# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Boston Scientific | Guideline | General | General | We are concerned that there is currently no liver directed therapy recommended in the guideline relating to treatment of metastatic colorectal cancer to the liver, which therefore limits the use of personalised therapy in liver dominant disease, and which is commissioned by the NHS. Similarly, we are concerned that there is no mention of Drug Eluting Beads with irinotecan (DEBIRI) in the guidelines.<br><br>Similarly, the use of cryotherapy has been omitted for liver metastases associated with colorectal cancer, as per NICE IPAC guidelines (IPG369, Dec 2010) | Thank you for this comment. The effectiveness of different liver directed therapies, including local ablation, stereotactic body radiation therapy, chemosaturation, transarterial chemoembolisation (including DEBIRI) and selective internal radiation therapy, were reviewed for this guideline update. Except for local ablation, the evidence was not strong enough for the committee to recommend them. Cryotherapy was not reviewed because it is largely a historic treatment and has been replaced by radiofrequency ablation or microwave ablation in most places. |
| Boston Scientific | Evidence review 14 | General | General | Further evidence which demonstrates the clinical benefit of using SIRT in the chemo refractory patient group is highlighted by Hickey et al[1]. This retrospective multi-centre study treated 531 patients with glass microspheres. All patients had unresectable mCRC refractory to previous systemic or locoregional therapy. Median overall survival was 10.6 months from the first TheraSphere treatment, predictors of survival included no extrahepatic metastases, tumour burden <25%, albumin > 3g/dL and receiving ≤2 chemotherapeutic agents.<br><br>Additionally, Kennedy et al[2] evaluated the use of SIRT in 606 mCRC patients and showed a favourable risk/benefit profile, even among patients who had received 3 or more lines of chemotherapy. with a median survival of 9.0 months in patients receiving SIRT as 3rd line therapy (2 prior lines of chemotherapy) | Thank you for this comment. For this review RCTs were determined to be the most appropriate evidence type and as the literature searches identified RCTs in which SIRT was evaluated non-randomised studies or consensus based guidelines were not considered, such as those listed in your comment: Hickey 2016; Kennedy 2015; Benson 2013; Lewandowski 2014; Abbott 2015; and Mulcahy 2009,Van Cutsem 2016, as these were all non-randomised studies. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | We would also like to highlight the following publications which support the Commissioning Through Evaluation findings:<br><br>**Benson III, Al B., et al. "Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study." European Journal of Cancer 49.15 (2013): 3122-3130.**<br>This study investigated the safety, response rate, progression-free and overall survival of patients with liver metastases treated with 90Y (glass) radioembolisation in a prospective, multicenter phase II study. 151 patients were included (61 with mCRC), the authors concluded that the therapy was safe and efficacious with a median PFS and OS for mCRC of 2.9 months and 8.8 months respectively and a DCR for mCRC of 59%.<br><br>**Lewandowski, Robert J., et al. "Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy." European journal of nuclear medicine and molecular imaging 41.10 (2014): 1861-1869.**<br>The study prospectively collected data of 214 patients treated with Y90 at a single center over 12 years. The median overall survival was 10.6 months from date of first Y90 treatment. Predictors of increased survival were - received <2 cytotoxic agents, received no biologic agents, | |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | had no extra hepatic disease, tumour burden <25%, ECOG of 0 and albumin >3g/dL.<br><br>**Abbott, A. M., et al. "Outcomes of Therasphere Radioembolization for Colorectal Metastases". Clin Colorectal Cancer. 14.13 (2015): 146-153.**<br>This retrospective review of mCRC patients undergoing Y90 from 2009-2013 included 68 patients. Median and 2 year OS were 11.6 months and 34% respectively. For patients with ≤25% tumour burden and 1 chemotherapy regimen 2 year OS was 63%. Prognostic factors for increased mortality included age, >25% tumour burden, ≥3 lines of chemotherapy and higher CEA.<br>**Mulcahy, M. F., et al. "Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres". Cancer. 115 (2009): 1849-1858.**<br>72 patients were included in the analysis to determine the safety and efficacy of Y90 therapy for patients with liver dominant mCRC. Toxicities were acceptable. The tumour response rate was 40.3%. The median time to hepatic progression was 15.4 months, and the median response duration was 15 months. The PET response rate was 77%. Overall survival from the first Y90 treatment was 14.5 months. Tumour replacement (≤25% vs >25%) was associated with significantly greater median survival (18.7 months vs 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months vs 21 months). Overall survival from the date of | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | initial hepatic metastases was 34.6 months. The median dose delivered was 118Gy.<br><br>Equally, the European Society Medical Oncology (ESMO) published consensus guidelines[3] for the management of patients with metastatic colorectal cancer which includes a "toolbox" of ablative treatments. Radioembolisation SIRT is included as an option within this toolbox. The ESMO guidelines highlight that for "patients with liver-limited disease failing the available chemotherapeutic options, radioembolization with yttrium-90 microsphere should be considered"<br><br>[1] Hickey, Ryan, et al. "Radioembolization of Colorectal Hepatic Metastases Using Glass Microspheres: Safety and Survival Outcomes from a." (2016)<br><br>[2] Kennedy AS, Ball D, Cohen SJ, Cohn M, Coldwell DM, Drooz A, Ehrenwald E, Kanani S, Rose SC, Nutting CW, Moeslein FM. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for 90Y resin microspheres. Journal of gastrointestinal oncology. 2015 Apr;6(2):134[33] Van Cutsem, E., "ESMO consensus guidelines for the management of patients with metastatic colorectal cancer". Annals of Oncology. 27.8 (2016): 1386-1422. | |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Boston Scientific | Evidence review 14 | 17 | 43 | We would like to highlight that the RCT evidence where SIRT was used as a first line treatment, was based on a study which had suboptimal patient selection and treatment (i.e. Extrahepatic disease and no personalised dosimetry), we would therefore recommend that SIRT requires further research in this area, particularly as benefit was show in right sided tumours which needs further investigation. In terms of the use of glass SIRT in second line, we are awaiting the BTG sponsored EPOCH study which will inform the decision, however in the meantime we would recommend further research and investigation. | Thank you for this comment. The included trials did allow for some extra-hepatic disease in their inclusion criteria but this was balanced between the treatment arms in the randomisation process and so the committee did not think it was a reason to downgrade the quality of the evidence. The committee acknowledged that since these trials were done there may have been developments in SIRT techniques and they considered making a research recommendation, but this area was not prioritised because several trials already exist in this area. |
| Boston Scientific | Evidence review 14 | 18 | 1-5 | The NICE IPAC committee has produced an updated consultation document (Selective internal radiation therapy for unresectable colorectal metastases in the liver, In development [GID-IPG10124 July 2019). This updated review includes a review of 3 publications from 4 RCTs, 2 non randomised comparative studies and 3 case series.[1-8] Key efficacy outcomes were considered to be quality of life, survival and reduction in tumour volume. The IPAC documentation highlights that for patients "who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, there is evidence of efficacy but this is limited, particularly for important outcomes such as quality of life" The recommendation is for use with special arrangements, which aligns with the aforementioned NHS England commissioning policy.<br><br>1. Wasan HS, Gibbs P, Sharma NK et al. (2017) First-line selective internal radiotherapy plus chemotherapy versus | Thank you for this comment. For this review RCTs were determined to be the most appropriate evidence type and as the literature searches identified RCTs in which SIRT was evaluated, non-randomised studies were not considered, such as the following studies included in GID-IPG10124: Bester 2012; Hickey 2016; Kennedy 2017; Seidensticker 2012; and White 2019 as these were all non-randomised studies. In addition, Gibbs 2018 was not included in the evidence review as it reports a post hoc analysis (from two RCTs included in our review) on the effect of tumour sidedness - an issue which the committee did not specify in advance as an area of interest. Two studies included in GID-IPG10124 were included in the evidence review (Hendlisz 2010 and Wasan 2017). |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncology 18: 1159-71<br>2. Gibbs P (2018) Effect of primary tumor side on survival outcomes in untreated patients with metastatic colorectal cancer when selective internal radiation therapy is added to chemotherapy: combined analysis of two randomized controlled studies. Clinical Colorectal Cancer 17: e617-e629<br>3. Hendlisz A, Van den Eynde M, Peeters M et al. (2010) Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. Journal of clinical oncology 28: 3687-94<br>4. Bester L, Meteling B, Pocock N et al. (2012) Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. Journal of Vascular & Interventional Radiology 23: 96-105<br>5. Seidensticker R, Denecke T, Kraus P et al. (2012) Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovascular & Interventional Radiology 35: 1066-73<br>6. White J, Carolan-Rees G, Dale M et al. (2019) Analysis of a National Programme for Selective Internal Radiation | The recommendations about SIRT in this guideline are not in contradiction with the draft NICE IPG or the NHS England commissioning document. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | Therapy for Colorectal Cancer Liver Metastases. Clinical Oncology 31: 58-66<br>7. Kennedy, A.; Cohn, M.; Coldwell, D. M. et al. (2017) Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. Journal of Gastrointestinal Oncology<br>8: 614-24 8. Hickey, R.; Lewandowski, R. J.; Prudhomme, T. et al. (2016) 90Y radioembolization of colorectal hepatic metastases using glass microspheres: Safety and survival outcomes from a 531-patient multicenter study. Journal of Nuclear Medicine 57: 665-71 | |
| Boston Scientific | Evidence review 14 | 18 | 10-12 | We are concerned that the data from the Commissioning Through Evaluation (CtE) registry of 399 adults with unresectable, chemotherapy-refractory, CRC liver metastases has not been fully evaluated[1] considered in this draft guideline. The CtE was carried out over five years at ten UK hospital sites. The study concluded that "SIRT is safe and well tolerated in patients who had previously received multiple lines of chemotherapy and it has shown that SIRT in this population results in overall survival (OS), Progression Free Survival (PFS) and Liver PFS (LPFS) that are consistent with previously published smaller studies". The NHS England decision to subsequently commission SIRT for chemotherapy refractory / intolerant metastatic colorectal cancer limited to the liver in adults *(according to specified criteria;(NHS England Reference 170102P*) | Thank you for this comment. The White 2019 study was published after the literature search cut-off date but it would still not have been included because for this review RCTs were determined to be the most appropriate evidence type and as the literature searches identified RCTs in which SIRT was evaluated, non-randomised studies were not included in the review.<br><br>The study is however included as evidence in the NICE interventional procedures guidance on SIRT currently in development. This is because the NICE IPG incorporates evidence on the safety and efficacy of SIRT, whereas the current guideline is concerned |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | highlights that there is a recognised role and clinical need for SIRT in salvage/chemorefractory patients.<br><br>[1] White J, Carolan-Rees G, Dale M, Patrick HE, See TC, Bell JK, Manas DM, Crellin A, Slevin NJ, Sharma RA. Yttrium-90 Transarterial Radioembolization for Chemotherapy-Refractory Intrahepatic Cholangiocarcinoma: A Prospective, Observational Study. Journal of Vascular and Interventional Radiology. 2019 Jun 27. | with the relative effectiveness of SIRT compared to other treatment options.<br><br>The recommendations about SIRT in this guideline are not in contradiction with the draft NICE IPG or the NHS England commissioning document. |
| Bowel Cancer UK | Guideline | General | General | **There are also a number of omissions from the NICE guidance which need to be addressed. The next few comments outline these.**<br><br>Firstly, **DPYD testing:**<br><br>It is paramount that this NICE guidance recommends or at least provides guidance on the routine testing of the dihydropyrimidine dehydrogenase (DPD) enzyme for all cancer patients receiving fluoropyrimidine-based chemotherapy, including those with bowel cancer.<br><br>Treatment with this class of chemotherapy, which includes the drugs 5-fluorouracil (5FU), capecitabine and the oral pro-drug tegafur, is usually well tolerated for people with normal DPD levels. This is because the DPD enzyme is responsible for breaking down the chemotherapy drug in the body. DPD deficiency therefore occurs when there is | Thank you for this comment. DPYD testing was not in the scope of this guideline update. The committee acknowledges the importance of this issue, which applies to not only colorectal cancer but also other cancers such as upper gastrointestinal cancers, breast cancer and neck cancers. |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | low or no level of the DPD enzyme, and affects between 3-6% of the population. However, severe and even fatal adverse drug reactions have been recognised to occur in 10-20% of the treated population, largely because of DPD deficiency[1]. A recent Dutch study even reports severe toxicity in up to 30% of patients[2]. This is because of an inter-individual genetic variation of the DPYD gene, which is responsible for the production of DPD in our bodies.<br>[29] https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency<br>[30] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30686-7/fulltext<br><br>Side effects for DPD deficient patients include diarrhoea, low white blood count with reduced resistance to infection and mucositis (mouth soreness and ulceration), feeling or being sick, and a severe skin reaction causing peeling and blistering of the skin[3]. Patients with this problem require often long admissions to hospital, including into intensive care, and can die as a result of these complications. This | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | includes patients who have early stage cancer, who are having adjuvant treatment with curative intent.<br>[31] https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency<br>The majority of these cases are completely avoidable. A number of variants (polymorphisms) in the DPYD gene coding for DPD have been identified to be associated with this toxicity. Leading scientific groups, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC)[4] and Dutch Pharmacogenetics Working group,[5] have provided updated gene and drug clinical practice guidelines recommending reductions in dosage of fluoropyrimidines for those with intermediate DPD deficiency, with larger dose reductions for more severe cases. This treatment modification is not possible if patients at risk cannot be identified. Moreover, two recent large prospective trials studied the implementation of DPYD-genotype guided individualised dosing as a standard of care, and have demonstrated reductions in toxicity, improvements in patient safety, cost savings per patient, and recommend routine DPYD genotyping[6] [7]. | |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | [32]https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/<br>[33]https://ascpt.onlinelibrary.wiley.com/doi/full/10.1038/clpt.2011.34<br>[34]https://www.ncbi.nlm.nih.gov/pubmed/30544060<br><br>Mandating routine testing will prevent patient harm and would be cost effective for the NHS[8]. Testing of the DPYD gene is relatively simple, inexpensive and a number of providers exist including Viapath and Oxford Biomarkers. Currently, testing costs £35 in-house at Guys' & St Thomas' NHS Trust and £60 to external NHS Trusts using Viapath. This can be performed on a blood sample and provides results in three to five days.<br><br>[36]https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30686-7/fulltext | |
| Bowel Cancer UK | Guideline | General | General | **Raltitrexed (Tomudex)**<br>A small number of patients suffer cardiac effects from the treatment of some fluoropyrimidines including 5FU and capecitabine. On such occasions it is routine practice to substitute this fluoropyrimidine for raltitrexed. This was in previous guidance and seems to have been omitted from the recent draft. It is essential to continue to recommend the use of this agent in patients who suffer from the cardiac | Thank you for this comment. This area was not prioritised in the scoping process and is therefore outside the scope of this guideline update. The use of raltitrexed for this indication is embedded in clinical practice and the BNF is clear about its indicated use, therefore, a NICE guidance on this was not considered necessary. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | effects of conventional fluorpyrimidines[9].<br>[37]https://www.ncbi.nlm.nih.gov/pubmed/23583220 | |
| Bowel Cancer UK | Guideline | General | General | **Perioperative management**<br>These drafted guidelines have omitted perioperative management of patients undergoing surgery for bowel cancer. Additionally, Bowel Cancer UK recommends guidelines on pre-operative (or indeed pre-chemotherapy) optimisation and cardiopulmonary exercise testing (CPEX) and pre-treatment risk assessment. The introduction of this type of assessment has helped reduce the mortality rates for patients according to the National Bowel Cancer Audit (NBOCA)[10].<br>[38]https://www.nboca.org.uk/content/uploads/2018/12/NBOCA-annual-report2018.pdf | Thank you for this comment. Perioperative patient management, pre-treatment optimisation, cardiopulmonary exercise testing or pre-treatment risk assessment were not in the scope of this guideline update and evidence for these were therefore not reviewed. NICE is currently developing a guideline on perioperative care for adults which covers some of these topics. While the committee recognises the potential importance of pre-treatment risk assessment, the committee does not think it is correct to state that the reason for a reduction in mortality rates is due to this. |
| Bowel Cancer UK | Guideline | General | General | **Need for reasoning throughout recommendations**<br>The guideline document needs to provide further clarification throughout the recommendations on the reasoning for these decisions. We appreciate that a full rationale is provided separately, however, we are concerned that clinicians will not have the time to read this and as such it would be beneficial to have a quick explanation throughout the recommendations. | Thank you for this comment. A 'summary' justifications for the recommendations are given in the 'Rationale and impact' section of the guideline. A more detailed discussion section is provided in each evidence report. In the final web version of the guideline the 'Rationale and impact' sections will be more easily accessible underneath the recommendations via a drop-down arrow, whereas in the consultation version of the guideline these could be found further down in the guideline document. |
| Bowel Cancer UK | Guideline | 6-7 | General | The techniques outlined in the first two columns of table one (TEA including TAMIS and TEMS and ESD) are not | Thank you for this comment. The committee recognises that currently transanal excision and |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | available in all hospitals. The treatment of early rectal cancer is contentious and there is a need for early rectal cancer multi-disciplinary teams (MDTs) containing clinicians with the appropriate skills (this may require regional MDTs). Bowel Cancer UK would refer the NICE team to the UK significant polyp and early colorectal cancer (SPECC) programme[11].<br>[5] https://www.pelicancancer.org/specc/ | particularly endoscopic submucosal dissection are not available in all hospitals and the guideline addressees the potential resource impact if this service were to be provided more widely. The committee agrees that treatment of early rectal cancer is contentious and the evidence is not clear on which treatment is the best. This is why a table with the treatment options outlining the differences and implications of each procedure to aid decision making has been included. Early rectal cancer MDTs already exist within wider colorectal cancer MDTs in many areas. |
| Bowel Cancer UK | Guideline | 8 | 6-7 | Bowel Cancer UK does not agree with recommendation 1.3.3 and has a number of concerns if this were to be implemented. This recommendation is based on data from trials performed over ten years ago where the plane of surgery achieved was shown to be an important prognostic factor for local recurrence[12]. However, these studies were prior to the widespread use of tumour microenvironment (TME) characterisation and should not inform a current recommendation.<br>[1] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60485-2/fulltext<br><br>Instead, NICE should call for both high quality surgery and monitoring to grade the quality of a tumour specimen to | Thank you for this comment.<br>We suspect there is a typo in the comment and the stakeholder means total mesorectal excision (TME), not tumour microenvironment (TME). While total mesorectal excision was not yet in widespread use in practice at the time of the trials, TME was used in the major trials about preoperative therapy, e.g. Dutch TME trial and MRC CR07. These trials still provide the best available evidence and the committee did not consider them to be irrelevant to current practice.<br><br>The committee recognises that there is a chance that some people might be over treated. However, the pooled evidence from several RCTs shows better survival and lower local recurrence for those receiving |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | determine whether radiotherapy or chemo-radiotherapy is required.<br>This approach would align with updated ESMO guidelines[13] that details which tumour, node and metastases (TNM) stages would require radiotherapy or chemo-radiotherapy pre-operatively. Photographs of tumour specimens should be used by a pathologist to help grade the quality of the specimen in order to identify the quality of the surgery. If the specimen has a clean excision and the circumferential resection margin (CRM) is not threatened microscopically, no radiotherapy or chemo-radiotherapy would be required post-operatively.<br>[2]<br>https://academic.oup.com/annonc/article/28/suppl_4/iv22/3958158<br>Furthermore, this recommendation does not take into account the side effects experienced by patients receiving radiotherapy or chemo-radiotherapy and as such should not be used as a blanket rule for patients that do not require this treatment.<br><br>We recommend the use of radiotherapy and/or chemo-radiotherapy administered to patients on an individual basis according to need, in line with the personalised care approach set out in the NHS Long Term Plan. | preoperative radiotherapy or chemoradiotherapy. As with any treatment decision, individualised consideration and clinical judgment should be exercised.<br><br>The guideline does not include recommendations about postoperative radiotherapy.<br><br>The committee agree that treatment for each individual patient should be personalised and treatment decisions should be made following careful consideration with the patient, taking into account the benefits and harms of treatments. Recommendation 1.2.2 says to "Give people information on all treatment options for colorectal cancer available to them, including…. the potential benefits, risks, side effects and implications of treatments". |
| Bowel Cancer UK | Guideline | 8 | 9-11 | This recommendation needs to be more clear that deferral of surgery for rectal cancer is for patients who have had a | Thank you for this comment. The recommendation has been amended to make it clearer. However, this would |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | complete pathological and radiological response to neoadjuvant chemo-radiotherapy. | be patients with complete clinical and radiological response (not pathological) to neoadjuvant therapy. |
| Bowel Cancer UK | Guideline | 10-11 | 11-15 and 1-2 | Three months of CAPOX is sufficient for most patients, however for patients with high-risk stage III disease (T4 and/or N2) a longer treatment time for CAPOX[14] may be considered.<br>[3]<br>https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30093-7/fulltext<br><br>Three months of FOLFOX has a worse disease-free survival (DFS) than six months' treatment[15]. While three months FOLFOX could be considered for some patients with low risk Stage III disease (T1-3, N1), for patients with high risk disease treatment with FOLFOX for up to six months should be considered.<br>4<br>https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30093-7/fulltext | Thank you for this comment. Whilst 6 month CAPOX showed a longer disease-free survival compared to 3 month CAPOX in patients with high-risk stage III disease (T4 and/or N2) the difference was small and not clinically significant (hazard ratio=1.02 [0.89,1.17]). Given the lower overall quality adjusted life years (as a result of being on chemotherapy longer) and large increase in costs the committee did not recommend a longer course of CAPOX for this high risk group.<br><br>The recommendations as they stand allow for up to 6 months FOLFOX in line with NICE technology appraisal on capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. The committee believes the recommendation is flexible and allows for a shorter course where this is appropriate. |
| Bowel Cancer UK | Guideline | 11 | 10-11 | With stenting preferable to surgery for palliative intent, there needs to be guidelines on standardising provision of services to provide colonic stents in the elective or emergency situation. The type of narrative about | Thank you for this comment. The committee recommends stenting for people who are to be treated with palliative intent. However, for people for whom curative treatment is suitable, the committee |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | endoscopic submucosal dissection (ESD) (in the table underneath recommendation 1.3.1) would be useful here. | recommends either stenting or emergency surgery because evidence on the benefits of stenting is not convincing enough to only recommend stenting. The committee did not consider this to be a patient preference sensitive decision point because the decision is not only based on the patient's preference but also on clinical and practical factors, including availability of surgical or stenting expertise at an emergency situation, therefore, a table such as the one for recommendation 1.3.1 was not created. |
| Bowel Cancer UK | Guideline | 15 | 3-6 | Follow-up should not only be recommended to detect recurrence but should also be used to detect potentially long-term treatment toxicities which affect survivors' quality of life[16]. These toxicities frequently have multiple systemic causes and may not be just localised issues relating to surgery[17 18]. Systematic management of symptoms is relatively cheap and improves quality of life[19].<br>[6] Downing, A., et al., Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol, 2015. 33(6): p. 616-24.<br>7 Andreyev, H.J.N., et al., Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. The Lancet, 2013. 382(9910): p. 2084-92. | Thank you for this comment. The committee agrees that follow-up for treatment toxicity is an important issue, however not all aspects of colorectal cancer care could be covered in this guideline update. In scoping this guideline the issue of follow-up for the detection of recurrence was identified as a priority for evidence review. In the recommendations the committee emphasises the importance of monitoring and managing side effects and that people should be given information about possible side effects (both short and long term), see recommendations 1.2.1-1.2.2 and 1.2.5-1.2.7. On discharge the committee recommends advice should be given on diet, physical activity and healthy lifestyle choices to promote recovery as well as how, when and where to seek help |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | 8 Larsen, H.M., et al., Clinical evaluation and treatment of chronic bowel symptoms following cancer in the colon and pelvic organs. Acta Oncol, 2019. 58(5): p. 776-781.<br>9 Muls, A.C., et al., The holistic management of consequences of cancer treatment by a gastrointestinal and nutrition team: a financially viable approach to an enormous problem? Clin Med, 2016. 16(3): p. 240-6.<br><br>The long term consequences of symptoms after treatment with surgery alone must be acknowledged.<br>After a right hemicolectomy, up to one in five patients have loose stool, increased bowel frequency and/ or nocturnal defecation. Sometimes these symptoms improve spontaneously over time but not in all patients. Some reported 'improvement' of bowel function may occur because these symptoms become part of a patient's everyday life, with their sense of 'normality' adjusted and symptoms tolerated even when severely limiting activities[20]. Published studies vary how much this affects quality of life after right hemicolectomy[21 22].<br>10 Jakobsson, J., E. Idvall, and C. Kumlien, The lived experience of recovery during the first 6 months after colorectal cancer surgery. J Clin Nurse, 2017. 26(23-24): p. 4498-4505.<br>11 Magdeburg, J., et al., Long-term functional outcome of colonic resections: how much does faecal impairment | if side effects become problematic, see recommendation 1.2.8. For the area of management of treatment toxicities the committee prioritised the issue of LARS, and made recommendations on this issue, see recommendations 1.6.2-1.6.4.<br><br>Although many of the other side effects mentioned in your comment (for example chronic fatigue, psychological distress and sexual dysfunction) have an adverse impact on quality of life, they are not specific to colorectal cancer and so were not prioritised for evidence review. Although no specific reviews were conducted on these topics, evidence on quality of life, including specific quality of life subscales on sexual function, bladder function and bowel function were sought, although evidence on these were often limited. |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | influence quality of life? Colorectal Dis, 2016. 18(11): p. O405-O413.<br>12 Bertelsen, C.A., et al., Long-term Functional Outcome After Right-Sided Complete Mesocolic Excision Compared With Conventional Colon Cancer Surgery: A Population-Based Questionnaire Study. Dis Colon Rectum, 2018. 61(9): p. 1063-1072.<br><br>Long-term difficult gastro-intestinal (GI) side effects have also been recognised, affecting the quality of life (QoL) in approximately 10% of patients following a sigmoid colectomy[23] [24].<br>[13] Van Heinsbergen, M., et al., Bowel dysfunction after sigmoid resection underestimated: Multicentre study on quality of life after surgery for carcinoma of the rectum and sigmoid. Eur J Surg Oncol, 2018. **44**(8): p. 1261-67.<br>[14] Elfeki, H., et al., Bowel dysfunction after sigmoid resection for cancer and its impact on quality of life. Br J Surg, 2019. **106**(1): p. 142-151.<br><br>After anterior resection, patients likely to develop severe low anterior resection syndrome symptoms can be accurately predicted[25]. However, after surgery alone one in three patients have severe long term bowel dysfunction and | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | this increases to approximately half of all patients who additionally receive chemo-radiotherapy[26] [27].<br>[15] Battersby, N.J., et al., Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. Gut, 2018. **67**(4): p. 688-696.<br>[16] Croese, A.D., et al., A meta-analysis of the prevalence of Low Anterior Resection Syndrome and systematic review of risk factors. Int J Surg, 2018. **56**: p. 234-241.<br>[17]van Heinsbergen, M., et al., Functional bowel complaints and quality of life after surgery for colon cancer: prevalence and predictive factors. Colorectal Dis, 2019. **Epub ahead of print**.<br><br>Bowel bacterial overgrowth and bile acid malabsorption are frequent after chemotherapy, pelvic radiotherapy, and any GI surgery. These all have treatable causes with effective treatment proving to improve patient wellbeing[28] [29] [30].<br>[18] Andreyev, H.J.N., et al., Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. The Lancet, 2013. **382**(9910): p. 2084-92. | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | [19] Larsen, H.M., et al., Clinical evaluation and treatment of chronic bowel symptoms following cancer in the colon and pelvic organs. Acta Oncol, 2019. **58**(5): p. 776-781.<br>[20] Gupta, A., et al., Outcomes from treating bile acid malabsorption using a multidisciplinary approach. Support Care Cancer, 2015. **23**(10): p. 2881-90.<br><br>Moreover, many patients also experience non-GI issues that should be properly acknowledged, diagnosed and treated optimally where possible [31]. Chronic fatigue and psychological distress are widely recognised as problematic in many patients, however, other problems such as sexual issues[32], urinary dysfunction[33] and the need for intervention to reduce the long-term increased risk of bone fracture after radiotherapy[34] are virtually never addressed systematically.<br>[20] Andreyev, H.J.N., et al., Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut, 2012. **61**: p. 179-192.<br>[21]Andreyev, H.J.N., et al., Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut, 2012. **61**: p. 179-192. | |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | [122] Thyø, A., et al., *Female sexual problems after treatment for colorectal cancer - a population-based study.* Colorectal Dis, 2019. **Epub ahead of print**.<br>[23] Hupkens, B.J.P., et al., *Quality of Life in Rectal Cancer Patients After Chemoradiation: Watch-and-Wait Policy Versus Standard Resection - A Matched-Controlled Study.* Dis Colon Rectum, 2017. **60**(10): p. 1032-40.<br>[24] van den Blink, Q.U., et al., Pharmacological interventions for the prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults. Cochrane Database Syst Rev, 2018. **2018**(Apr 23;4:CD010604).<br><br>These updated draft NICE guidelines fail to address the key issue of long-term toxicity and do not reflect recent progress that has been made in understanding the frequency, causes and management of toxicity. The final guideline must state that assessment of treatment toxicity is one of the main roles of follow-up and should outline the optimal route to identify patients who have toxicity, how best to investigate this toxicity, and what management approaches work. | |
| Bowel Cancer UK | Guideline | 15-16 | 8-21 and 1-2 | Evidence suggests that patients with LARS experience an increased number of daily bowel movements, erratic defecatory patterns, urgency, tenesmus, obstructed defaecation and recurrent faecal leakage. It can often be accurately predicted pre-treatment[35] and while it sometimes | Thank you for this comment. The committee recognises the significance of LARS on the affected people's lives which is why there is a section about it in the guideline. The committee agreed that LARS should be actively monitored and reviewed regardless of the |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | improves by the one year point, it remains problematic in two thirds of patients and can impact severely on long term quality of life[36]. The updated NICE guidelines therefore need to outline:<br><br>• Major LARS is very unlikely to settle spontaneously;<br>• LARS must be actively monitored and reviewed at each follow-up meeting between healthcare professional and patient where the patient has undergone lower anterior resection with or without radiotherapy and/or chemotherapy;<br><br>Systematic approaches to manage the symptoms have been described and are effective[37 38].<br>[25] Battersby, N.J., et al., Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. Gut, 2018. **67**(4): p. 688-696.<br>[26] Bryant, C.L., et al., Anterior resection syndrome. Lancet Oncol, 2012. **13**(9): p. e403-8.<br>[27] Andreyev, H.J.N., et al., Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. The Lancet, 2013. **382**(9910): p. 2084-92. | care setting, and have removed the reference to primary care from their LARS assessment recommendation because this is not just a primary care responsibility. The review did not find any evidence from randomised trials to support specific treatments for LARS however, and this is why the committee agreed to make a research recommendation.<br><br>Battersby 2018 was not included because it did not examine treatments for LARS.<br>Bryant 2012 was not included because it was a narrative review about anterior resection syndrome.<br>Andreyev 2013 was not included because it was not a rectal cancer study and not all patients had low anterior resection.<br>Martelluccci 2016 was not included because it was a narrative article suggesting a treatment algorithm for LARS. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | [28] Martellucci, J., Low Anterior Resection Syndrome: A Treatment Algorithm. Dis Colon Rectum, 2016. **59**(1): p. 79-82 | |
| British Dietetic Association | Guideline | 5 | 19-21 | We recommend including changes in dietary habits post-surgery as a possible side effect. Someone with short bowel or high output stoma would have significant dietary and fluid restrictions, and would therefore require the expertise of a specialist dietitian to support with management. | Thank you for this comment. The committee (including a co-opted dietitian specialised in colorectal cancer) agrees that this would be relevant for someone with short bowel or high output stoma, however, this is not common and was therefore not included in this list. The list is not exhaustive but includes the issues applicable to the greatest proportion of people undergoing surgery for colorectal cancer. |
| British Dietetic Association | Guideline | 6 | 15-16 | We recommend including dietary changes as an example of healthy lifestyles, for example, reduced red or processed meat and higher fibre. | Thank you for this comment. The recommendation already includes a point about giving advice on diet, therefore, this change was not considered necessary. |
| British Division of the International Academy of Pathology | Guideline | 6 and subsequent | 19 onwards | Offering treatment to people with rectal cancer:<br>How is the stage decided? Presumably by imaging? It may be obvious but we think still worth stating. For example, subsequently on page 11 regarding adjuvant therapy the document states: Base the choice on the person's histopathology | Thank you for this comment. The type of staging to the TNM classification has been added to the recommendations, depending on the situation either clinical (cTNM) based on evidence acquired before treatment including imaging, physical examination and endoscopy, or pathological (pTNM) based on histopathology. This has also been clarified in the 'Terms used in this guideline' section. |
| British Division of the International Academy of Pathology | Guideline | 9 | 17 and 19 | Statements as follows might risk ambiguity:<br>*1.3.11 Hospitals performing major resection for rectal cancer should operate on at least 10 patients per year.*<br>*1.3.12 Individual surgeons performing major resection for rectal cancer should operate on at least 5 patients per year.* | Thank you for this comment. The wording of the recommendations has been amended to minimise ambiguity. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | Does it mean 10 or 5 major resections for rectal cancer per year? Or 10 or 5 resections for rectal cancer? Etc. | |
| British Division of the International Academy of Pathology | Guideline | 11 and 30-31 | 19 | Section 1.4.1 (p11) and also on pages 30-31.<br>As there is current variation in RAS testing strategies, to avoid confusion it should be specified if the recommendation to test for RAS mutations includes both K-RAS and N-RAS testing, rather than just K-RAS. | Thank you for this comment. The committee's view was that in diagnostics RAS implies both KRAS and NRAS. However, this has been added for clarity in the 'How the recommendations might affect practice' section. |
| British Division of the International Academy of Pathology | Guideline | 13-14 etc | 24 etc | MDT is "multidisciplinary team", so we suggest "discussion by a MDT" rather than "in a MDT". Or we could say "discussion in a MDT meeting" | Thank you for this comment. The text has been amended as suggested. |
| British Division of the International Academy of Pathology | Guideline | 14 | 15 | *1.5.9 For people with colorectal cancer metastases limited to the peritoneum:*<br>*• offer systemic anti-cancer therapy, and*<br>*• refer to a recognised specialist centre to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).*<br><br>We wonder if this is practical? Are there enough established specialist centres for this recommendation to be implementable? As the document says, there are only 3 centres. Also, is the evidence strong enough? Should the option be discussed with each individual patient, perhaps? | Thank you for this comment. We have amended the recommendation to say the referral should be discussed within the multidisciplinary team. The criteria for CRS/HIPEC is set out in the NHSE commissioning document and the MDTs should discuss which patients might be eligible for the procedure before referring. The committee recognises that the number of referrals to the specialist centres might increase, which in turn may increase the workload at the specialist centre. However, the majority of the people referred would not be eligible for CRS and HIPEC. The recommendation aims to standardise care and provide an opportunity for people to get the best possible assessment and treatment. If the demand exceeds the capacity in the specialist centres, there may be a need to either increase the capacity in the existing centres |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | or develop new specialist centres in the future. The evidence around CRS and HIPEC is not strong enough to recommend offering it to everyone with metastatic colorectal cancer limited to the peritoneum, however, the decision about who might benefit from these treatments should be made by the experts in these treatments. All treatment options should be discussed with the individuals, as recommendation 1.2.2 states. |
| British Division of the International Academy of Pathology | Guideline | 15 | 3 | *1.6.1 For people who have had potentially curative surgical treatment for non-metastatic colorectal cancer, offer follow-up for detection of local recurrence and distant metastases for the first 3 years that includes carcinoembryonic antigen (CEA) and CT.*<br><br>We would add "serum" before CEA. We would clarify CT (i.e. CT of where?). | Thank you for this comment. The recommendation has been amended as suggested. |
| British Division of the International Academy of Pathology | Committee membership document | General | General | Dr Salto-Tellez is Manuel not Manual. | Thank you, the typo has been corrected. |
| British Geriatrics Society | Guideline | General | General | Although we are aware that there is limited evidence specifically concerning the treatment of bowel cancer in older patients, 44% of patients diagnosed with bowel cancer were over the age of 75 years (CRUK https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One accessed | Thank you for this comment. The committee recognises that a significant proportion of the colorectal cancer patient population is older people. The committee however considered that age is not as important as performance status or comorbidities as a determinant of care. The committee has, throughout developing the guideline, taken performance status |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | 23/8/2019). Older adults, especially those over 80 years, have been shown to have reduced rates of surgery, chemotherapy and radiotherapy as well as worse outcomes (NCIN older people with cancer http://www.ncin.org.uk/publications/older_people_and_cancer).<br><br>This may relate to reduced fitness or frailty in older patients but there is significant variation in treatment delivered both within the UK and internationally. There is increasing support for inclusion of geriatric assessment in the management of older people with cancer, including recent ASCO guidelines https://ascopubs.org/doi/10.1200/JCO.2018.78.8687.<br><br>There is still a definite need to strengthen the evidence base in the assessment and management of older patients, especially those who are frail, in particular and therefore it is difficult to suggest specific recommendations for this patient group. However the guidelines could potentially highlight that a significant minority of patients will not be suitable for the treatment as outlined in the guidance and that this is an area of unmet need.<br><br>Given the highest prevalence of colorectal cancer is in patients aged over 70 years old, we are surprised to note that no reference is made to the older patient throughout the document. | and comorbidities, and age where relevant, into consideration and sought for evidence based on these attributes. Unfortunately, no evidence stratified by age, performance status or comorbidity status was identified and no recommendations were made based on these characteristics. However, clinicians are expected to use their clinical judgement when discussing treatment options with the person with colorectal cancer. As recommendation 1.2.1 states, the discussions should be tailored according to individuals needs and circumstances. Furthermore, recommendation 1.3.14 on duration of adjuvant chemotherapy specifically states to take into consideration the person's performance status, comorbidities and age. Pre-operative risk assessment and enhanced recovery protocols were not in the scope of this guideline update. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | While age is no longer an arbitrary measure of health, co morbidity or multimorbidity that increases treatment / surgical risk is associated with ageing. While the use of enhanced pathways of care, such as ERAS, are mentioned, no comment is made on how patients are assessed prior to treatment (surgery, radiotherapy or chemotherapy) and how early this early intervention can help direct care.<br>We are presuming this guideline will link to the NICE preoperative testing, multimorbidity and perioperative care guidelines. These links should be given explicitly. | |
| British Geriatrics Society | Guideline | 1 | 1 | Who is it for? Why not useful for primary / community care settings? It would also be useful for GPs supporting those undergoing secondary cancer care. | Thank you for this comment. The committee agrees that this guideline is also for healthcare professionals in primary care and have changed the text in the guideline. |
| British Geriatrics Society | Guideline | 4 | 7 | Would like to see the decision making / information giving section highlight the older patient. While it directs to the 'decision making and mental capacity' guidance, it would be worthwhile reinforcing that many of the new colorectal cancer diagnosis are in our older population. These individuals come with a burden of disease that may limit ability to assimilate information provided. In these cases information delivery must be tailored to the individual. | Thank you for this comment. The committee recognises that a significant proportion of the colorectal cancer patient population is older people. The committee however considered that age is not as important as performance status or comorbidities in determining how information should be shared, what should be discussed and what treatment options are available to the individual. The committee has, throughout developing the guideline, taken performance status and comorbidities, and age where relevant, into consideration and sought for evidence based on these attributes. Unfortunately, no evidence stratified by age, performance status or comorbidity status was identified, thus no recommendations were made based on these characteristics. The committee |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | emphasised that the way information is shared should be tailored to the individual's needs and circumstances, see recommendation 1.2.1. |
| British Geriatrics Society | Guideline | 5 | 1 | No mention of the importance in engagement with the MDT before appropriate patient specific treatment plan decided. This might be a standard or enhanced assessment process, but should aim to assess for risk and help inform shared decision making process. Possibly link with NICE perioperative guideline. | Thank you for this comment. This was not in the scope of this guideline update, however, colorectal MDTs generally already exist. The NICE guideline on perioperative care is currently being developed. |
| British Geriatrics Society | Guideline | 6 | 1 | In the colorectal patient group cognitive decline is not only seen with chemotherapy. After surgery, patients with mild cognitive impairment, dementia or mental illness may see an acceleration in their cognitive decline which in turn impacts on their functional state (ability to care for self / stoma). Suggestion that chemotherapy related cognitive decline be changed to include detail about older patients presenting with specific conditions like cognitive impairment, dementia and mental illness. | Thank you for this comment. The committee recognises that surgery may have an additional impact on a person with mild cognitive impairment, dementia or mental illness. The committee thinks it is already covered by the text "mental and emotional changes" whereas chemotherapy-related cognitive decline is a specific potential side-effect from chemotherapy. The recommendations also state that the information shared should be tailored to individual needs and circumstances, see recommendation 1.2.1. |
| British Society of Gastroenterology | Guideline | General | General | Section on LARS<br>There are a number of issues here. LARS tool was published in 2012 and validated in English in 2015. The term 'LARS' itself has only been relatively common parlance since about 2012 therefore I think there are real issues with the literature search which looked at 'management of low anterior resection syndrome' as functional complications (and their treatment) have been described a lot longer than they have been called 'LARS'. For example paper by Laforest A was excluded as said | Thank you for this comment. The literature search was not restricted to studies mentioning LARS, the search strategy also included terms to pick up studies about post-operative complications that did not mention LARS.<br><br>The Laforest study was not included because it was a prophylactic treatment study and the committee prioritised treatment for people with established LARS (even if not called LARS in the publication) as the |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | 'population not relevant' yet this paper looks at pre-emptive management of functional consequences. Similarly it is unclear why probiotic therapy (study by Stephens J) is not an 'intervention of interest'?<br>I think to suggest that LARS is managed in primary care for 6 months before referral to secondary care needs reconsidering - diagnosis of LARS is often difficult to make and diarrhoea post anterior resection can be due to anastomotic stricture, Bile acid malabsorption (particularly post chemorad patients) and one would not expect GP to recognise or treat that. In addition there is usually another 12-18 week wait for secondary care opa meaning that some patients with LARS are potentially waiting for 10 months before they access specialist care. | more important clinical issue. Stephens was not included because probiotic therapy was not prioritised as an intervention of interest in the review protocol.<br><br>The reference to primary care has now been removed from the recommendation about assessment of LARS. The committee acknowledge that LARS should be assessed regardless of the care setting when appropriate.<br><br>The reference to 6 months' duration of treatment in primary care has now been removed from the rationale section. The committee agreed that this cut-off was somewhat arbitrary and that timing should be based on individual circumstances, severity of symptoms and according to clinical judgement. |
| British Society of Gastroenterology | Guideline | General | General | Rectal cancer section<br>I had a look at the rectal cancer bit and have no particular comments;<br>the only issue that may be relevant is that they suggest all patients with T1 - T2 with nodal disease and T3 tumours should be offered RTh . they do not comment on the effect of a clear CRM and good surgery. | Thank you for this comment. The aim of the recommendation about preoperative radiotherapy is to standardise practice as there is currently variation in practice, although considerations for individual patients should be taken into account. The committee recognises that clear CRM preoperatively might be an indication to go straight to surgery. However, the randomised trials addressing the issue of preoperative radiotherapy did not prospectively study the impact of clear margins and the best available evidence considered by the committee indicated an improvement in local recurrence rates and survival in patients who had radiotherapy prior to surgery. Hence |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | the committee made the recommendation for preoperative treatment for this group of people. |
| British Society of Gastroenterology | Guideline | General | General | Rectal cancer section<br>Comments<br>1. If histology after transanal early rectal cancer suggests R1, then the subsequent TME maybe more difficult.<br>2. No mention of ELAP has been made?<br>3. No mention of Papillon therapy (could just be within radiotherapy) | Thank you for this comment.<br>1. The committee recognises that in cases where full thickness excision has been done this may be the case.<br>2. The committee recognises that extralevator abdominoperineal excision may be used as a type of abdominoperineal resection in some cases but did not consider it separately.<br>3. Papillon therapy was considered as one of the interventions of interest in the review on preoperative therapy for rectal cancer (see evidence report C2, instead of "Papillon therapy" the term "internal contact radiotherapy" was used) as well as in the review on treatment for early rectal cancer (see Evidence report C1) although no evidence was identified that fit the latter review's protocol. |
| British Society of Gastrointestinal and Abdominal Radiology | Guideline | General | General | What about new imaging and staging for colorectal cancer? Streamline C: Whole body MRI vs standard imaging for metastatic disease in newly diagnosed colorectal cancer: similar accuracy with reduced tests required, staging time and costs.<br><br>https://www.thelancet.com/journals/langas/article/PIIS2468-1253(19)30056-1/fulltext | Thank you for this comment. Diagnosis and staging were not included in the scope of this guideline update. Your comment will be passed to the NICE surveillance team which monitors guidelines to ensure that they are up to date. |
| British Society of | Guideline | 5 | 17 | I have a number of comments (and concerns) about some aspects of this Guideline: | Thank you for this comment. The committee agrees with this and have added urinary symptoms to the recommendation. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Gastroenterology | | | | Section 1.2.5 I would have thought urinary symptoms should be mentioned as well. | |
| Coloplast Limited | Guideline | 15 | 20 | In section 1.6.4, the Guideline document provides some information about first-line treatment of LARS in primary care, and the recommendation to refer to secondary care if treatment is not successful. We fully agree with this recommendation, and we would think it could be extended to provide some guidance to secondary care professionals once the patient is referred to them. The guideline would enormously benefit from including recommendation for management of LARS once patients arrive at secondary care. The guideline draft states in its very first page, in the section "Who is this guidance for?: Health professionals working in secondary care." Therefore, more guidance on treatments and approaches typically used in secondary care should be included, since the guideline aims to target that group of health professionals. | Thank you for this comment. Unfortunately, no randomised controlled trials on treatment for LARS were identified that that were relevant for the review question specified in the review protocol. The committee was therefore unable to make detailed recommendations but agreed that it was appropriate (based on their expertise) to recommend that conservative treatments be offered in primary care. |
| Coloplast Limited | Guideline | 37 | 22 | The Guideline states that "No comparative evidence on different treatments for LARS was available". This stakeholder wants to bring to the attention of the Committee that, shortly after the literature and evidence search was performed by NICE, a comparative study of Transanal Irrigation (TAI) versus conservative bowel care was published in the peer-reviewed British Journal of Surgery (Rosen et al, BJS Open 2019). Since the study is a randomized study comparing two types of interventions for the management of LARS, this study shall be included, and its results considered, prior to publication of the final guideline. | Thank you for this comment. The Rosen 2019 RCT was considered for inclusion in the review however the committee agreed that it would not be appropriate to include this study because it did not fit the inclusion criteria set in the review protocol for the following reasons: the intervention was prophylactic for people who had undergone surgery and the study population did not all have LARS. The study has been added to the excluded studies reference list to reflect that it was considered for inclusion. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Coloplast Limited | Guideline | 38 | 1 | The Guideline states "Because of the lack of evidence on the effectiveness of treatments for LARS, a research recommendation was made to compare sacral nerve stimulation and transanal irrigation in people with LARS for whom conservative treatments have not worked." This stakeholder agrees to the recommendation of researching on a comparison of Transanal Irrigation and sacral nerve modulation in people with LARS. However, evidence on the role of Transanal Irrigation in the management of LARS already exists, which suggests the treatment should have a recommendation for secondary care in patients that have failed conservative treatments, and not only a research recommendation. Besides the above-mentioned randomized clinical trial, at least 2 other studies have shown the efficacy of transanal irrigation in the improvement of LARS symptoms (Rosen et al, 2011 and Martellucci et al, 2018). Additionally, NICE produced in February 2018 a medical technology guidance (MTG 36) for the Peristeen device (a transanal irrigation device) where its recommendation was that "The case for adopting Peristeen for transanal irrigation in people with bowel dysfunction is supported by the evidence". Reference. NICE MTG36. Published February 23, 2018.In this MTG guidance, studies of the product in people with LARS were part of the evaluated body of evidence. | Thank you for this comment. The Rosen 2019 RCT was considered for inclusion in the review however the committee agreed that it would not be appropriate to include this study because it did not fit the inclusion criteria set in the review protocol for the following reasons: the intervention was prophylactic for people who had undergone surgery and the study population did not all have LARS. The study has been added to the excluded studies reference list to reflect that it was considered for inclusion.<br><br>The Rosen 2011 and Martellucci 2016 studies were identified in our literature searches but were excluded due to lack of a comparison group. None of the studies included in the NICE MTG36 met the criteria for inclusion in our review because they were not randomised controlled trials on interventions for LARS. |
| Coloplast Limited | Evidence Review E2 | General | General | The literature search was last performed 12/02/2019. This stakeholder would encourage the committee to produce a second search (with identical search criteria) prior to the next steps in the development of the guideline, since we | Thank you for this comment. The literature searches were done according to the timings laid out in Developing NICE guidelines: the manual. These have not been rerun following consultation, but the |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | are aware of at least 1 study that would meet the criteria for inclusion and that was published just 6 days after the date of the last search by NICE, and hence has not been captured by it. | committee considered the Rosen 2019 RCT for inclusion in the review. The study was screened against the inclusion criteria in the review protocol and it was not included for the following reasons: the intervention was prophylactic for people who had undergone surgery and the study population did not all have LARS. The study has been added to the excluded studies reference list to reflect that it was considered for inclusion. |
| Coloplast Limited | Evidence Review E2 | 10 | 1 | At that time, the literature search did not find any comparative study between 2 or more interventions to manage LARS. However, a few days after the date of the literature search, a randomized controlled trial comparing transanal irrigation and conservative measures was published in the journal BJS Open (British Journal of Surgery) by Rosen HR et al. Reference: Rosen HR, Kneist W, Fürst A et al. *Randomized clinical trial of prophylactic transanal irrigation versus supportive therapy to prevent symptoms of low anterior resection syndrome after rectal resection*. BJS Open, accepted 18 February 2019. This stakeholder encourages the Committee to consider the inclusion of this study in its Evidence Review, since we are concerned that omitting it would pose an insufficient representation of the body of evidence available at the date the guideline would be final and published. | Thank you for this comment. The Rosen 2019 RCT was considered for inclusion in the review. The study was screened against the inclusion criteria in the review protocol and it was not included for the following reasons: the intervention was prophylactic for people who had undergone surgery and the study population did not all have LARS. The study has been added to the excluded studies reference list to reflect that it was considered for inclusion. |
| Coloplast Limited | Evidence Review E2 | 10 | 13-18 | The Evidence Review document states that randomized trials are needed in order to confirm the effectiveness of transanal irrigation in the management of LARS. As indicated in the comment above, a randomized trial | Thank you for this comment. The Rosen 2019 RCT was considered for inclusion in the review. The study was screened against the inclusion criteria in the review protocol and it was not included for the |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | involving the Peristeen Transanal Irrigation device was published just 6 days after the date of the literature search. (Rosen HR, Kneist W, Fürst A et al. *Randomized clinical trial of prophylactic transanal irrigation versus supportive therapy to prevent symptoms of low anterior resection syndrome after rectal resection*. BJS Open, accepted 18 February 2019). The data from this study shows that TAI (Transanal Irrigation) may offer superior clinical outcomes in managing and preventing LARS, when compared to best-supportive therapy such as dietary modifications, biofeedback or anti-diarrheal agents Hence, this stakeholder kindly suggests to the Committee that this study in order to produce the necessary recommendations, and that the sentences regarding the lack of randomized studies for TAI be amended to reflect the existence of at least 1 randomized trial. | following reasons: the intervention was prophylactic for people who had undergone surgery and the study population did not all have LARS. The study has been added to the excluded studies reference list to reflect that it was considered for inclusion. |
| Intuitive | Guideline | General | General | The NICE recommendations for people with rectal cancer states that "there seemed to be no difference in effectiveness between laparoscopic and robotic techniques." A review of the published literature suggests a number of clinical benefits of robotic assisted surgery. These include<br>- A lower rate of conversions to open surgery (see Comment 2, publications include: )<br>- A reduction in length of stay (see Comment 3)<br>- Reduction in positive circumferential resection margins (see Comment 4)<br>- Reduction in urinary dysfunction (see Comment 5)<br>- Improved sexual function (see Comment 6) | Thank you for this comment. Please see replies to your above comments - the evidence in favour of robotic surgery relies on non-randomised studies. When limited to randomised trials there does not appear to be a clinically important difference. The evidence review was based on randomised trials where available and only included evidence from non-randomised studies for outcomes where there was no RCT evidence. |

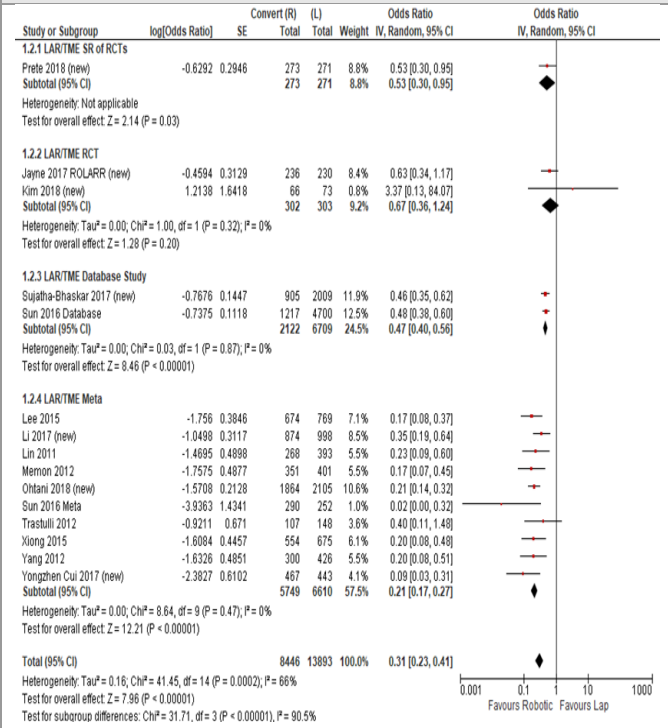
**Colorectal cancer**

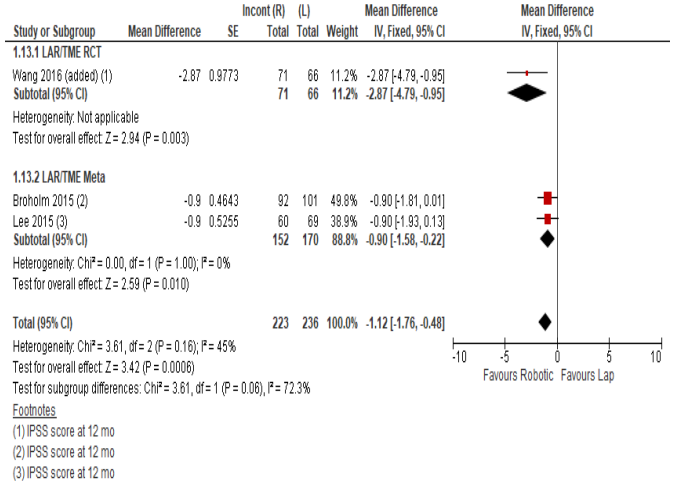
**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | - Improved recovery of bowel function (see Comment 7)<br><br>We would note that in November 2018, the Scottish Health Technology Group advice statement and evidence statement comparing robotic assisted surgery with lap surgery for rectal cancer, concluding that robotic-assisted surgery is beneficial for certain patient populations.<br>"*Robot-assisted surgery should be considered for patients w obese (BMI≥30), and/or have a tumour located in the mid-to the form of reduced risk of conversion to open surgery in the evidence is currently lacking. Expert opinion indicates that c these patients*." | |
| Intuitive | Evidence Review C3 | General | General | As noted in the NICE guideline evidence reviews the ROLARR study found no significance difference in conversion rate between lap and robotic-assisted surgery for colon cancer. That said it is important to note that this study involved experienced lap surgeons compared with less experienced robotic counterparts. This topic was addressed in a publication by Corrigan, et al 2018. | Thank you for this comment. The Corrigan 2018 study was a secondary analysis of the ROLARR trial, but looking at the non-randomised comparison of more versus less experienced surgeons. Surgeon experience was not prioritised as a subgroup analysis by the committee. |
| Intuitive | Evidence review C3 | General | General | The literature demonstrates a reduced conversion rate for robotic-assisted surgery for rectal cancer procedures compared with lap.<br><br>The evidence highlights that there is a 69% greater likelihood of a conversion to open surgery after lap rectal resection than robotic rectal resection ($p < 0.00001$).<br><br>Figure: Forest Plot of Conversion Rate (Robotic vs. LAP) | Thank you for this comment. Although you note a statistically significant difference in the supplied forest plot, this is only for the subgroup of non-randomised studies. The evidence review in this guideline was limited to the randomised trials (Kim 2018 and ROLARR) which did not show a difference in conversion rates. Conversion to open surgery was not included as an outcome in the evidence review. |

## Colorectal cancer

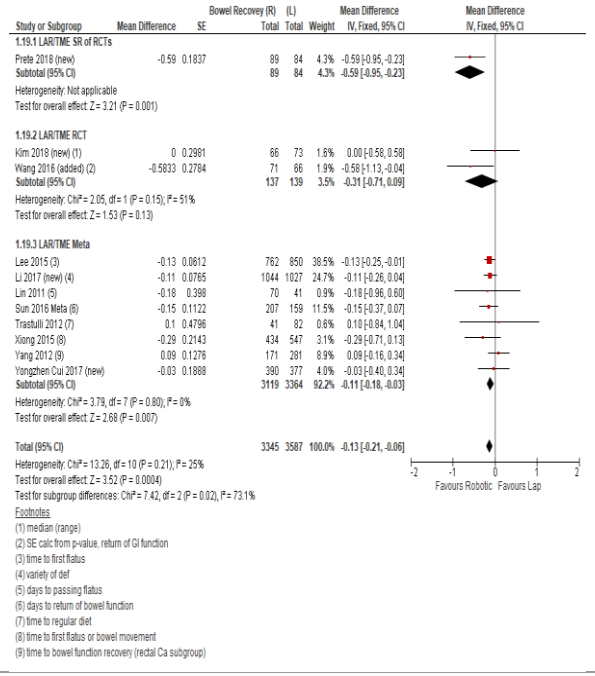
### Consultation on draft guideline - Stakeholder comments table
### 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | |  | |
| Intuitive | Evidence review C3 | General | General | The literature shows an improvement of urinary function for robotic-assisted surgery as compared to lap. | Thank you for this comment. The attached list of studies was screened against the review protocol. While most were not included in our evidence because they were not randomised, two of the suggested |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | At 12 months, mean IPSS score was lower for Robotic than LAP with 1.12 points, indicating a better urinary function within the Robotic cohort (P=0.0006).<br><br>Figure: Forest Plot of Urinary Dysfunction at 12 months LAR/TME (Robotic vs. LAP)<br>  <br><br><br>In the studies included in the forest plots the urinary dysfunction was measured using the International Prostate Symptom Score (IPSS) score, where low scores indicate mildly symptomatic patients and high scores signal highly symptomatic patients. | studies have been added to the evidence review because they were randomised trials (Wang 2017 and Baik 2008). These trials were not picked up by our literature search.<br><br>These did not change the conclusions of the review however, which was no clinically important difference in urinary symptoms between robotic and laparoscopic surgery. |

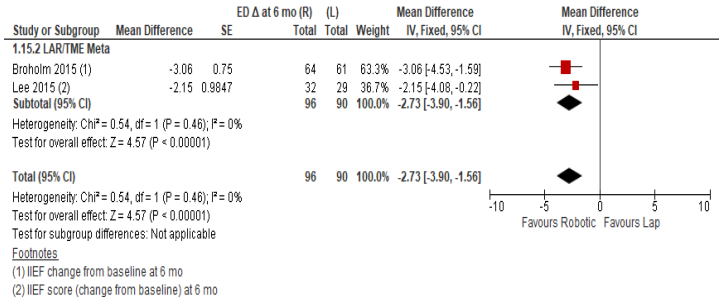
**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Intuitive | Evidence review C3 | General | General | The literature shows faster bowel function recovery for robotic assisted surgery versus lap (P=0.0004).<br><br><u>Figure: Forest Plot of Recovery of Bowel Function (Robotic vs. LAP) (time to first flatus, time to first bowel movement)</u><br>  <br> | Thank you for this comment. Recovery of bowel function was not prioritised as an outcome in the evidence review. However the RCTs in the attached forest plot (Kim 2018 & Wang 2016) do not show a statistically significant difference between robotic and laparoscopic surgery. |

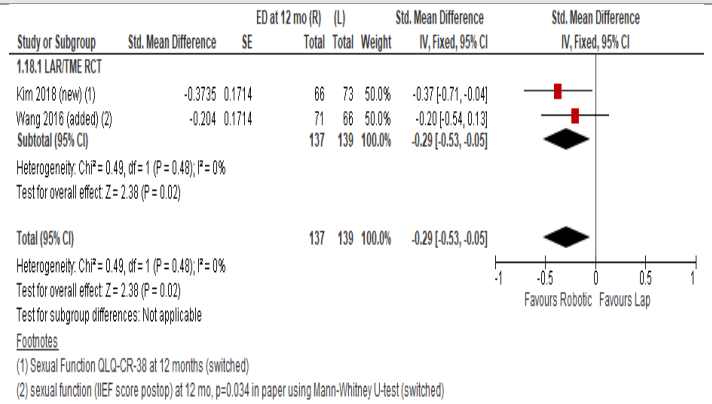
**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Intuitive | Evidence Review C3 | 24 | 21 - 39 | The literature shows an improvement in sexual function for robotic-assisted surgery versus lap at 6-months and 12-months.<br>At 6 months, the mean IIEF score was lower for Robotic cohort than LAP with 2.73 points, indicating lower incidence of sexual dysfunction among the Robotic group ( P<0.00001). At 12 months, Robotic cohort is significantly superior to LAP with a mean difference of -0.29 (P=0.02).<br><br>Figure: Forest Plot of Sexual Dysfunction at 6 months (Robotic vs. LAP)<br>  <br><br><br>Figure: Forest Plot of Sexual Dysfunction at 12 months (Robotic vs. LAP) | Thank you for this comment. The attached list of studies was screened against the review protocol. While most were not included in the review because they were not randomised, two of the suggested studies have been added to because they were randomised trials (Wang 2017 and Baik 2008). These trials were not picked up by our literature search.<br><br>These did not change the conclusions of the review however, which was no clinically important difference in male sexual dysfunction between robotic and laparoscopic surgery. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | |  <br><br>In the studies included in the forest plots the urinary dysfunction was measured using the International Index of Erectile Function (IIEF) score, where low scores indicate no or mild erectile dysfunction and high scores indicate severe erectile dysfunction. Also, QLQ-CR29 quality of life questionnaire for colorectal cancer was used to assess the sexual function. | |
| Intuitive | Evidence Review C3 | 25 | 4 – 10 | The evidence in the forest plot above demonstrates that there is a significantly lower rate of positive CRM for robotic surgery in comparison to open rectal resection (p <0.0001).<br><br>The NICE draft guideline do not appear to include in the studies below. | Thank you for this comment. Although you note a statistically significant difference in the supplied forest plot, this is only for the subgroup of non-randomised studies. The evidence review was limited to the |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
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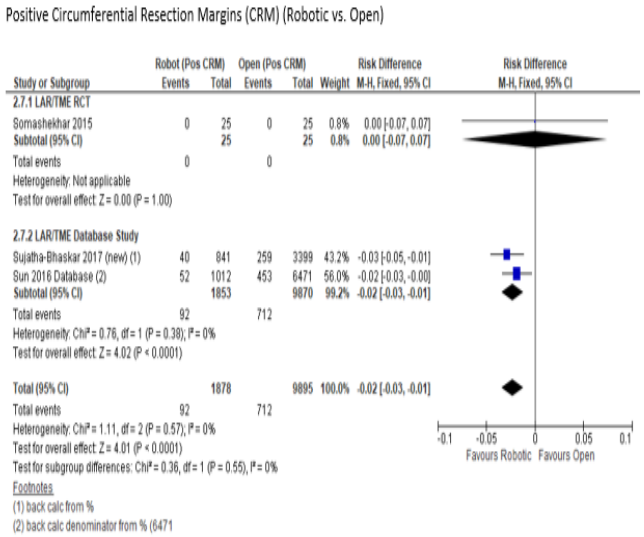
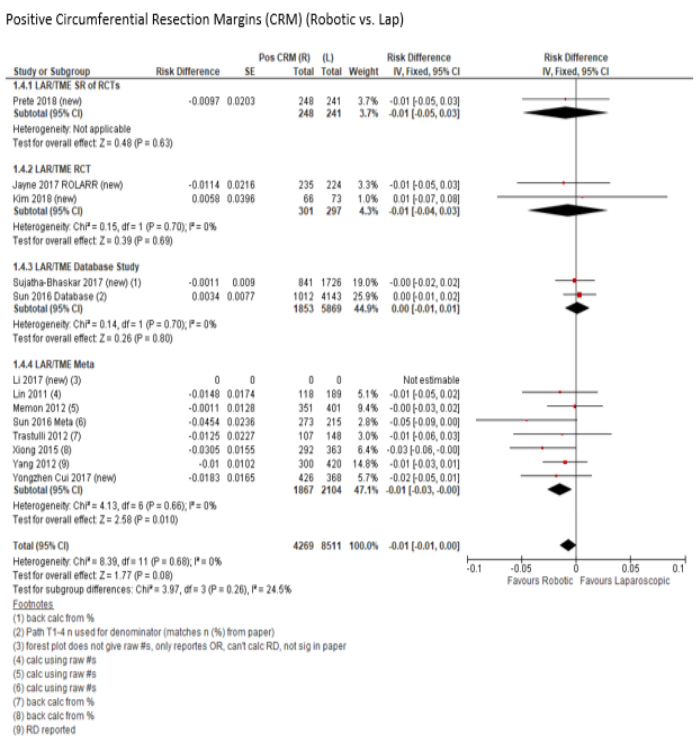
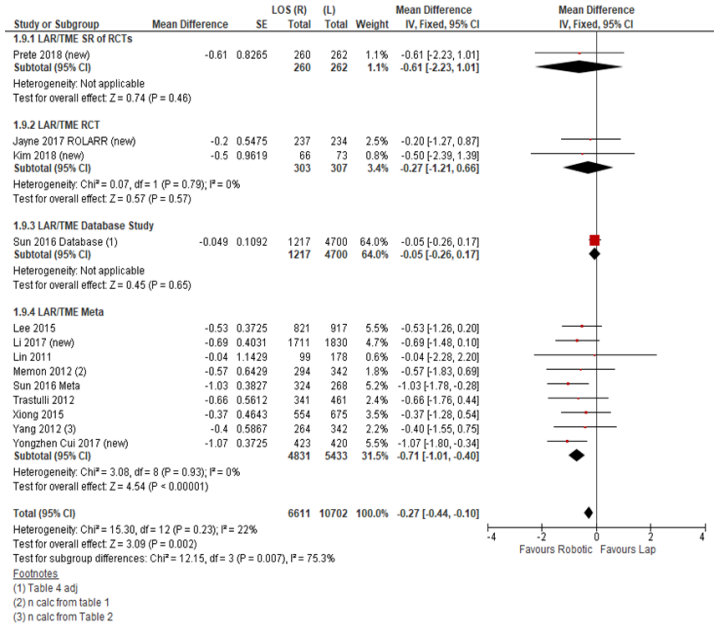
| | | | |  <br><br>Comparable CRM have been found between robotic and lap rectal resection (p = 0.08). Whilst we reached the conclusion, we wish to highlight that the studies below have not been mentioned in the draft NICE clinical guidelines. | randomised trials (ROLARR and Kim 2017) and did not show a difference in positive CRMs. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | |  | |
| Intuitive | Evidence Review C | 25 | 14 - 17 | The forest plot below shows that there is a statistically significant reduction in length of stay between robotic and lap rectal resection p = 0.002. | Thank you for this comment. Although you note the statistically significant difference in the supplied forest plot, this is only for the subgroup of non-randomised |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | Figure: Forest Plot of Length of Hospital Stay (Robotic vs. LAP)<br>  <br> | studies. The evidence review was limited to the randomised trials (Kim 2018 and ROLARR). These are also included as a subgroup in the supplied forest plot and show the same (non-significant) pooled result as in the evidence review for this guideline. |
| Johnson & Johnson | Guideline | General | General | Johnson & Johnson Medical is aligned to the recommendations within the draft colorectal clinical | Thank you for this comment and the support for this guideline. |

## Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Medical Limited | | | | guideline, particularly around patient information, ERAS and follow-up. | |
| Johnson & Johnson Medical Limited | Guideline | General | General | The introduction of minimum surgical volumes for cancer surgeries is appropriate and aligned to policy initiatives across other specialties to reduce variation in clinical practice and outcomes. | Thank you for this comment and the support for this guideline. |
| Johnson & Johnson Medical Limited | Guideline | General | General | The recommendations around robotic surgery could be limiting to new innovation at this time. Johnson & Johnson Medical is aligned to the statement by NICE that 'the evidence is evolving as robotic technology develops rapidly'. However, whilst outcomes after surgery should be audited, recommending robotic surgery 'only within established programmes' could be restrictive to new innovation. | Thank you for this comment. The committee makes recommendations on the basis of evidence reviews on clinical and cost effectiveness data. The evidence review did not find robotic surgery to be cost-effective. However, the committee recognised that evidence is evolving alongside the technology and so they recommended the use of robotic surgery only within centres with established programmes that have appropriately audited outcomes. |
| NCEL Cancer Alliance | Guideline | General | General | We were surprised to see nothing on the Enhanced Recovery Programme as part of perioperative patient management. It would have also been interesting to see something on preoperative (or indeed pre chemotherapy) optimisation and cardiopulmonary exercise testing (CPEX) and pre-treatment risk assessment. The introduction of this type of assessment has helped reduce the mortality rates for patients according to my colleagues who run the Bowel Cancer Audit. | Thank you for this comment. Enhanced recovery programmes, perioperative patient management, pre-treatment optimisation, cardiopulmonary exercise testing or pre-treatment risk assessment were not in the scope of this guideline update and evidence for these were therefore not reviewed. However, the guideline states that if recovery protocols are being used, that it should be explained what these involve and their value in improving recovery after surgery. NICE is currently developing a guideline on perioperative care for adults which covers some of these topics. While the committee recognises the potential importance of pre-treatment risk assessment, |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | we do not think it is correct to state that the reason for a reduction in mortality rates is due to this. |
| NCEL Cancer Alliance | Guideline | 8 | 6-7 | This is seen my most colleagues as over treatment resulting in complications for a significant proportion of patients. | Thank you for this comment. The best available evidence was used to inform these recommendations. The committee recognises that there is a chance that some people might be over treated. However, the pooled evidence from several RCTs shows better survival and lower local recurrence for those receiving preoperative radiotherapy or chemoradiotherapy. As with any treatment decision, individualised consideration and clinical judgment should be exercised. The committee thinks that the risks and benefits of the treatment should be discussed with patients and an individualised treatment plan agreed taking all relevant factors, including the patient's wishes, into account. Recommendation 1.2.2 says to "Give people information on all treatment options for colorectal cancer available to them, including…. the potential benefits, risks, side effects and implications of treatments". |
| NCEL Cancer Alliance | Guideline | 8 | 9-11 | It is not clear that deferral is for patients who have had a complete pathological and radiological response to neoadjuvant chemoradiotherapy. | Thank you for this comment. The recommendation has been amended to make it clearer. However, this would be patients with complete clinical and radiological response (not pathological) to neoadjuvant therapy. |
| NCEL Cancer Alliance | Guideline | 9 | 2-3 | There have been 2 trials suggesting non-inferiority of open surgery for rectal cancer, so the guidance should be more nuanced. NICE 2006 technology appraisal is very old. | Thank you for this comment. The evidence review comparing laparoscopic and open surgery for rectal cancer details the results for the available randomised controlled trials (see evidence review C3). The results of the pooled analysis in the clinical evidence review |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | and the bespoke economic analysis generally favour laparoscopic surgery over open surgery. However, the committee recognised that in some cases open surgery would be the preferred technique when clinically indicated, for example for locally advanced tumours, or when the person has had multiple previous abdominal operations or previous pelvic surgery. |
| NCEL Cancer Alliance | Guideline | 9 | 17-18 | 'surgeries' in English means more than one GP practice. The word we use is operation or procedures | Thank you for this comment. We have changed the wording as suggested. |
| NCEL Cancer Alliance | Guideline | 10 | 3-4 | The guidance should be more positive in support of laparoscopic surgery for colonic cancer and differentiate from the advice for rectal cancer. | Thank you for this comment. This guideline update did not review evidence on surgical technique for colon cancer but refers to the NICE technology appraisal on laparoscopic surgery for colorectal cancer. However, evidence on different surgical techniques for rectal cancer was reviewed because the committee recognises the importance of differentiating between colon and rectal cancer surgery and rectal cancer surgery is generally more challenging to perform. |
| NCEL Cancer Alliance | Guideline | 11 | 10-11 | Stenting is preferable to surgery for palliative intent (the alternatives would be a major operation and stoma or the patient dying in bowel obstruction) There is no standardisation of the provision of services to provide colonic stents in the elective or emergency situation. The type of narrative about ESD (in Information needs to 1.3.1) would be useful here. | Thank you for this comment. The committee recommends stenting for people who are to be treated with palliative intent. However, for people for whom curative treatment is suitable, the committee recommends either stenting or emergency surgery because evidence on the benefits of stenting is not convincing enough to only recommend stenting. The committee did not consider this to be a patient preference sensitive decision point because the decision is not only based on the patient's preference |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | but also on clinical and practical factors, including availability of surgical or stenting expertise at an emergency situation, therefore, a table such as the one for recommendation 1.3.1 was not created. |
| NCRI-ACP-RCP-RCR | Guideline | General | General | Our experts note that while we welcome this review and understand that NICE GDG's are constrained by the output from the scoping exercise, which defines the questions to be addressed by the GDG, we have some specific concerns that some of the recommendations are contrary to best practice and most recent published evidence. We appreciate that these questions are set by consultation prior to establishing the GDG, and are absolute and that the GDG is not permitted to stray from 'the scope' however we do strongly believe that the SACT recommendations must be in line with published data.<br><br>Our experts feel there should be clear recommendations to participate in clinical trials wherever possible. | Thank you for this comment. As the stakeholder points out, the committee worked on topics that were within the scope of the guideline. There are many other issues pertinent to colorectal cancer that are not covered by this guideline as they were not prioritised during scoping.<br><br>Throughout the development of the guideline, the best available evidence was sought and used to inform the recommendations. It is not clear which recommendations about SACT the stakeholder is referring to.<br><br>Specific references to clinical trials were made where the committee considered this to be important, for example, when some patients refuse the gold standard treatment option but evidence is lacking on an alternative pathway (e.g. deferral of surgery). |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.1 | Aspirin dose – The guidance has commented that the evidence from CAPP2 was for a dose of 600mg PO OD, although lower doses (they only mention 150 and 300 mg) may be better tolerated. We feel it is important to reframe the wording of the evidence based document to make it clear that the best evidence is for 600 mg and that in appropriate patients this should be the selected first dose; | Thank you for this comment. The evidence base informing this recommendation came from the CAPP2 trial as well as an observational study. The CAPP2 trial used a high dose of 600mg of aspirin per day and in the per-protocol analysis showed a beneficial effect. However, there is uncertainty around the adverse effects from such a dose as no long-term adverse |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | whilst reducing the dose to 300 or 150 mg may be required in terms of toxicity. | events data was collected. The observational study on the other hand had smaller doses (varying self-reported doses). A higher dose could potentially increase the risk of adverse effects, whereas a smaller dose might not be effective in prevention of colorectal cancer. Until the CaPP3 trial results are published, the committee was not able to recommend a dose for this indication but discussed the doses commonly used in current practice. The rationale section has been amended to clarify the doses used in the studies. |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.3.1.3 | Neoadjuvant chemo for cT4N0M0 and cTxN1-2M0 colon adenoca is now included as an option based mainly on FOXTROT data although this trial has not yet been through peer-reviewed publication. This fact should be mentioned in the evidence review. | Thank you for this comment. The rationale for this recommendation has now been amended to make it clear that the results from FOxTROT used to inform the guideline were non-peer-reviewed. This has also been clarified in the evidence report. |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.3.1.4 | 3 months CAPOX or 3-6 months FOLFOX is specified for the duration of adjuvant treatment. The proposed guidance does not include the option of 6 months of adjuvant CAPOX for high risk (pT4N1 or pTxN2) stage III colon cancer despite better efficacy for this than 3 months CAPOX. We see this as a major issue and strongly believe that this wording needs to be revised to include 6 months CAPOX as an option for appropriate patients. We would suggest "the results of the SCOT study and IDEA collaboration suggest for high risk Dukes C (pT4N1 or pTxN2) there is a small additional gain for 6 vs 3 months of CAPOX, and a larger different for 6 vs. 3 months FOLFOX but in both cases this comes with additional toxicity, in particular neuropathy, and therefore the decision of duration of | Thank you for this comment. Whilst 6-month CAPOX showed a longer disease-free survival compared to 3 month in patients with high-risk stage III disease (T4 and/or N2) the difference was small and not clinically significant (hazard ratio=1.02 [0.89,1.17]). Given the lower overall quality adjusted life years (as a result of being on chemotherapy longer) and large increase in costs the committee did not recommend a longer course of CAPOX for this high-risk group. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | treatment will be based on a discussion with patients and their families and carers". | |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.4 | There is no mention has been made of either DPYD genotyping or uracil phenotyping in the section on molecular testing. This should definitely be included as a very important patient safety issue. | Thank you for this comment. DPYD testing was not in the scope of this guideline update. The committee acknowledges the importance of this issue, which applies to not only colorectal cancer but also other cancers such as upper gastrointestinal cancers, breast cancer and neck cancers. |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.5.2 | There is no mention in this section of complexity of SACT in mCRC including duration of treatment, use of treatment breaks, rechallenge if previously stopped regimen without PD. It just refers back to the individual NICE technology appraisals for the drugs as monotherapy or combination. It does not mention Raltitrexed here or in the adjuvant section either (We are unclear why raltitrexed has been removed as it is used and was previously included, in particular for patients with cardiac toxicity). | Thank you for this comment. SACT for metastatic colorectal cancer, including raltitrexed, was outside the scope of this guideline update. The use of raltitrexed for this indication is embedded in clinical practice and the BNF is clear about its indicated use, therefore, a NICE guidance on this was not considered necessary. |
| NCRI-ACP-RCP-RCR | Guideline | General | 1.5 | There is no discussion of resection/ablation of other sites of solitary or limited metastatic disease beyond lung, liver and peritoneum e.g. ovary, adrenal, bone or brain. These should also be included. | Thank you for this comment. Liver, lung and peritoneum were prioritised because they are the most common sites for metastases in colorectal cancer. |
| NCRI-ACP-RCP-RCR | Guideline | General | General | The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by the British Society of Gastroenterology (BSG). We have also liaised with our experts and would like to make the following comments. | Thank you for this comment. |
| Newcastle University | Guideline | General | General | **CaPP3 study update**: | Thank you for this comment. It is anticipated that evidence from CaPP3 could inform future updates of |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | CaPP3 closed to recruitment on 31st March 2019 with 1882 recruits. The minimum recruitment target was 1500. The initial analysis of effects of the 3 aspirin doses (100,300 & 600 mg daily) will be performed in 2024. | this guideline with respect to aspirin dose. Your comment will be passed to the NICE surveillance team which monitors guidelines to ensure that they are up to date. |
| Newcastle University | Guideline | General | General | **Decision aid for Aspirin & Lynch syndrome**<br>We support the proposal by Dr Sam Smith of Leeds University to develop a decision aid for aspirin & Lynch syndrome. We understand that Dr Smith is submitting this proposal to the current consultation. | Thank you for this comment. The committee welcomed the idea of a decision aid on this topic area and recognised its potential usefulness in supporting decision making, NICE is considering the option of a patient decision aid further. |
| NHS England/Improvement | Guideline | General | General | 1.4.1 Test all people with metastatic colorectal cancer suitable for systemic anti- cancer treatment for *RAS* and *BRAF* V600E mutations.<br><br>***Molecular biomarkers to guide systemic anti-cancer therapy***<br>Also see the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer.<br><br>**Why the committee made the recommendations**<br>The evidence showed that *RAS* and *BRAF* V600E mutations were predictive of response to anti-EGFR targeted therapy in people with metastatic colorectal cancer. People with *RAS* or *BRAF* V600E mutant metastatic colorectal cancer also had poorer progression-free and overall survival than those without such mutations. While *RAS* testing is already used to select those people with metastatic colorectal cancer most likely to benefit from | Thank you for this comment. This comment is a quote from the draft guideline and includes no other comment. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | anti-EGFR targeted therapy, *BRAF* V600E testing has the potential to further refine this group.<br>The committee noted evidence that testing for deficient DNA mismatch repair may inform systemic therapy choices for those with non-metastatic colorectal cancer, but NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed. For this reason no further recommendations were made about testing for deficient DNA mismatch repair.<br><br>**How the recommendations might affect practice**<br>*RAS* testing is current practice. *BRAF* V600E testing is not done routinely in current practice. *BRAF* V600E test can be done from the extended colorectal cancer molecular test panel which is part of the recommendations in NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer, so the recommendation should not have a large impact on practice or costs.<br>Full details of the evidence and the committee's discussion are in evidence review B1: Use of molecular biomarkers to guide systemic therapy. | |
| NHS England/Improvement | Guideline | General | General | I was surprised to see nothing on the Enhanced Recovery Programme as part of perioperative patient management. It would have also been interesting to see something on preoperative (or indeed pre chemotherapy) optimisation and cardiopulmonary exercise testing (CPEX) and pre- | Thank you for this comment. Enhanced recovery programmes, perioperative patient management, pre-treatment optimisation, cardiopulmonary exercise testing or pre-treatment risk assessment were not in the scope of this guideline update and evidence for |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | treatment risk assessment. The introduction of this type of assessment has helped reduce the mortality rates for patients according to my colleagues who run the Bowel Cancer Audit. | these were therefore not reviewed. However, the guideline does state that if recovery protocols are being used, the content and purpose of these and their value in improving recovery after surgery should be explained (see recommendation 1.2.4). NICE is currently developing a guideline on perioperative care for adults which covers some of these topics. While the committee recognises the potential importance of pre-treatment risk assessment, they did not think it correct to state that the reason for a reduction in mortality rates is due to this. |
| NHS England/Improvement | Guideline | General | 1.2.11 | 'Surgeries' in English means more than one GP practice. The word we use is operation or procedures. | Thank you for this comment. The wording has been changed as suggested. |
| NHS England/Improvement | Guideline | General | 1.3.13 | The guidance should be more positive in support of laparoscopic surgery for colonic cancer and differentiate from the advice for rectal cancer. | Thank you for this comment. This guideline update did not review evidence on surgical technique for colon cancer but refers to the NICE technology appraisal on laparoscopic surgery for colorectal cancer. However, evidence on different surgical techniques for rectal cancer was reviewed because the committee recognise the importance of differentiating between colon and rectal cancer surgery and rectal cancer surgery is generally considered more challenging and debated. |
| NHS England/Improvement | Guideline | General | 1.3.15 | Stenting is preferable to surgery for palliative intent (the alternatives would be a major operation and stoma or the patient dying in bowel obstruction) There is no standardisation of the provision of services to provide colonic stents in the elective or emergency situation. The | Thank you for this comment. The committee recommends stenting for people who are to be treated with palliative intent. However, for people for whom curative treatment is suitable, the committee recommends either stenting or emergency surgery |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | type of narrative about ESD (in Information needs to 1.3.1) would be useful here. | because evidence on the benefits of stenting is not convincing enough to only recommend stenting. The committee did not consider this to be a patient preference sensitive decision point because the decision is not only based on the patient's preference but also on clinical and practical factors, including availability of surgical or stenting expertise at an emergency situation, therefore, a table such as the one for recommendation 1.3.1 was not created. |
| NHS England/Improvement | Guideline | General | 1.3.3 | Offering radiotherapy to patients who have clear resection margins (1.3.3) is seen my most colleagues as over treatment resulting in complications for a significant proportion of patients. | Thank you for this comment. The best available evidence was used to inform these recommendations. The committee recognises that there is a chance that some people might be over treated. However, the pooled evidence from several RCTs shows better survival and lower local recurrence for those receiving preoperative radiotherapy or chemoradiotherapy. As with any treatment decision, individualised consideration and clinical judgment should be exercised. The committee thinks that the risks and benefits of the treatment should be discussed with patients and an individualised treatment plan agreed taking all relevant factors, including the patient's wishes, into account. Recommendation 1.2.2 says to "Give people information on all treatment options for colorectal cancer available to them, including…. the potential benefits, risks, side effects and implications of treatments". |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| NHS England/Improvement | Guideline | General | 1.3.4 | Also 1.3.4 is not clear that deferral ids for patients who have had a complete pathological and radiological response to neoadjuvant chemoradiotherapy. | Thank you for this comment. The recommendation has been amended to make it clearer. However, this would be patients with complete clinical and radiological response (not pathological) to neoadjuvant therapy. |
| NHS England/Improvement | Guideline | General | 1.3.6 | there have been 2 trials suggesting non-inferiority of open surgery for rectal cancer, so the guidance should be more nuanced. NICE 2006 technology appraisal is very old. | Thank you for this comment. The evidence review comparing laparoscopic and open surgery for rectal cancer details the results for the available randomised controlled trials (see evidence review C3).The results of the pooled analysis in the clinical evidence review and the bespoke economic analysis generally favour laparoscopic surgery over open surgery. However, the committee recognised that in some cases open surgery would be the preferred technique when clinically indicated, for example for locally advanced tumours, or when the person has had multiple previous abdominal operations or previous pelvic surgery. |
| NHS England/Improvement | Guideline | 14 | | 1 Treatment for metastatic colorectal cancer in the lung<br>What is the cost effectiveness and safety of non-surgical ablation and stereotactic body radiotherapy compared to resection for people with metastatic colorectal cancer in the lung amenable to local treatment?<br>To find out why the committee made the research recommendation on treatment for metastatic colorectal cancer in the lung see rationale and impact. | Thank you for this comment. This comment is a quote from the draft guideline and includes no other comment. |
| NHS England/Improvement | Guideline | 17 | | **Key recommendations for research**<br>**1 Treatment for metastatic colorectal cancer in the lung**<br>What is the cost effectiveness and safety of non-surgical ablation and stereotactic body radiotherapy compared to | Thank you for this comment. This comment is a quote from the draft guideline and includes no other comment. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | resection for people with metastatic colorectal 9 cancer in the lung amenable to local treatment? | |
| NHS England/Improvement | Guideline | 21 | 20 | The guideline details concern regarding providers ability to deliver increased radiotherapy requirements due to the number of oncologists and provision of radiotherapy equipment. Delivery of Radiotherapy requires the skills of a multi professional team, including therapeutic radiographers this Allied Health profession have recognised workforce challenges as a small yet vital profession. We would like to see reference also to Therapeutic radiographers within this section. Additionally, Therapeutic Radiographers are increasingly undertaking roles at advanced and consultant level site to support oncologists within specific specialisms. (SC). | Thank you for this comment. The committee agrees that different professionals, not only oncologists, are needed to provide radiotherapy. This might include therapeutic radiographers, nurses etc. The text has been amended to reflect this. |
| NHS England/Improvement | Guideline | 30 | | **Molecular biomarkers to guideline systemic anti-cancer therapy**<br>Recommendation 1.4.1<br>Why the committee made the recommendations<br>The evidence showed that RAS and BRAF V600E mutations were predictive of response to anti-EGFR targeted therapy in people with metastatic colorectal cancer. People with RAS or BRAF V600E mutant metastatic colorectal cancer also had poorer progression-free and overall survival than those without such mutations. While RAS testing is already used to select those people with metastatic colorectal cancer most likely to benefit from anti-EGFR targeted therapy, BRAF V600E testing has the potential to further refine this group.<br>How the recommendations might affect practice | Thank you for this comment. This comment is a quote from the draft guideline and includes no other comment. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | RAS testing is current practice. BRAF V600E testing is not done routinely in current practice. BRAF V600E test can be done from the extended colorectal cancer molecular test panel which is part of the recommendations in NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer, so the recommendation should not have a large impact on practice or costs. | |
| NHS England/Improvement | Guideline | 37 | | The recommendation advises that LARS should be screened for in primary care using a LARS score and patients offered symptomatic treatment by their GP.<br>The recommendation was made because LARS only becomes apparent after hospital discharge following anterior resection for bowel cancer.<br>There are several concerns about these NICE recommendations that will have an impact on capacity in primary care.<br>The guidance states:<br>'Primary care clinicians are not necessarily aware of LARS or how to assess it and administering the questionnaire might need extra work and time. However, it is patient-administered and easy to score, and no training should be needed. Bowel dysfunction treatment for associated symptoms are commonly delivered in primary care, therefore, the recommendation is not expected to have a large impact on current practice except raising awareness of LARS.' | Thank you for this comment. The committee changed the recommendation about assessment of LARS to apply more generally, i.e. not only within primary care. However, the first-line treatment of LARS should still generally be offered within primary care.<br>The committee fully recognises that GPs might not be familiar with LARS or the LARS score and increasing awareness of LARS is needed within primary care as well as among people with colorectal cancer. This is one of the reasons this topic was included in this guideline update. While the committee acknowledges the need to raise awareness about LARS they do not think this will have a large impact on the workload of GPs. People with LARS will be a small number of the total patient population GPs will see. GPs are experienced with treating people with bowel dysfunctions and if they have concerns about tumour recurrence, it would be appropriate to refer the patient for further checks. Please note that the committee included a GP representative who supported this recommendation. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | However, this recommendation will require raising awareness of LARS among GPs (educational need, capacity to learn/protected learning time-PLT)<br>Raising patient awareness-patient education/media/comms<br>Capacity to offer the self-assessment tool to patients, adequate computer 'read coding' available<br>Knowledge of how to successfully treat post-operative bowel dysfunction after tumour surgery-many GPs would have a low threshold to re-refer back to colorectal being concerned about the risk of recurrence of tumour<br>In conclusion the statement 'the recommendation is not expected to have a large impact on current practice except raising awareness of LARS' is false. It will have a large implication and GPs do not currently have the capacity to take on this role.<br>It is suggested that the best professional to follow these patients up and screen for the LARS would be the liaison bowel nurse in secondary care. | |
| NHS England/Improvement | Guideline | 39 | | Diagnosis and staging of colorectal cancer are well established with histology and appropriate imaging, and are not covered by this guideline. | Thank you for this comment. This comment is a quote from the draft guideline and includes no other comment. |
| Pierre Fabre Limited | Guideline | 11 | 19-20 | In addition to the specific need for RAS and BRAF V600E mutation biomarker testing, it is important to note that there can be a significant variation in the turnaround time of these tests across UK laboratories which may delay the timely access to appropriate targeted treatment options.<br><br>We would suggest addition of the following **bullet point** to the draft guideline section 1.4.1 to offer clarity on this point: | Thank you for this comment. The committee agrees that there is variation in the turnaround time, however, this is a wider issue and applies to all laboratory testing and not only RAS and BRAF V600E testing. No changes were made to the recommendation. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | *1.4.1 Test all people with metastatic colorectal cancer suitable for systemic anti-19 cancer treatment for RAS and BRAF V600E mutations.*<br><br>• ***Ideally, the turnaround time for BRAF V600E mutation testing will be short enough for the result to be available at first consultation between patient and Oncologist; expediting treatment planning.*** | |
| Pierre Fabre Limited | Guideline | 30 | 23-29 | We would suggest additional **wording** to ensure this guideline remains current when published, through recognition of potential targeted BRAF V600E therapy options that may be available in 2020.<br><br>*The evidence showed that RAS and BRAF V600E mutations were predictive of response to anti-EGFR targeted therapy in people with metastatic colorectal cancer. People with RAS or BRAF V600E mutant metastatic colorectal cancer also had poorer progression-free and overall survival than those without such mutations. While RAS testing is already used to select those people with metastatic colorectal cancer most likely to benefit from anti-EGFR targeted therapy, BRAF V600E testing has the potential to further refine this group* ***and this guideline recognises the fact that emergent targeted treatment options specific to the BRAF V600E mutation may be available in the future.*** | Thank you for this comment. The committee do not think this needs to be added to what was already written as the potential for new treatments in the future would apply to other recommendations as well. Emerging treatments can be considered in future iterations of this guideline. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Royal College of Pathologists | Guideline | 6 and subsequent | 19 onwards | Offering treatment to people with rectal cancer:<br>How is the stage decided? Presumably by imaging? It may be obvious but I think still worth stating. For example, subsequently on page 11 regarding adjuvant therapy the document states: Base the choice on the person's histopathology. | Thank you for this comment. The type of staging to the TNM classification has now been added to the recommendations, depending on the situation either clinical (cTNM) based on evidence acquired before treatment including imaging, physical examination and endoscopy, or pathological (pTNM) based on histopathology. This has also been clarified in the 'Terms used in this guideline' section. |
| Royal College of Pathologists | Guideline | 9 | 17 and 19 | Statements as follows might risk ambiguity:<br>*1.3.11 Hospitals performing major resection for rectal cancer should operate on at least 10 patients per year.*<br>*1.3.12 Individual surgeons performing major resection for rectal cancer should operate on at least 5 patients per year.*<br><br>Does it mean 10 or 5 major resections for rectal cancer per year? Or 10 or 5 resections for rectal cancer? Etc. | Thank you for this comment. The wording of the recommendations has been amended to minimise ambiguity. |
| Royal College of Pathologists | Guideline | 11 and 30-31 | 19 | Section 1.4.1 (p11) and also on pages 30-31.<br>As there is current variation in RAS testing strategies, to avoid confusion it should be specified if the recommendation to test for RAS mutations includes both K-RAS and N-RAS testing, rather than just K-RAS. | Thank you for this comment. The committee's view was that in diagnostics RAS implies both KRAS and NRAS. However, this has been added for clarity in the 'How the recommendations might affect practice' section. |
| Royal College of Pathologists | Guideline | 13-14 etc | 24 etc. | MDT is "multidisciplinary team", so we suggest "discussion by a MDT" rather than "in a MDT". Or we could say "discussion in a MDT meeting". | Thank you for this comment. The text has been amended as suggested. |
| Royal College of Pathologists | Guideline | 14 | 15 | *1.5.9 For people with colorectal cancer metastases limited to the peritoneum:*<br>*• offer systemic anti-cancer therapy, and* | Thank you for this comment. We have amended the recommendation to say the referral should be discussed within the multidisciplinary team. The criteria for CRS/HIPEC is set out in the NHSE commissioning document and the MDTs should discuss which |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | • *refer to a recognised specialist centre to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).*<br><br>We wonder if this is practical? Are there enough established specialist centres for this recommendation to be implementable? As the document says, there are only 3 centres. Also, is the evidence strong enough? Should the option be discussed with each individual patient, perhaps? | patients might be eligible for the procedure before referring. The committee recognises that the number of referrals to the specialist centres might increase which in turn may increase the workload at the specialist centres, however, the majority of the people referred would not be eligible for CRS and HIPEC. The recommendation aims to standardise care and opportunity for people to get the best possible assessment and treatment. If the demand exceeds the capacity in the specialist centres, there may be a need to either increase the capacity in the existing centres or develop new specialist centres in the future. The evidence around CRS and HIPEC is not strong enough to recommend offering it to everyone with metastatic colorectal cancer limited to the peritoneum, however, the decision about who might benefit from these treatments should be made by the experts in these treatments. All treatment options should be discussed with the individuals, as recommendation 1.2.2 states. |
| Royal College of Pathologists | Guideline | 15 | 3 | *1.6.1 For people who have had potentially curative surgical treatment for non-metastatic colorectal cancer, offer follow-up for detection of local recurrence and distant metastases for the first 3 years that includes carcinoembryonic antigen (CEA) and CT.*<br><br>We would add "serum" before CEA. We would prefer to clarify CT (i.e. CT of where?). | Thank you for this comment. The recommendation has been amended as suggested. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| Royal College of Pathologists | Committee membership | General | General | Dr Salto-Tellez is Manuel not Manual. | Thank you, the typo has been corrected. |
| Sirtex Medical UK Limited | Guideline | 14 | 4-6 | **Sirtex Medical encourage the Committee to consider people refractory or intolerant to standard chemotherapy as the primary indication of selective internal radiation therapy (SIRT) among other potential positions for this therapy for people with colorectal liver metastases**. This is supported by the vast experience available on SIRT using yttrium-90 (Y-90) resin microspheres, of which more than 100,000 doses have been delivered to date in more than 1,050 centres worldwide, this indication being the most commonly approved for public reimbursement globally. This indication is also supported by the current NHS England commissioning for SIRT using Y-90 microspheres, in adults with chemotherapy-refractory or chemotherapy-intolerant metastatic colorectal cancer that is limited to the liver, following a national assessment under the Commissioning through Evaluation (CtE) programme.<br><br>The evidence on SIRT using Y-90 resin microspheres for patients with chemotherapy-refractory colorectal liver metastases and for chemotherapy-intolerant patients has led to recommendations supporting this intervention in the major clinical guidelines and health technology assessments in Europe and the United States:<br>• The ESMO 2016 guidelines for the management of patients with metastatic colorectal cancer state that | Thank you for this comment. The evidence indicated that even though SIRT produced a benefit in terms of liver progression there was no benefit on overall survival. There were more grade 3 or 4 adverse events among patients who underwent SIRT. No difference was observed in quality of life, resectability or treatment-related mortality. With no effect on overall survival or quality of life but increased adverse events and costs, the committee agreed that SIRT should not be offered as a first line treatment for people with colorectal liver metastases.<br><br>Whilst the committee recognises that SIRT may be recommended by other organisations, NICE guidelines are based on the best available evidence. For this review RCTs were determined to be the most appropriate evidence type and as the literature searches identified RCTs in which SIRT was evaluated it would not be possible to include information from the references listed in this comment because as |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | "for patients with liver-limited disease failing the available chemotherapeutic options radioembolization with yttrium-90 microspheres should be considered" based on evidence for SIRT using Y-90 resin microspheres (Van Cutsem E et al. Ann Oncol, 2016 Aug;27(8):1386–422);<br>• The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology state that arterially directed catheter therapy, and in particular SIRT using yttrium-90 microspheres is an option in highly selected patients with chemotherapy resistant/refractory disease and with predominantly hepatic metastases (Benson AB et al. J Natl Compr Canc Netw. 2018 Apr 1;16(4):359–69);<br>• The French intergroup clinical practice guidelines for diagnosis, treatments and follow-up recommend SIRT using Y-90 resin microspheres in the following settings (Phelip JM et al. Dig Liver Dis. 2019 Jul;S159086581930636X):<br>- ""Progression and/or intolerance during cytotoxic chemotherapy (5FU, irinotecan and oxaliplatin), EGFRi antibodies (if RAS WT) therapy and VEGFi antibodies therapies […] in case of exclusive or predominant liver metastases with maintained liver function"<br>- "Intra-arterial therapies for patients with liver exclusive or predominant disease": "when hepatic function is maintained (bilirubin <1.5 N) | consensus based guidelines they do not meet the inclusion criteria the review.<br><br>For the other studies listed in the comment:<br><br>Hendlisz A 2010 was an RCT and was included in our evidence review<br><br>Foubert F 2014 was an expert review and was not included for this reason<br><br>The remaining studies were excluded because they were not randomised trials:<br>Bester L 2012;<br>Cosimelli M 2010;<br>Seidensticker R 2012;<br>Golfieri R 2015;<br>Kennedy AS 2015;<br>Saxena A 2015;<br>Tohme S 2014;<br>Lahti SJ 2015;<br>Fendler WP 2013;<br>Sofocleous CT 2015;<br>Nace GW 2011;<br>Maleux G 2016. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | and metastases are liver-limited/liver-predominant and chemorefractory to systemic treatment";<br>• A group of Spanish multidisciplinary experts representing specialty societies of Medical Oncology, Surgery, Radiation Oncology, Vascular and Interventional Radiology, Nuclear Medicine and Molecular Imaging recommend SIRT "in third-line liver dominant disease after chemotherapy or in combination with chemotherapy", considering that "there is clinical evidence that the use of [SIRT] is safe and well tolerated" (Vera R et al. Clin Transl Oncol. 2019 Jul 29). These clinical guidelines corroborate previous recommendations issued by a nationwide group of Spanish experts recommending SIR Spheres Y-90 resin microspheres as third line treatment for chemotherapy-resistant or chemotherapy intolerant mCRC in patients with "minimal extrahepatic disease" (Aranda E et al. Future Oncol, 2017 Oct;13(23):2065–82);<br>• The French national health technology assessment (HTA) body (*Haute Autorité de Santé, HAS*) recommends SIR-Spheres Y-90 resin microspheres in selected patients with colorectal liver metastases who are refractory or intolerant to available systemic therapy (Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé. SIR-SPHERES, | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | Microsphères d'Yttrium-90. Saint-Denis La Plaine: HAS; 2015 Mar. Report No.: CEPP-4825). SIRT using Y-90 microspheres is also recommended in a similar setting by the Dutch national HTA body (*Zorginstituut Nederland, ZIN*) (Frankema-Mourer J, Heymans J. Standpunt Yttrium-90 radioembolisatie bij colorectale levermetastasen. 2016. Available from: https://www.zorginstituutnederland.nl/werkagenda/publicaties/standpunten/2016/02/18/standpunt-yttrium-90-radioembolisatie-bij-colorectale-levermetastasen).<br><br>It should be noted by the Committee that patients with colorectal liver metastases who are refractory or intolerant to standard chemotherapy have a poor survival prognosis and limited treatment options. For these patients, disease management options are restricted to best supportive care, with a palliative intent. Best supportive care is associated with median survival times of 4 to 6 months in cases of disease progression after two lines of treatment (Foubert F et al. Dig Liver Dis, 2014 Feb;46(2):105–12), constituting an unmet medical need for these patients. Available evidence from a RCT (Hendlisz A et al. J Clin Oncol, 2010 Aug 10;28(23):3687–94), two comparative studies (Bester L et al. J Vasc Interv Radiol, 2012 Jan;23(1):96–105; Seidensticker R et al. Cardiovasc Intervent Radiol, 2012 Oct;35(5):1066–73) as well as a prospective Phase II study (n=50) (Cosimelli M et al. Br J Cancer. 2010 Jul | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | 27;103(3):324–31) demonstrates that SIRT using Y-90 resin microspheres is well-tolerated by patients and has no detrimental impact on their quality of life, while significantly prolonging their overall survival. Outcomes of SIRT using Y-90 resin microspheres in this population are confirmed in single-arm studies: in ten studies published in 2010-2019, with n≥50, totalling 1,476 patients with chemotherapy-refractory or -intolerant, liver-dominant colorectal metastases, median OS was between 6.9 and 13.8 months (median 10.2 months, pooled mean 9.9 months), consistently exceeding outcomes reported for patients receiving best supportive care (Cosimelli M et al. Br J Cancer. 2010 Jul 27;103(3):324–31; Golfieri R et al. La radiologia medica, 2015 Aug;120(8):767–76; Kennedy AS et al. J Gastrointest Oncol, 2015 Apr;6(2):134–42; Saxena A et al. Ann Surg Oncol. 2015 Mar;22(3):794–802; Tohme S et al. HPB, 2014 Dec;16(12):1110–6; Lahti SJ et al. J Vasc Interv Radiol, 2015 Aug;26(8):1102–11; Fendler WP et al. J Nucl Med, 2013 Aug 1;54(8):1202–8; Maleux G et al. Acta Oncol. 2016;55(4):486–95; Sofocleous CT et al. Clin Colorectal Cancer, 2015 Dec;14(4):296–305; Nace GW et al. Int J Surg Oncol, 2011 Mar 20;2011:e571261).<br><br>**Based on the above clinical practice guidelines and HTA recommendations as well as the evidence base for SIRT using Y-90 resin microspheres, including the comparative evidence noted in comment number 2, we encourage the Committee to recommend the use of this intervention in a third-line setting, for patients with** | |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | **colorectal liver metastases who are refractory or intolerant to standard chemotherapy.**<br><br>As noted in comment number 5, we further encourage the Committee to recommend for additional evidence to be collected on the use of SIRT as a first-line treatment for people with colorectal liver metastases. | |
| Sirtex Medical UK Limited | Guideline | 34 | 1-3 | **Sirtex Medical encourage the Committee to consider SIRT using Y-90 resin microspheres as an emerging strategy as first-line treatment for a subgroup of people with colorectal liver metastases, with developing clinical evidence.**<br><br>While we appreciate that the Committee has considered in issuing their recommendation that available evidence on SIRT in this indication was "high quality evidence from 3 RCTs (N=1,103)" (meta-analysis of the SIRFLOX, FOXFIRE and FOXFIRE-Global RCTs reported in Wasan HS et al. Lancet Oncol. 2017 Sep;18(9):1159–71), we encourage the Committee to consider evidence from the post hoc meta-analysis reported by Gibbs et al. on 2 of the above trials (n=739) (Gibbs P et al. Clin Colorectal Cancer, 2018 Dec;17(4):e617–29). This was an individual patient data meta-analysis of the SIRFLOX and FOXFIRE Global trials in which primary tumour location data had been collected prospectively. In the combined analysis of all 739 patients enrolled, SIRT had no effect on OS (median OS, 24.3 vs. 24.6 months; HR=1.021; P=0.810). However, for the 179 patients (24.2%) with a right-sided primary (RSP) | Thank you for this comment. Gibbs 2018; Holch 2017; Loupakis 2015; Petrelli 2017; and Price 2015 report on the effect of tumour sidedness, and were not included in the evidence review as they focus on the effect of tumour sidedness - an issue which the committee did not specify in advance as an area of interest. |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | colorectal tumour, OS was improved with the addition of SIRT to SACT compared to SACT alone (median OS, 22.0 vs. 17.1 months; HR=0.641; P=0.008). The addition of SIRT to SACT was not associated with a significant difference in OS compared to SACT alone among the 540 patients with a left-sided primary (LSP) colorectal tumour (median, 24.6 vs. 26.6 months; HR, 1.120; P=0.264). These results were consistent in both trials included in the analysis. In a univariate Cox proportional hazards model for OS, the interaction between tumour side and treatment was also statistically significant (P=0.002). In a multivariate Cox proportional hazards model in patients with RSP colorectal tumours, the following parameters were found to be independent predictors of OS: treatment with SIRT plus SACT vs. SACT alone (HR=0.641, 95% CI 0.461-0.890; P=0.008); a percentage of tumour to liver volume ("tumour burden") >25% versus ≤25% (HR=1.620, 95% CI 1.100-2.384; P=0.014); primary tumour in situ vs. resected (HR=1.494, 95% CI 1.020-2.188); P=0.039) (Gibbs P et al. Clin Colorectal Cancer, 2018 Dec;17(4):e617–29).<br><br>The safety profile of SIRT using Y-90 resin microspheres in combination with first-line chemotherapy is also improved in the subgroup of patients with RSP colorectal tumours. No statistically significant difference was observed in the incidence of treatment-emergent Grade 3-5 adverse events (AEs) in patients with a RSP colorectal tumour, in the SIRFLOX and FOXFIRE Global trials: such events were reported in 77.2% of patients receiving SIRT plus SACT | |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | versus 77.4% of patients receiving SACT alone. However, among patients with a LSP tumour, treatment-emergent Grade 3-5 AEs were more frequent in the SIRT plus SACT group versus the SACT alone group: 84.4% vs 71.3% (P<0.001) (Gibbs P et al. Clin Colorectal Cancer, 2018 Dec;17(4):e617–29).<br><br>**Based on the above findings, we encourage the Committee to consider that there is evidence supporting the effectiveness and safety of SIRT using Y-90 resin microspheres as a first-line treatment for people with colorectal liver metastases in the subgroup of patients with a right-sided primary colorectal tumour.** It should also be noted by the Committee that patients with metastatic colorectal cancer with a right-sided primary tumour are less likely to benefit from available systemic therapy options (Loupakis F et al. J Natl Cancer Inst [Internet], 2015 Mar 1;107(3); Petrelli F et al. JAMA Oncol, 2017 Feb 1;3(2):211; Holch JW et al. Eur J Cancer, 2017 Jan;70:87–98) and represent a poorly met medical need for which additional treatment options are needed. This can also raise an equality issue as patients with a RSP colorectal tumour are more likely to be female than patients with a LSP tumour (Loupakis F et al. J Natl Cancer Inst [Internet], 2015 Mar 1;107(3); Price TJ et al. Cancer, 2015 Mar 15;121(6):830–5). **Considering this medical need, we further encourage the Committee to recommend for additional evidence to be collected on the use of SIRT** | |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | **as a first-line treatment for people with colorectal liver metastases.** | |
| Sirtex Medical UK Limited | Guideline | 34 | 3-5 | Please see comment number 1 regarding the proposed recommendation and rationale for patients with colorectal liver metastases refractory or intolerant to standard chemotherapy and comment number 3 regarding the available comparative evidence on SIRT using Y-90 resin microspheres in this setting.<br><br>We encourage the Committee to consider all available evidence and international clinical guidelines on SIRT using Y-90 resin microspheres to issue a recommendation supporting the use of this intervention in a third-line setting, for patients with colorectal liver metastases who are refractory or intolerant to standard chemotherapy. | Thank you for this comment. Whilst the committee recognise that SIRT may be recommended by other organisations, NICE guidelines are based on the best available evidence. For this review RCTs were determined to be the most appropriate evidence type and as our searches identified RCTs in which SIRT was evaluated it would not be possible to include information from the guidelines listed in this comment. Similarly, as RCT evidence was identified non randomised studies were excluded. |
| Sirtex Medical UK Limited | Evidence Review D2b | 14 | 1-4, 30-33 | As noted in comment number 1, we encourage the Committee to recommend the use of SIRT using Y-90 resin microspheres in a third-line setting, for patients with colorectal liver metastases who are refractory or intolerant to standard chemotherapy. This position is supported by international clinical guidelines and a wide body of clinical evidence, including comparative evidence on this intervention demonstrating statistically significant and clinically relevant improvements in overall survival (OS) for SIRT compared to best supportive care.<br><br>We appreciate that the Committee has considered that one RCT (n=44) (Hendlisz A et al. J Clin Oncol, 2010 Aug | Thank you for this comment. The results from Hendlisz 2010 were included in evidence review D2b where it is acknowledged that there is moderate quality evidence of better liver progression-free survival in people refractory to chemotherapy who received SIRT plus SACT compared to those who received SACT alone. The trial was small (N=46) and despite the effect shown on liver-progression free survival, the committee did not think there was sufficient evidence to recommend it.<br><br>For this review RCTs were determined to be the most appropriate evidence type and as the literature |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | 10;28(23):3687–94) provides "Moderate quality evidence […] in people refractory to chemotherapy who received SIRT plus [systemic anti-cancer therapy] (SACT) compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent". We encourage the Committee to acknowledge that this RCT met its primary endpoint of a statistically significant improvement in liver progression-free survival, defined as a "critical outcome" in the evidence review supporting the Clinical Guideline, and that this trial was not designed nor powered to demonstrate a statistically significant difference in OS for SIRT compared to best supportive care (administration of 5-fluorouracil [5-FU] alone): patients receiving 5-FU alone were indeed allowed to cross-over to receive SIRT after progression, which confounded OS results (10/23 patients crossed-over from 5-FU alone to SIRT after disease progression).<br><br>We further recommend for the Committee to consider all comparative studies of SIRT using Y-90 resin microspheres versus best supportive care. Bester et al evaluated the safety and effectiveness of SIRT using Y-90 resin microspheres in patients with chemotherapy-refractory liver metastases (Bester L et al. J Vasc Interv Radiol, 2012 Jan;23(1):96–105). For patients with colorectal liver metastases, the median OS was 6.6 months for patients receiving standard care, versus 11.9 months for patients receiving SIRT (95% CI, 10.1–14.9 months; log-rank test, P = 0.001). Seidensticker et al published a matched pair | searches identified RCTs in which SIRT was evaluated, non-randomised studies (i.e. Bester 2012 and Seidensticker 2012) were not included. |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | comparison of SIRT using Y-90 resin microspheres versus best supportive care for chemotherapy refractory liver-dominant colorectal metastases (Seidensticker R et al. Cardiovasc Intervent Radiol, 2012 Oct;35(5):1066–73). They found that median OS was statistically longer in the SIRT group: 8.3 months versus 3.5 months (HR = 0.26; 95% CI 0.15-0.48; P < 0.001). Multivariate analysis showed that SIRT was the only significant predictor for prolonged survival (HR 0.3 ;95%CI 0.16-0.55; P < 0.001). | |
| Sirtex Medical UK Limited | Evidence Review D2b | 14 | 6-29 | Please consider results from the individual patient data meta-analysis of the SIRFLOX and FOXFIRE Global trials reporting in the first-line setting on the overall survival of patients receiving SIRT using Y-90 resin microspheres in combination with first-line chemotherapy for patients with a right-sided primary colorectal tumour (see comment number 5, Gibbs P et al. Clin Colorectal Cancer, 2018 Dec;17(4):e617–29). | Thank you for this comment. Gibbs 2018 was not included in the evidence review as it reports a post hoc analysis (from two RCTs included in our review) on the effect of tumour sidedness - an issue which the committee did not specify in advance as an area of interest. |
| Sirtex Medical UK Limited | Evidence Review D2b | 15 | 18-21 | Please consider results from a post-hoc review of imaging data from the SIRFLOX RCT (n=472) in the first-line setting (Garlipp B et al. Br J Surg, 2019 Aug 19;bjs.11283). This review was performed by a group of 14 expert hepato-biliary surgeons, blinded to treatment assignment and determined that more patients were technically resectable as a result of tumour response following SIRT plus SACT than after SACT alone (93/244 patients (38.1%) vs 66/228 patients (28.9%), p<0.001), despite no baseline imbalances and no effective increase in resection rates having been observed in the SIRFLOX trial. This discrepancy may explain why the increase in tumour response rates in the | Thank you for this comment. The Garlipp 2019 study was published after the literature search cut-off date and so was not included. Data on resectability (from 3 RCTs) in the first-line setting were included but the analysis did not find a clinically important difference. The issue of deciding the resectability of liver metastases out of the scope of this evidence review and so the committee could not make recommendations about it. |

# Colorectal cancer

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | SIRT plus SACT group did not translate into an overall survival benefit in the trial, although the resectability of colorectal liver metastases is indeed recognised by the Committee to be associated with prolonged survival. | |
| Sirtex Medical UK Limited | Evidence Review D2b | 15 | 23-26 | Please consider results from the individual patient data meta-analysis of the SIRFLOX and FOXFIRE Global trials reporting in the first-line setting on the safety profile of SIRT using Y-90 resin microspheres in combination with first-line chemotherapy for patients with a right-sided primary colorectal tumour (see comment number 5, Gibbs P et al. Clin Colorectal Cancer, 2018 Dec;17(4):e617–29). | Thank you for this comment. Gibbs 2018 was not included in the evidence review as it reports a post hoc analysis (from two RCTs included in our review) on the effect of tumour sidedness - an issue which the committee did not specify in advance as an area of interest. |
| Sirtex Medical UK Limited | Evidence Review D2b | 17-18 | 43-5 | Please see comment number 5 regarding the available evidence and proposed interpretation of this evidence for SIRT using Y-90 resin microspheres in the first-line setting. | Thank you for this comment. Gibbs 2018 was not included in the evidence review as it reports a post hoc analysis (from two RCTs which were included in the review) on the effect of tumour sidedness - an issue which the committee did not specify in advance as an area of interest. |
| Sirtex Medical UK Limited | Evidence Review D2b | 18 | 6-12 | As noted in comments number 1 and 3, we encourage the Committee to consider all available evidence on the use of SIRT using Y-90 resin microspheres in patients with colorectal liver metastases who are refractory or intolerant to standard chemotherapy, including but not limited to studies considered in the NHS England commissioning guidance on SIRT as third-line treatment. We further encourage the Committee to consider international clinical guidelines supporting the use of SIRT with Y-90 resin microspheres in this setting, including ESMO 2016 guidelines, and to recommend the use of this intervention in this indication. | Thank you for this comment. The evidence review was limited to randomised trials as the best source of evidence about treatment effectiveness. The review included one RCT (Hendlisz 2010) in patients refractory or intolerant to chemotherapy. The evidence suggested a benefit with SIRT in terms of liver progression-free survival and progression-free survival but not for overall survival. Because the evidence had limitations (serious imprecision due to the small sample size) the committee was not able to make a recommendation either for or against SIRT in this setting. The committee were aware of NHS England |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | | commissioning guidance approving SIRT as third-line treatment, which used observational data in addition to the small RCT as their evidence base. The committee was also aware of NICE interventional procedures guidance on SIRT currently in development as well as other guidelines (e.g. ESMO 2016), however, for this review RCTs were determined to be the most appropriate evidence type. The ESMO 2016 guideline is not accredited by NICE, so the committee were not able to endorse the recommendations in it. |
| Society and College of Radiographers | Guideline | General | General | The Society & College of Radiographers and advisory group members who responded to the consultation consider the imaging and treatment options in colorectal cancer to be both up to date and reflecting current clinical practice.<br><br>However, this guideline does strongly indicate a lack of studies to establish quality of life decision making. This is acknowledged in the supporting documentation:<br><br>**Colorectal cancer (update) [C1] Treatment for early rectal cancer NICE guideline TBC Evidence reviews July 2019**<br><br>Page 13:<br>Comparison 4: Internal radiotherapy versus transanal excision 8<br>No evidence was identified to inform this comparison. 9 | Thank you for this comment and your support for this guideline. The committee agree that there is a lack of evidence for some of the treatments. Each evidence report includes evidence statements specifying whether data were available for each of the comparisons or outcomes specified in the review protocol. These are also discussed in the sections entitled 'The committee's discussion of the evidence'. Alongside survival, improving quality of life is the main aim of this guideline and quality of life was one of the key outcomes used to inform decision making. However, the evidence base on quality of life was often limited or lacking altogether. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | Comparison 6: Total mesorectal excision versus internal radiotherapy 12<br>No evidence was identified to inform this comparison. 13<br><br>Comparison 7: Endoscopic resection versus external radiotherapy or 14<br>chemoradiotherapy with or without surgery 15<br>No evidence was identified to inform this comparison. 16<br><br>Comparison 8: Endoscopic resection versus internal radiotherapy 17<br>No evidence was identified to inform this comparison. 18<br><br>Comparison 9: Total mesorectal excision versus internal radiotherapy 19<br>No evidence was identified to inform this comparison | |
| University of Leeds | Guideline | 17-18 | 13-15 | The rationale and impact statement related to recommendation 1.1.1. (Prevention of colorectal cancer in people with Lynch Syndrome) states that *'…the potential harms and benefits of long-term aspirin use should be discussed so that people are able to make an informed choice'.* We agree that informed decision-making should be prioritised for people considering the use of aspirin. However, given the amount of complex information described in Evidence Review A1, we believe information resources that are informed by modern risk communication | Thank you for this comment. The committee welcomed the idea of a decision aid on this topic area and recognised its potential usefulness in supporting decision making. NICE is considering the option of a patient decision aid further. |

**Colorectal cancer**

**Consultation on draft guideline - Stakeholder comments table**
**2nd August 2019 – 13th September 2019**

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | techniques are needed to achieve this goal. The Cochrane systematic review of 'Decision aids to help people who are facing health treatment or screening decisions' provides comprehensive evidence that decision support tools can improve patient knowledge and risk perceptions, clarify values, and encourage a more active role in the decision-making process[1]. We urge the committee to invest time and resources into the development of a decision-aid to support patients and their clinicians in the decision-making process for initiating aspirin. Our team are willing to support this process.<br><br>References<br>Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. (2017) Decision aids to help people who are facing health treatment or screening decisions. Cochrane Database of Systematic Reviews. Issue 4. Art. No.: CD001431. DOI: 10.1002/14651858.CD001431.pub5. | |
| University of Leeds | Guideline | 18 | 16-20 | The committee were unable to recommend a dose of aspirin, which may make the implementation of recommendation 1.1.1. difficult, particularly if aspirin is to be prescribed in primary care. We previously undertook a survey of 1007 UK general practitioners asking about their knowledge of Lynch Syndrome, and attitudes towards the use of aspirin for cancer prevention in this group.[2] Approximately two-thirds (71%) of general practitioners had heard of Lynch Syndrome, and among those only 47% were aware of the cancer preventive effects of aspirin | Thank you for this comment. The committee welcomed the idea of a decision aid on this topic area and recognised its potential usefulness in supporting decision making. NICE is considering the option of a patient decision aid further. |

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | among carriers. This highlights that educating and supporting general practitioners should be a key part of the strategy for implementing this guideline. Our survey also showed that willingness to prescribe aspirin (in a hypothetical scenario) was affected by the dose: 91%, 82% and 62% of the GPs were willing to prescribe at a dose of 100mg, 300mg, and 600mg, respectively. Without effective communication between clinical genetics and primary care, a significant proportion of GPs could be reluctant to prescribe aspirin for people with Lynch Syndrome.<br><br>Within a report of these findings[3], a series of recommendations were suggested to address the potential barriers to implementing aspirin for people with Lynch Syndrome. These included:<br><br>• A decision-aid that can be used by both patients and clinicians when discussing the decision to use medication for the primary prevention of cancer should be developed.<br>• The Cancer Alliances should work with research scientists, clinical networks and NICE to develop standardised pro-formas for secondary care clinicians (e.g. clinical geneticists), to send to GPs when they are referring high-risk patients to discuss chemoprevention.<br>• Prescriptions could be initiated in secondary care and continued in primary care. | |

# Colorectal cancer

## Consultation on draft guideline - Stakeholder comments table
## 2nd August 2019 – 13th September 2019

| Stakeholder | Document | Page No | Line No | Comments | Developer's response |
|---|---|---|---|---|---|
| | | | | References<br><br>1. Smith SG, Foy R, McGowan J, Kobayashi LC, Burn J, Brown K, Side L, Cuzick J. General practitioner attitudes towards prescribing aspirin to carriers of Lynch Syndrome: findings from a national survey. (2017) Familial Cancer. 16(4), 509-516.<br>2. Smith, SG and Beck, H on behalf of the Chemoprevention Implementation Group. Understanding GP Attitudes to Cancer Preventing Drugs, London: Cancer Research UK, 2017. https://www.cancerresearchuk.org/chemoprevention | |

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*