**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<br>Differences of more than 10 points are clinically meaningful | 55.9% with any level of concern<br>Clinically significant different between CRC and general population under 60 years<br>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).<br><br>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<br>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<br>Higher mental functions<br>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<br>Postoperative cognitive dysfunction/impairment<br>Cognitive brain dysfunction<br>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.<br><br>Total cognitive impairment study group 16%, control 64%. |

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|---|---|---|---|---|---|
| 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).<br><br>Proportion of worsened cognitive domain:<br>3 months APR 41%, LAR 40%,<br>6 months APR 35%, LAR 41%,<br>12 months APR 23%, LAR 31%,<br>18 months APR 19%, LAR 33%,<br>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.<br>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=<br>good, 76-100= very good | Cognitive function changed from good before surgery to very good at both follow ups. |

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|---|---|---|---|---|---|
| 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.<br><br>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<br>Postoperative cognitive dysfunction (POCD)<br>Postoperative consciousness dysfunction<br>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<br>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<br>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<br>Postoperative neuropsychological dysfunction<br>Long-term cognitive deterioration<br>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<br>Postoperative cognitive dysfunction (POCD)<br>Cognitive decline | Score < 26 is considered abnormal | Significantly difference between control and Remote ischemic preconditioning group one day and three days after surgery. |

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|---|---|---|---|---|---|
| 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<br>(Persistent) postoperative cognitivie dysfuntion<br>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<br>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,<br>Brief Visuospatial Memory Test-Revised,<br>Trail-Making Test;<br>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<br>Post-operative cognitive dysfunction (POCD)<br>(Neuro)cognitive deficit<br>performance deficit in cognitive/hippocampus dependent memory<br>cognitive impairment<br>memory dysfunction/deficit<br>neurocognitive dysfunction | POCD was determined using Z score recommended by International Study of Postoperative Cognitive Dysfunction (ISPOCD) studies<br><br>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 %. |

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| Liu, 2021 | MMSE | One day before surgery, Postoperative days (POD) 1, 2, and 3 | Postoperative cognitive decline (POCD)<br>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.<br><br>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 was >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<br>Postoperative cognitive dysfunction<br>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<br>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. |

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| 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<br>Cognitive status<br>Cognitive dysfunction<br>Mental function | Scores from 0 to 10 of a total of 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<br>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.<br>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<br>Cognitive capacity<br>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<br>(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. |

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| 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)<br>CANTAB and modified FACT-COG | Assessment after surgery before adjuvant treatment or before any treatment if neoadjuvant treatment was planned | Cognitive impairment<br>Cognitive decline | Global cognitive impairment was defined as Global Deficit score (GDS) of >0.5. Impairment on individual cognitive tests in ≥2 domains.<br>International Cognition and Cancer Task Force (ICCTF), as 2 standard deviation (SD) below the HC on at least one cognitive test, or >1.5 SD below on two or more tests<br><br>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.<br><br>Frequency of cognitive impairment:<br>Clinical test (GDS:ICCTF) / CANTAB (GDS:ICCTF)<br>Localised cancer 45%:51% / 30%:39%<br>Metastatic cancer 47%:49% / 31%:33<br>Healthy controls 15%:17%%/13%:17%<br><br>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)<br>(T2) First follow up (median 3,6 months after T1)<br>(T3) One year follow up | Trouble concentrating<br>Memory impairment | Symptoms of at least moderate severity<br>(4 or above out of 10) | Trouble concentrating :<br>Above 20% at T1, reduced to less than 20% at T2-T3<br>Problems with memory:<br>Less than 20% at T1, reduced at T2 and increased to 20% at T3. |

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| Visovatti, 2016 | Attention Network, Test (ANT),,<br>The digit span, The Trail Making Test ,<br>The Rey Auditory Verbal Learning Test , The Attentional Function Index,<br>The Everyday Memory Questionnaire | Within six months of a new diagnosis | Cognitive impairment<br>Cognitive changes<br>Cognitive problems<br>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;<br>clinically significant change of 5–10 ‘‘little”, 10–20 ‘‘moderate”, > 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 decrease 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.<br>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<br>Cognitive impairment | Declined on SPMSQ at discharge<br><br>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.<br><br>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)<br>Cognitive impairment<br>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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|---|---|---|---|---|---|
| Yang, 2019 | MMSE | Before anaesthesia and 4 h, 24 h and 48 h after anaesthesia. | Postoperative cognitive function<br>Cognitive ability | NR | Significantly higher scores for sevoflurane group (SEV) than isoflurane group (ISO) up to second follow up (24 4h).<br><br>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.<br><br>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<br>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).<br><br>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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|---|---|---|---|---|---|
| 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<br>Cognitive changes<br>Postoperative cognitive impairment<br>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.<br><br>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.<br><br>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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