight impairments of cognitive functioning.
Vardy, 2014	Battery of clinical neuropsychological test (Letter-Number Sequencing, Digit Span, Spatial Span, Digit symbol, Trail Making Test A&B, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised) CANTAB and modified FACT-COG	Assessment after surgery before adjuvant treatment or before any treatment if neoadjuvant treatment was planned	Cognitive impairment Cognitive decline	Global cognitive impairment defined as Global Deficit score (GDS) of >0.5. Impairment on individual cognitive tests in all domains. International Cognition and Cancer Task Force (ICCTF), ≥1 standard deviation (SD) below the HC on at least one cognitive test, or >1.5 SD below on two or more tests A score <1.5 SD below the HC mean on the FACT-Cog was classified as perceived cognitive impairment (≤119/168)	Significant difference between localised cancer and healthy controls in cognitive impairment regardless of objective test method and definition. There was no significant difference between those evaluated pre- and post surgery in those with localised cancer. Frequency of cognitive impairment: Clinical test (GDS:ICCTF) / CANTAB (GDS:ICCTF) Localised cancer 45%:51% / 30%:39% Metastatic cancer 47%:49% / 31%:33 Healthy controls 15%:17%%/13%:17% Frequency of perceived cognitive impairment; localized cancer 21%, metastatic 18.5%, healthy controls 17%.
Vardy, 2021	Patient's Disease and Treatment Assessment Form-General	(T1) Initial visit (median 11 months after diagnosis) (T2) First follow up (median 3,6 months after T1) (T3) One year follow up	Trouble concentrating Memory impairment	Symptoms of at least moderate severity (4 or above out of 10)	Trouble concentrating : Above 20% at T1, reduced to less than 20% at T2-T3 Problems with memory: Less than 20% at T1, reduced at T2 and increased to 20% at T3.

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Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Visovatti, 2016	Attention Network, Test (ANT),, The digit span, The Trail Making Test , The Rey Auditory Verbal Learning Test , The Attentional Function Index, The Everyday Memory Questionnaire	Within six months of a new diagnosis	Cognitive impairment Cognitive changes Cognitive problems Cognitive decline	NR	Participants with cancer had significantly slower response time on ANT, lower scores at digit span forward and trail making test A and attention composite score.
Wang, H., 2015	EORTC QLQ-C30	Preoperatively and postoperative day (POD) 3, 6, 10, 14, 21, 28	Cognitive functioning	EORTC guidelines; clinically significant change: 10 ‘‘little”, 10–20 ‘‘moderately” 20 ‘‘very much” better or worse	Significant less decline of cognitive function scale in ERAS-group than control POD3 and POD6. Recovery to preoperative values for ERAS-group at POD21 and control at POD28.
Wang, P., 2021	MMSE	Admission and the 7th day post-surgery	Postoperative (neuro)cognitive impairment	Postoperative cognitive impairment defined as decline in MMSE score of 3 or more points	Probiotic group (twice daily until discharge) had significantly higher MMSE score than control at 7 days after surgery. Postoperative cognitive impairment at day 7 probiotic group 5.1%, control 16.4%
Wang, Y., 2020	Short Portable Mental Status Questionnaire	Day before the surgical procedure, discharge, 30 days after discharge	Cognitive changes Cognitive impairment	Declined on SPMSQ at discharge; 0 to 2 errors indicate normal mental functioning;	Significantly higher proportion of intact cognitive function in patients on tailored family-involved Hospital Elder Life Program (t-HELP) units which increased over time compared to usual care units which decreased. Significant lower with decline on SPMSQ at discharged in t-HELP units 0,8% vs usual care units 7%.
Wu, 2016	CANTAB	On the day before surgery, and at 7 days and at 3 months after the surgery	Postoperative cognitive dysfunction (POCD) Cognitive impairment Cognitive function change"	POCD was defined when the reliable change index RCI score was <–1.96 at least on 2 tests or when the combined Z score was <–1.96	POCD 26.4% at 7 days, no report for 3 months.

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Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Yang, 2019	MMSE	Before anaesthesia and 4 h, 24 h and 48 h after anaesthesia.	Postoperative cognitive function Cognitive ability	NR	Significantly higher scores for sevoflurane group (SEV) than isoflurane group (ISO) up to second follow up (24 4h). Significantly lower scores for both groups compared to before anaesthesia at 4 h and 24 h after anaesthesia
Zhang, C., 2020	MMSE	At 1h, 6h, 24h and 48h after surgery	Cognitive functioning	NR	Significant higher scores for combination (epidural blockade and parecoxib) group compared to epidural only group and control during all follow up, as well as epidural against control.
Zhang, J., 2019	MMSE	One day before surgery and 1 day and 3 days after surgery.	Postoperative cognitive dysfunction (POCD)	28-30 normal cognition, 24-27 mild cognitive dysfunction, 19-23 moderate cognitive dysfunction and 0-18 severe cognitive dysfunction	Significant higher score in experiment group (dexmedetomidine) than control (saline) during follow-up. Significantly lower scores in both groups compared to before surgery at both follow-ups. POCD in experiment group 9 % day 1 and no day 3. In control 22% day 1 and 13 % day 3.
Zhang, X., 2020	EORTC QLQ-C30	At admission, 3 month and 6 month follow up	Cognitive function	NR	No significant difference in cognitive function between control group and group which received psychological intervention.
Zhang, X., 2019	MMSE	Before anaesthesia, 1 day, 3 days and 5 days after operation	Postoperative perceptual function Postoperative cognitive impairment/dysfunction"	NR	Observation group (sevoflurane inhalation combined with epidural anaesthesia) had significantly higher scores at day 1 and 3 compared to control group (propofol general anaesthesia). Significant lower for both groups day 1 and 3 compared to baseline. Significant recovery day 3 compared to day 1 as well as day 5 compared to day 3 and day 1.

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Report	Instrument	Time of assessment	Nomenclature	Criteria for cognitive dysfunction	Outcome
Zhang, Y., 2019	MMSE, visual verbal learning test, digital span test, digital symbol test	One day before surgery Seven days after surgery	Postoperative cognitive dysfunction (POCD)	POCD was diagnosed when the score was greater than 1.96 or the combined Z score was ≥1.96	POCD 24.7%.
Zhou, 2018	Attention Network Test (ANT)	Pre-operatively and at day 1 and day 5	Postoperative attention network dysfunction Cognitive changes Postoperative cognitive impairment Postoperative cognitive dysfunction (POCD)	NR	Significant difference between bispectral index monitoring group (BIS) and non-BIS (control) group on alerting and orientation on day 5. Significant change for both groups in all domains (alerting, orientation, and executive control) at day 1 compared to baseline. At day 5 significant change in executive control for BIS and all domains for non-BIS group. Age was significantly correlated with pre-operative alerting function in the BIS and non-BIS group. Propofol (general anaesthesia) was significantly correlated with alerting, orientation, and executive control at postoperative day 1 and 5.

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Table of study characteristic

Report	Population (n, cancer, country)	End points	Summary
Arndt, 2004	309, Colorectal cancer 100%, Germany	Quality of life	Observational study comparing cancer survivors with general population.
Bao, 2020	178, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical trial on comparing dexmedetomidine to ulinastatin combined with dexmedetomidine in elderly after laparoscopic surgery with no previous chemo or radiation therapy.
Beaussier, 2006	52, Colorectal cancer 100%, France	Postoperative recovery including mental function	Randomised controlled trial comparing intrathecal morphine with IV PCA morphine compared to intravenous morphine alone in elderly patient undergoing major colorectal surgery.
Brown, 2014	614, Colorectal cancer 100%, United Kingdom	Quality of life	Longitudinal observational study of complications effect on long-term quality of life after colorectal cancer surgery comparing patient with 30 days complications to those with no complications.
Chen, 2020.	88, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial investigating protective effect of dexmedetomidine.
Couwenberg, 2018	270, Rectal cancer 100%, the Netherlands	Quality of life	Longitudinal observational study comparing to general population to patient undergoing low anterior resection and abdominoperineal resection.
Couwenberg, 2018	345, Rectal cancer 100%, the Netherlands	Postoperative complications and quality of life	Longitudinal observational study comparing older and younger patient with rectal cancer to reference population and the impact of postoperative complication in elderly.
D'Ambrosia, 2019	39, Rectal cancer 100%, Italy	Quality of life	Longitudinal observational study of patient with T2-T3 rectal cancer comparing laparoscopic total mesorectal excision and endoluminal locoregional resection. Patients with adjuvant chemotherapy was excluded.
De Souza, 2018	29, Rectal cancer 100%, Brazil	Quality of life	Longitudinal observational study of patient treated with curative intent.
Deckx, L., et al., 2015	321, Colorectal cancer 24%, Belgium and the Netherlands	Cognitive function, depression, and fatigue	Longitudinal observational study comparing older and younger cancer patient to older persons without cancer.
Ding, 2022	40, Colorectal cancer 100%, China	Postoperative recovery and cognitive function	Randomised controlled trial on effects of dexmedetomidine in elderly patients after laparoscopic surgery.
Fagard, 2017	190, Colon cancer 86%, Rectal cancer 14%, Belgium	Postoperative complications	Observational study of association between geriatric screening and 30 days complication after colorectal cancer surgery in older patients. Patients receiving neoadjuvant therapy where excluded.

Report	Population (n, cancer, country)	End points	Summary
Frick, 2017	1129, Colon cancer 70%, Rectal cancer 19%, international	Sequelae in cancer survivors	Cross-sectional study of persons using an internet-based tool for creating Survivorship care plans.
Gamerio, 2008	70, Colorectal cancer 100%, Germany	Postoperative cognitive function and mood	Observational study comparing laparoscopic and open colectomy.
He, 2017	90, Colon cancer 100%, China	Postoperative cognitive function	Randomised clinical trial on effects of remote ischemic preconditioning in elderly.
How, 2012	62, Rectal cancer 100%, United Kingdom & Germany	Quality of life	Longitudinal observational study comparing low anterior resection and abdominoperineal excision.
Janssen, 2020	265, Colorectal cancer, proportion not reported, Netherlands	Quality of life, cognitive function, and depressive symptoms	Observational study on impact of postoperative delirium after elective surgery for colorectal cancer and aortic repair and in older patients.
Kinoshita, 2018	120, Rectal cancer 100%, Japan	Quality of life	Longitudinal observational study of age-related factors after sphincter saving surgery comparing those older or younger than 60 years old.
León Arellano, 2020	40, Colorectal cancer 100%, Spain	Postoperative recovery and quality of life	Observational study on enhanced recovery after surgery program (ERAS).
Li, 2013	114, Colorectal cancer 37%, China	Postoperative complications	Observational study of relationship between blood lactate concentration and complications after 30 days in patients undergoing major elective abdominal surgery.
Lidenzi, 2015	82, Colorectal cancer 100%, Lithuania.	Quality of life	Observational longitudinal study in early postoperative period.
Lin, 2014	50, Colorectal cancer 46%, China	Postoperative cognitive function	Observational study on the role of HMGB1 on cognitive decline after major gastrointestinal surgery.
Liu, T., 2021	100, Colon cancer 100%, China	Postoperative cognitive function	Randomised controlled trial on effects of transcutaneous electrical acupoint stimulation in elderly patients undergoing laparoscopic surgery.
Liu, Y., 2020	96, Colorectal cancer 100%, China	Postoperative recovery	Randomised clinical trial comparing dexmedetomidine, epidural blockade, and combination of both in elderly after radical resection.
Mann, 2000	70, Colon cancer 66%, France	Postoperative recovery	Randomised controlled trial comparing general anaesthesia with postoperative morphine (PCA) or epidural bupivacainesufentanil anaesthesia (PCEA) after major abdominal surgery in elderly patients.

Report	Population (n, cancer, country)	End points	Summary
Miniotti, 2019	203, Colon cancer 71%, Rectal cancer 29%, Italy	Quality of life and psychological outcome	Cross-sectional study of supportive care needs in colorectal cancer patients compared to reference population.
Monastyrska, 2016	100, Rectal cancer 100%, Poland	Quality of life	Longitudinal observational study comparing lower anterior resection and abdominoperineal resection.
Ng, 2013	74, Rectal cancer 100%, China	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery.
Nusca, 2021	11, Colon cancer 73%, Rectal cancer 27%, Italy	Quality of life, function, and nutrition	Pilot study of effects of postoperative physical exercise program after laparoscopic surgery.
Olin, 2005	51, Colon cancer (proportion not reported), Sweden	Postoperative delirium	Observational study investigating occurrence and associated factors of delirium in elderly patients undergoing major abdominal surgery.
Samuelsson, 2019	49, Colorectal cancer 100%, Sweden	Postoperative complications and recovery	Longitudinal observational study investigating predictive value geriatric assessment tools in patients 75 year or older.
Scarpa, 2014	116, Colorectal cancer 100%, Italy	Quality of life	Longitudinal observational study comparing laparoscopic and open surgery in patient older and younger than 70 years.
Soares-Miranda, 2021	71, Colorectal cancer 100%, Portugal	Quality of life	Cross sectional study exploring association of physical fitness and health related quality of life 6 months after surgery.
Tang, 2021	100, Colon cancer 62%, Rectal cancer 38%, China	Cerebral oxygenmetabolism	Randomised clinical trial on effects of dexmedetomidine assisted intravenous inhalation.
van der Vlies, 2022	273, Colon cancer 71%, Rectal cancer 29%, the Netherlands	Quality of life	Longitudinal observational study of determinants for decreased health related quality of life 3 months after colorectal cancer diagnosis.
Vardy, 2021	206, Colorectal cancer 68%, Australia	Quality of life and lifestyle factors	Longitudinal observational study of persons attending Sydney Cancer Survivorship Center Clinic.
Vardy, 2014	363, Colorectal cancer 100%, Canada & Australia	Cognitive function and fatigue	Cross-sectional report of localised and metastatic colorectal cancer patients before adjuvant or neoadjuvant treatment compared to healthy control.
Visovatti, 2016	50, Colorectal cancer 100%, United states	Cognitive function	Cross-sectional report of colorectal cancer patients compared to healthy controls.
Wang, H., 2015	117, Colon cancer 100%, China	Quality of life	Observational study comparing patients using enhanced recovery after surgery program (ERAS) and conventional perioperative management.

Report	Population (n, cancer, country)	End points	Summary
Wang, P., 2021	120, Colorectal cancer 43%, China	Postoperative cognitive function	Randomised controlled trial investigating effect of probiotic intervention on cognitive impairment in elderly after non-cardiac surgery.
Wang, Y., 2020	281, Colorectal cancer 19%, China	Postoperative recovery and function	Randomised controlled trial investigating effectiveness of Tailored Family-Involved Hospital Elder Life Program after noncardiac surgical procedure.
Wu, 2016	110, Colon cancer 100%, China	Postoperative cognitive dysfunction	Observational study of association between miRNA-155 and cognitive function after laparoscopic surgery.
Yang, 2019	130, Colon cancer 100%, China	Postoperative recovery and cognitive function	Randomised trial on effect of sevoflurane compared to isoflurane anaesthesia in elderly patients.
Zhang, Y., 2019	77, Colon cancer 100%, China.	Postoperative cognitive dysfunction	Observational study to reveal risk factors for early postoperative cognitive dysfunction. No patients received preoperative chemotherapy or radiotherapy.
Zhang, C., 2020	186, Colorectal cancer 100%, China	Postoperative recovery	Randomised trial on effects of epidural blockade and combination of epidural blockade and pre intravenous injection of parecoxib in patients who didn't receive chemotherapy before surgery.
Zhang, J., 2019	140, Colorectal cancer 100%, China	Postoperative cognitive function	Clinical study of dexmedetomidine in elderly. Patients undergoing radiotherapy or chemotherapy before surgery was excluded.
Zhang, X., 2020	159, Colorectal cancer 100%, China	Quality of life and psychological outcome	Randomised controlled trial on effect of psychological interventions in colorectal cancer patients.
Zhang, X., 2019	78, Colorectal cancer 100%, China	Postoperative cognitive function	Retrospective observational study of sevoflurane inhalation combined with epidural anaesthesia compared to propofol general anaesthesia in elderly.
Zhou, 2018	81, Colon cancer 100%, China	Postoperative cognitive function and delirium	Randomised controlled trial on effects of bispectral index monitoring in elderly patients.

Questionnaires

Attentional Function Index (AFI)

Everyday Memory Questionnaire (EMQ)

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 3.0 (EORTC QLQ-C30)

Functional Assessment of Cancer Treatment – Cognitive function issues (FACT-Cog)

Patient's Disease and Treatment Assessment Form—General (PtDATA)

Screening tools

Abbreviated Mental Test (AMT)

Hasegawa's Dementia Scale - Revised (HDS-R)

Mini-Mental State Examination (MMSE)

Montreal Cognitive Assessment (MoCA)

Short Portable Mental Status Questionnaire (SPMSQ)

Neuropsychological test

Attention Network Test (ANT)

Benton Judgment of Line Orientation (JLO)

Brief Visuospatial Memory Test-Revised (BVMT-R)

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Digit Span Test

Digit Symbol Substitution Test (DSST)

Hopkin Verbal Learning Test-Revised (HVLT-R)

Letter-Number Sequencing

Rey Auditory Verbal Learning Test (RAVLT),

Stroop Test

Symbol-Digit Modalities Test (SDMT)

Trail-Making Test, (TMT)

Visual verbal learning test (VVLT)

Verbal fluency test

Word recall