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Suggestions, Opinions, Recommendations for the diagnosis, management, treatment and surveillance of for colon and rectal cancer

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In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

Evidence Level and Recommendation Grade

Level of Evidence	
I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Strength of Recommendation	
A	A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,..) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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1 Diagnostics and staging for colon and rectal cancer

1.1 Rectal cancer

1.1.1 Diagnostic means for initial staging (before chemoradiation)

The accurate diagnosis of local tumor extension, location, N-stage and potential CRM (*circumferential resection margin)* positivity is essential for defining the treatment strategy.

Typically the primary lesion is identified by a rigid or flexible endoscopy, accompanied by biopsy. Current preoperative staging techniques include digital rectal examination, endorectal ultrasonography (US), and computed tomography (CT). However, these modalities are poor indicators of the relationship between the tumor and the circumferential resection margin, and they have not been shown to enable accurate measurement of the local depth of tumor spread. [MERCURY, 2007]

Definition of rectal vs colosigmoid cancer

Anatomical landmark is the anal verge. Tumor is measured beyond digital rectal examination with rigid or flexible rectosigmoidoscopy or more recently the addition of CT or preferably, MRI.

Rectal cancers are categorized according to their distal edge measured from the anal verge. Depending on the methodology used (rigid vs flexible endoscopy) the measurements are different. Radiotherapy does not appear to have an impact on the rate of local recurrence for rectal cancers beyond 10 cm

- → ***By rigid proctoscopy the categories are: low (up to 5 cm), mid (from >5 to 10cm) or high (from >10 up to 15cm). (LOE IV; SOR A)***
- → ***Definition for low vs mid/high with rigid proctoscopy is accurate and more reliable than flexible endoscopy. (LOE IV; SOR B)***
- → ***Multidetector row CT is equivalent to rigid proctoscopy for definition of location. (LOE IV; SOR C)***

→ MRI is highly accurate for definition of location and additionally for determining length of the tumour.
For definition of tumour location rigid proctoscopy or flexible endoscopy in combination with MRI have comparable accuracy. *(**LOE** IV; **SOR** B).*

Definition of T-stage (according to TNM)

Subclassification of T1 cancers is based upon depth of invasion into the submucosal layer: sm1 upper third, sm2 middle third and sm3 lower third.

Endorectal ultrasound (ERUS) and endorectal MRI have similar accuracy in the differentiation between T1 sm1/sm2 and sm3 and furthermore between superficial (T1 and/ or T2) and T3 tumours. MR imaging with use of an endorectal coil offers the maximum amount of information by a single modality in the staging of rectal cancer [Kwok et al., 2000]. Endorectal imaging is not an adequate method for the assessment of local tumor extent in bulky T3 or T4 tumours. Sphincter infiltration can be measured with comparable accuracy by ERUS or MRI. In a relatively recent multicenter trial, the use of staging using endoluminal US resulted in substantial preoperative overstaging and consequent overtreatment. Therefore, it is important that an accurate preoperative staging system is developed [Sauer et al., 2004].

EUS tends to overestimate tumour depth [Akasu et al., 1997] because of the obliquity of the probe in relation to the lesion and difficulty in differentiating peritumoral inflammation or fibrosis from true tumour. Apart from being operator dependent, there are problems when scanning high lesions. It is difficult for EUS not only to assess CRM or to identify lymph nodes close to the mesorectal facia (because the mesorectal fascia is not identified on endoluminal US) but also to depict other prognostic features such as extramural vascular invasion.

More accurate interpretation of rectal tumors has become feasible by using standardized imaging criteria, thin-section MRI with 3-mm slices and a small field of view. MRI can now be used to identify several prognostic features that will allow better selection of patients who will benefit from more intensive treatment [Taylor et al., 2008]. MRI or multidetector-row CT has an equal accuracy in distinguishing T3 from T4 tumors in the middle and higher rectum [Bipat et al., 2004]. However,

multidetector-row CT does not correlate well enough with MRI findings to replace it in rectal cancer staging [Maizlin et al., 2010].

CT has limitations in differentiating and distinguishing the different layers of the rectal wall and in demonstrating the mesorectal fascia [Bipat et al., 2004]. MRI is superior for imaging in lower rectal tumors especially the sphincter complex and assessment of the mesorectal fascia infiltration.

The two major advantages of thin section MR imaging are the ability to differentiate malignant tissue from the muscularis propria and clear delineation of the mesorectal fascia which forms the circumferential resection margin [Brown et al., 2004].

MRI fails to differentiate adequately between T2 and borderline T3, mainly due to overstaging [Beets-Tan et al., 2001].

The T component of the TNM classification is the traditional method of prognostically stratifying patients, but this approach has limitations. The main limitation of T staging is that T3 tumors comprise the majority of rectal cancers seen at presentation, they are a very inhomogeneous group regarding local recurrence and survival rates, because the outcome of patients with these tumors depends on the depth of extramural spread.

From existing pathologic studies, it is clear that patients with more than 5 mm of extramural spread should be identified because they have a markedly worse prognosis than do patients who have T3 tumors with 5 mm or less of spread [Compton et al., 2000]. Thus, the distinction between T2 stage and T3 stage is not relevant when the T3 tumor has less than 2 mm spread. Therefore, distinction between T2 and borderline T3 tumor by MRI will not cause major inconvenience in decision making regarding patient management, as long as both tumors will receive the same treatment (surgery) in the absence of any negative prognostic factors.

MRI has been shown to accurately identify the depth of extramural invasion, the presence of lymph node metastases, extramural vascular invasion and CRM involvement. By demonstration of accurate measurement of the depth of extramural tumor spread, the MERCURY Study enabled accurate preoperative prognostication [MERCURY, 2007].

Low rectal cancer tumors need special attention because they have worse prognosis due to the particular anatomy of the mesorectum at the level of the levators, thus

conventional MRI staging system may result in inconsistencies. In this area specific mention should be made on the MRI staging report, regarding the relationship of the infiltrating margin of tumor with the levators, the intersphincteric plane, the internal and external sphincter [Taylor et al., 2008]. Low rectal tumors that require an abdominoperineal resection (APR) and thus being at higher risk of CRM involvement, need to be accurately staged with MRI in order to determine the need for neoadjuvant therapy or a modified surgical procedure [Shihab et al., 2009].

Recommendations

→ Depending on availability and expertise, ERUS is preferably used in early mobile rectal tumors (T1,T2) to accurately define T stage. (LOE IV; SOR B).

→ For advanced (T3/4) mid or high rectal cancers MRI should be performed to accurately define T stage. Multidetector CT could be used as an alternative in case MRI is unavailable. (LOE IV; SOR B) .

→ Low rectal tumors should be assessed by MRI, although for determination of sphincter infiltration ERUS could be used alternatively. (LOE III; SOR A)

→ Extramural depth of tumor spread can be measured with high accuracy with thin section high resolution MR imaging, equivalent to the corresponding measurement at histopathologic analysis. (LOE III; SOR A).

Circumferential resection margins (CRM)

Treatment strategy is dependent also on CRM *(status.* CRM involvement is an independent prognostic factor for pelvic recurrence and poor survival [Birbeck et al., 2002]. MRI is the method of choice for the prediction of positivity of CRM. Multidetector CT seems to be *an alternative to MRI in tumors in the mid and high rectum, when the latter is not available.*

A potentially positive CRM margin is defined as tumor lying within 1 mm (< 1 mm) of the mesorectal fascia [MERCURY, 2007]. Measurements are also taken of the main tumor, suspicious lymph nodes, extramural vascular invasion, and tumor deposits or satellite nodules within the mesorectal planes.

Extramural vascular invasion is another important independent prognostic feature that can be readily identified on MRI [Smith et al., 2008].
Multidisciplinary Team (MDT) discussion of MRI and implementation of preoperative treatment strategy results in significantly reduced positive CRM in rectal cancer patients [Burton et al., 2006].

Recommendations

→ For determination of CRM positivity MRI should be used. If MRI is not available CT could be used for the mid and high rectal cancer. (LOE III; SOR A).

→ MRI-based MDT discussion is highly recommended preoperatively to define prognostic factors and treatment strategy in patients with rectal cancer, in order to reduce CRM positivity (LOE V; SOR B).

N-stage

Identification of nodal disease is still a diagnostic problem for radiologists. Prediction of nodal metastases has traditionally relied on size. Nodes >8mm in the pelvic side wall are defined as malignant nodes. MRI and multisclice CT are equivalent in detection of suspect pelvic side wall lymph nodes, defined by size >8mm. A recent meta-analysis has shown that no significant differences existed among endorectal sonography, CT, and MRI in nodal staging using size criteria [Bipat et al., 2004]. Several studies using MRI and endoscopic US have shown the inaccuracies of using only the size criteria to discriminate between benign and malignant nodes, because size is not a good predictor of malignancy. Particularly for mesorectal lymph nodes, a cutoff value of 10 mm gives high specificity but low sensitivity, whereas the reverse is true, if a cutoff value of 3 mm is employed [Vogl et al., 1997]. Nodes less than 5 mm in diameter and difficulty in exploring the entire mesorectum, are a limitation for using endoluminal US in determining the stage of rectal cancer [Detry et al., 1996]. However, morphological features of high resolution MRI based on the outline and signal intensity of the lymph nodes have been shown to be more reliable [Brown et al., 2003].
Two meta-analyses have shown that, for the identification of nodal disease on a patient-by-patient basis in primarily rectal cancer, all currently used imaging

modalities lack sufficient accuracy for clinical decision making. The estimated sensitivity for endoluminal ultrasonography (US), magnetic resonance (MR) imaging, and computed tomography (CT) was 67%, 55%, and 66%, with corresponding specificity estimates of 78%, 74%, and 76%, respectively [Bipat et al., 2004].

The nodes are judged suspicious if they have irregular borders, mixed signal intensity, or both and then a note is made about their number. Any node lying within 1 mm of the circumferential resection margin is recorded and then, is further identified by suspicious features. The same criteria can be used for pelvic side wall lymph nodes. By assessing the nodal morphology at MRI, malignant nodes can be detected with a greater degree of sensitivity (85%; 95% CI, 74–92%) and specificity (97%; 95% CI, 95–99%) compared with nodal size measurement [Brown et al., 2003].

The good performance of USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer has been shown with a high sensitivity and specificity of approximately 95% for detection of malignant lymph nodes [Lahaye et al., 2008].

FDG-PET has shown disappointing results for N staging, particularly in the mesorectal fascia, but PET-CT imaging could have a potential role in identifying lateral spread to nodes along the internal iliac chain [Koh et al., 2006].

Recommendations

→ Employing high-spatial-resolution MR imaging and morphologic criteria, such as the signal intensity and border characteristics of nodes, rather than size criteria, considerably improves prediction of nodal status in rectal cancer staging. (LOE III; SOR B).

→ MRI and multisclice CT are equivalent in detection of suspected pelvic sidewall lymph nodes, defined by size ≥ 8 mm. (LOE IV; SOR B).

→ USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer has been shown to achieve a high sensitivity and specificity of approximately 95% for detection of malignant lymph nodes, but USPIO is not yet available on the market. (LOE III; SOR C).

M-staging

Thoracic and abdominal CT is recommended to detect or rule out distant metastases. The real value of CT is its accuracy in detecting distant metastases. MRI is helpful in further characterisation of liver lesions suspected for metastases diagnosed by CT scan. MR imaging is the preferred first-line modality for evaluating colorectal liver metastases in patients who have not previously undergone therapy. In a recent meta-analysis, [Niekel et al., 2010] sensitivities of MRI in detection of colorectal metastases was higher than CT particularly for lesions less than 10 mm .

FDG-PET could be considered for detection of liver metastases and peritoneal disease when there is clinical, biochemical or radiological suspicion of systemic disease [Samee and Selvasekar, 2011]. FDG/PET is mainly useful in the assessment of local recurrence and metastatic disease when conventional imaging is not helpful [Cho et al., 2009]. Currently it is not used as a primary staging modality in rectal cancers.

Bone scan and brain imaging are required for clinical symptoms only.

Recommendations

→ Abdominal CT or MRI and chest X-ray,(although chest CT is preferred), are the minimal requirements for staging of distant metastases. (LOE V; SOR B).

→ MR imaging is the preferred imaging modality for evaluating colorectal liver metastases and problem solving method. (LOE IV; SOR B).

→ FDG-PET should not be used routinely for initial staging. (LOE V; SOR D).

→ Bone scan and brain imaging should only be performed for patients according symptoms. (LOE V; SOR D).

1.1.2 Diagnostic means after chemoradiation

Restaging rectal cancer after chemoradiotherapy using different imaging diagnostic means has been the subject of several studies, most of which suggested that none of the available imaging modalities, (endorectal ultrasound, MRI, FDG-PET or CT) are sufficiently accurate for identifying complete remission with positive predictive values of 17-50% [Janssen et al., 2010;Kim et al., 2009;Suppiah et al., 2009]. Although downsizing can be assessed with these methods, accuracy for T-stage is relatively low. Solely phased array MRI can accurately distinguish pT0-2 from pT3 and pT4 disease and assess the infiltration of the mesorectal fascia. Diffusion-weighted MRI increases specificity of response assessment, if used before, during and after preoperative chemoradiation. However, availability and expertise should be taken in consideration when modern imaging techniques are used for restaging rectal cancer after chemoradiation.

Preoperative radiation therapy combined with chemotherapy is now widely recognized as the standard of care for locally advanced rectal cancer. Given the fact that major pelvic surgery for locally advanced rectal cancer is associated with high postoperative morbidity rate of 40-50% [Larsen et al., 2008], selecting patients for local excision after chemoradiation, meaning, patients with both residual tumor (ypT0-2) limited to bowel wall and a negative lymph node status (ypN0) status, is essential from the part of the surgeon and a major challenge for the radiologist. The clinical question that arises is how to handle a good response after radiation therapy with combined chemotherapy.

Most of the treated tumors become smaller and chemoradiation with a regimen comprising 45-50.4 Gy and 5-fluorouracil-based chemotherapy, results in complete remission in 15%-30% of cases and almost 50% partial response rates for the primary tumor bed. Eradication of tumor in lymph nodes occurs in almost half the patients [Sauer et al., 2004].

Downsizing of rectal cancer after radiation therapy with concomitant chemotherapy to ypT0–2 tumor can be predicted accurately by using MR imaging with a high PPV at

the cost of a lower NPV, because of diffuse fibrosis that can be seen after radiation therapy and because, no distinction can be made between fibrosis with or without tumor cell nests (although the prognostic relevance of these nests remains to be determined.) Given the fact that phased array MRI is nowadays more available than before, a restaging MR image could be a useful tool for clinicians to consider transanal local excision in good responders after chemo radiation therapy with less morbidity and mortality than after standard surgery [Dresen et al., 2009]. The same study revealed that volumetric analysis can help in restaging, that is when the initial tumor volume is less than 50 cm^3 and the decrease in volume after chemoradiation is more than 75%, then a ypT0-2 can be predicted.

It has recently been shown that MRI can identify the presence of residual tumor foci with good agreement between MRI tumor regression grade and histopathologic tumor regression grade. The interpretation of these images is becoming increasingly important, because some patients show a complete response to treatment; there is ongoing work in this area.

Before reporting MRI's following neoadjuvant therapy, the pretreatment images should be reviewed. Optimally, pre and post chemoradiation therapy MRI scans should be done with the same, optimized High Resolution MRI protocol using the same parameters. This allows for a more accurate assessment of tumor regression and potential operability and type of surgery to be reconsidered. Parameters to be reassessed are in particular a. tumor height for reduction of craniocaudal length, which may have an impact for the choice of operation and b. new potential CRM, which should be clear of areas of fibrosis, which now forms the margins of resection , rather than tumor (where regression has occurred after CRT) and may still harbour malignant cells [Shihab et al., 2009].

However, to select patients for local transanal excision after chemoradiotherapy, is not only a matter of accurate prediction of ypT0–2, but also accurate prediction of ypN0 lesions. Accurate nodal restaging after chemoradiation may be very important for therapeutic decision-making, because minimally invasive treatment could be a

safe alternative with a good response and node negative status, although these treatment alternatives are still under debate [Lambregts et al., 2011a]. Accurate non-invasive MRI assessment of regression of poor-prognosis stage N2 disease to N0 or N1 can indicate effective therapy [Koh et al., 2008].

The most reliable predictors for identifying benign lymph nodes in patients with locally advanced rectal cancer on a USPIO-enhanced MR image for restaging after radiation therapy with concomitant chemotherapy are the 30% estimated percentage of the white region within the node and Ratio A. The high agreement in both criteria between a more experienced and a less experienced reader indicates reproducibility of the readings in a general setting [Lahaye et al., 2009]. The specificity, sensitivity, NPV and PPV of USPIO –enhanced MRI on a patient –by-patient basis in a large multicenter cohort strudy are: 80%, 90%, 95% and 65% [Engelen et al., 2010]. The high NPV in this study suggests that the use of contrast media is useful for safe clinical decision making. The drawback with the use of USPIO is that in Europe this contrast agent is not yet available at the market.

Interestingly, the response of the primary tumor frequently parallels that of the nodal response as revealed from the surgical specimen and recent studies [Hughes et al., 2006;Koh et al., 2008]. In contrast to the results with MR imaging for primary staging, size measurements on standard 2D T2-weighted fast spin-echo images offer reasonably good accuracy to identify benign nodes after radiation therapy with concomitant chemotherapy. The knowledge coming from histopathology that the nodes that are still malignant after chemoradiotherapy are the larger ones and that the initially small nodes often are benign after therapy, can increase the radiologist's confidence in restaging smaller nodes [Lahaye et al., 2009].

The question for the surgeon remains whether a 80-90% NPV can be safely accepted for nodal regression, when local excision is considered after a good response of rectal cancer to chemoradiation. This question probably does not apply for a 10-20% understaging for depth of invasion of residual tumor, because after a local resection tumor will be histologically examined and probably the patient will undergo a standard TME resection. For nodal involvement and consideration of local excision, this is more difficult to answer, because there will be a 10% risk of leaving behind metastatic mesorectal nodes [Engelen et al., 2010].

The most recent multicenter, prospective study in the field [Patel et al., 2011], evaluated the prognostic relevance of post–neoadjuvant therapy MRI assessment of tumor stage, nodal status, CRM, and MRI assessment of tumor regression grade (mrTRG) system, associated to overall survival, disease-free survival and local recurrence,, in patients undergoing neoadjuvant therapy and TME surgery in the MERCURY trial (Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study). This study has first demonstrated a correlation between radiologically determined tumor response and long-term outcomes and has shown that MRI assessment of tumor regression grade after preoperative therapy predicts overall survival, disease-free survival and patient prognosis, before surgery. Therefore, high- resolution MRI protocols with assessment of post treatment MRI TRG and CRM, the quality of which is ensured by training workshops of the radiologists, can effectively help the multidisciplinary team to individualize treatment options before definitive surgery.

Diffusion-weighted MRI (DWI) uses differences in water motion to discriminate between tissues of varying cellularity and could be a potentially valuable oncological imaging technique. Residual tumor has higher cellularity and possesses a high signal on DWMRI, whereas fibrosis with poor cellular density shows low signal on high b –value (b 1000) diffusion images [Vandecaveye et al., 2007].

By combining morphological with functional imaging information, MRI and DWI can significantly improve sensitivity for selection of complete responders and thus reduce interpretation difficulties when the primary tumor bed has become fibrotic after radiation treatment, resulting in less overestimation of tumor in patients with a complete tumor response. Nevertheless, interpretation errors can still occur with DWMRI. Furthermore, specificity is 90%, which indicates that the risk for underestimation and undertreatment of residual tumor can be brought to less than 10% [Lambregts et al., 2011b]. Adding DWMRI to T2-weighted imaging can improve the prediction of tumor clearance in the mesorectal fascia after neoadjuvant chemoradiation, before curative surgery compared with T2-weighted imaging alone in patients with locally advanced rectal cancer [Park et al., 2011]. But the challenge of

detecting small clusters of tumor, difficult to detect even at histology, still remains beyond the detection level of any imaging modality.

CT, endoluminal ultrasound and MRI are all known to be insufficiently accurate in staging rectal nodes after chemoradiation, with sensitivities and specificities in the 55–78% range, although some authors have reported more encouraging results after CRT [Bipat et al., 2004;Lahaye et al., 2009;Suppiah et al., 2009]. The main gain from the addition of DWI for nodal characterisation in rectal cancer after CRT is an increase in the number of detected nodes (benign and malignant) and an improved PPV for identification of metastatic nodes. However, it does not improve overall diagnostic performance and after CRT, T2W-MRI on its own is already sufficiently accurate [Lambregts et al., 2011a].

Although PET using 18-fluorodeoxyglucose tracer can help in the evaluation and prediction of response to treatment, PET is less reliable in identifying complete responders after completion of chemoradiation and cannot help in the differentiation between ypT0-2 and ypT3–4 tumors or fibrosis with or without tumor. By overlooking up to 55% of residual tumors, patients are erroneously interpreted as complete responders and are under the risk of undertreatment [Capirci et al., 2004]. PET is used to evaluate metastatic or recurrent disease, but its role for assessing mesorectal nodes is not defined because mesorectal nodes are most frequently found at the level of the tumor, and the avid metabolic uptake of 18FDG tracer within the primary tumor obscures visualization of the nodes [Koh et al., 2006].Therefore PET performs poorly in the evaluation of involved nodes either before or after chemoradiation [Llamas-Elvira et al., 2007].

Recommendations

→ ***Phased array MRI, which is nowadays available in most MR scanners established in hospitals, using high resolution examination protocols, , can more accurately distinguish pT0-2 from pT3 rectal tumors, with a high positive predictive value after neoadjuvant chemoradiotherapy, than , standard MRI, CT or ERUS and could be used as a useful tool for identification of residual tumor***

confined to the rectal wall and accordingly, for selecting patients for local excision. (LOE III; SOR B).

→MRI assessment of tumor regression grade after preoperative therapy with high resolution MRI protocols, predicts overall survival, disease-free survival and patient prognosis, before definitive surgery (LOE III; SOR B).

→ Before reporting restaging MRIs, the pretreatment images should be reviewed and optimally, pre and after chemoradiation therapy MRI scans should be done with the same , optimized High Resolution MRI protocol with the same parameters (LOE V; SOR B).

→ In contrast to the use of MR imaging for primary staging of nodes in rectal cancer, size measurements on 2D T2-weighted images offer a good accuracy in assessment of downsizing and downstaging lymph nodes after chemoradiation (LOE V; SOR C).

→ FDG-PET is not the appropriate imaging modality to identify true complete responders to chemoradiotherapy (LOE IV; SOR C).

→Diffusion-weighted MRI (DWI) could be a valuable oncological imaging technique. Addition of DWI to optimized rectal MRI protocol, improves the selection of complete responders after chemoradiation (LOE IV; SOR B).

→USPIO-enhanced MRI increases sensitivity and specificity for detection of malignant nodes after chemoradiotherapy for rectal cancer and could be a useful tool to select patients for local excision, but the USPIO contrast agent is not yet available in the market (LOE III; SOR C).

1.1.3 Pathology

The Guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. They are available at http://www.rcpath.orgjindex.asp?pageID=1153. The macroscopic examination of the specimen is critical and of prognostic significance.

Preparation and assessment of specimen

Histological examination of the colorectal specimen is based on a method described by Quirk et al [Quirke and Morris, 2007]. The surgical specimen should be photographed to document the plane of surgical dissection. The lateral resection margin of the fresh surgical specimen must be inked. The surgical specimen is opened leaving intact the tumour area and 2cm below and above it and is then fixed in formalin solution for 48 hours. In rectal specimens in particular, after fixation the specimen is sliced transversely at 3-4mm intervals, looking for continuous spread and or discontinuous tumor deposits and for involved lymph nodes at the CRM. The macroscopic CRM is measured with a ruler, the microscopic CRM measurement is best done by using a sheet of graph paper that is photocopied onto a sheet of acetate and cut to size than to use the Vernier scale [Maughan et al., 2007;Quirke and Morris, 2007]. CRM is divided in two categories: 1.an involved (positive) CRM when the tumor extends to within 1mm of the circumferential margin and 2.an uninvolved (negative) CRM when the distance between tumor and CRM is more than 1mm.To record any perforation and the plane of surgical dissection anterior and posterior surfaces should be photographed [Compton et al., 2000;Compton, 2003;Maughan and Quirke, 2003;Quirke et al., 2011;Rodel et al., 2005].

The histologicy report must include:

A.Gross description: length of surgical specimen, site of tumour (tat or below the peritoneal reflection, or the distance from the dentate line if an abdominoperineal excision is performed), tumour size (3 dimensions), distance from proximal or distal margin, depth of invasion, tumour perforation, other lesions not related with the tumour such as (Crohn disease, ulcerative colitis, polyp, familial adenomatous polyposis) andnumber of lymph nodes. The distance of direct tumour spread outside

the muscularis propria should be recorded and the area in which tumour spreads closest to the CRM should be identified macroscopically. In rectal specimens in particular, blocks should be taken from the area closest to the circumferential margin and any area where the tumour extends to within less than 3 mm from the margin [Maughan and Quirke, 2003;Maughan et al., 2007;Quirke and Morris, 2007;Sanjuan et al., 2010].

Microscopic description:

The microscopic description must include:

Histologic type

The main histologic types in WHO classification are adenocarcinoma, mucinous adenocarcinoma (>50% mucinous), signet ring carcinoma (>50% signet ring), squamous carcinoma, adenosquamous, small cell, medullary and undifferentiated carcinoma. Although most histological types do not have any proven prognostic significance there are exceptions. The signet–ring carcinoma and small cell carcinoma have poor prognosis. Mucinous carcinoma when associated with microsatellite instability (MSI) has a favourable prognosis. Another carcinoma with favourable prognosis is medullary carcinoma which has a strong relation with MSI [Compton et al., 2000;Compton, 2003;Quirke and Morris, 2007;Quirke et al., 2011].

Histologic grade

A large number of grading systems exist in the literature and most systems in the past used three or four grades (grade 1 / well differentiated, grade 2/ moderately differentiated, grade 3 poorly differentiated, grade 4 undifferentiated).

At present a 2-tiered grading system is used (low and high grade). The system is based on the proportion of gland formation and in this way the inter-observer variation is avoided. Low grade has a proportion > 50% glandular formation and in this grade the well and moderately differentiated carcinomas are included. In the high grade category the poorly differentiated and undifferentiated carcinomas are included

(<50% glandular formation) [Compton et al., 2000;Compton, 2003;Sanjuan et al., 2010].

Lymph nodes

All lymph nodes found in the surgical specimen should be sampled. It has been shown that a minimum of 12 lymph nodes must be found to predict the real lymph node status.

The interpretation of the discrete nodules of tumour in the adipose tissue on microscopic examination is many times problematic. According to the old guideline extramural tumour nodules that measured > 3mm in diameter but lacked evidence of residual lymph node tissue were considered as positive lymph nodes. According to the updated guideline a discrete extramural nodule with smooth contours irrespective of size is considered as positive lymph node [Compton et al., 2000;Compton, 2003;Maughan et al., 2007;Sanjuan et al., 2010].

Blood, lymphatic vessel invasion and perineural invasion

In the literature there are several studies investigating the prognostic significance of blood or lymphatic vessel invasion. Most of these showed that vascular invasion was prognostically significant, irrespective of the type of vessel involved (blood, lymphatic). Other studies have found a strong prognostic significance for extramural vascular invasion and its association with increased risk of liver metastasis. The prognostic importance of involvement of small vessels in the submucosa has been well documented in the polypectomies for malignant polyps and is associated with risk of lymph node metastasis.

In the histology report it must be specified whether there is extramural venous invasion or small vessels in the bowel wall. Extramural vascular invasion is recorded when tumour is present within a space lined by endothelium and or is surrounded by muscle and when inside the space erythrocytes are observed. Studies have shown that the detection of venous invasion depends on the number of blocks taken from the tumour periphery. The College of American Pathologists recommends three- five

blocks from the deepest part of the tumour to be examined [Compton et al., 2000;Compton, 2003;Quirke and Morris, 2007;Quirke et al., 2010].
Another significant microscopic feature is perineural invasion. Studies have shown that perineural invasion is an independent indicator of poor prognosis [Compton et al., 2000;Compton, 2003].

Tumour infiltrating lymphocytes (TILs)

The intratumoral lymphocytic infiltration is associated with MSI, medullary architecture and is considered as a favourable prognostic factor. The presence of moderate and severe lymphocytic infiltrates are considered significant [Compton et al., 2000;Compton, 2003].

Residual tumour classification

Surgical margin status should be reported. For the resection margins after surgery the R classification system can be used. The classification has four different grades: Rx (the presence of residual tumour cannot be assessed) R0 (no residual tumour). The distance from the closest margin must be mentioned. R1 (microscopic residual tumour) and R2 (macroscopic residual tumour) [Compton et al., 2000;Compton, 2003;Sanjuan et al., 2010].

Total mesorectal excision (TME)

Macroscopic examination of the mesorectal surface helps us evaluate the quality of the surgical specimen. Mesorectal defects are classified into three categories a) complete: mesorectum is intact, smooth with only minor irregularities without defect greater than 5mm.b) moderate: moderate bulk to mesorectum but irregularity of the mesorectal surface. Muscularis propria is not visible with the exception of the area of insertion of levator muscles. c) incomplete: little bulk to mesorectum with defects down into muscularis propria.
There is also a grading system used to determine the completeness of the mesorectal excision in which, grade 1 indicates incomplete resection, grade 2 nearly complete

and grade 3 complete resection [Maughan and Quirke, 2003;Quirke and Morris, 2007].

Circumferential resection margin (CRM)

The most well known are the proximal and distal margins of the tumour in a resection specimen. The most important margin for rectal cancer is that created around the mesorectum (CRM). This margin may be infiltrated either by direct spread or incomplete removal of lymph nodes that lie just under the mesorectal fascia. Any small deviation from the correct surgical plane could enter tumour cell deposits, potentially compromising cure. There is an increased risk for local recurrence, distant metastases, and poorer survival, when the CRM is involved or measures less than 1 mm [Compton et al., 2000;Compton, 2003;Maughan and Quirke, 2003;Quirke and Morris, 2007].

pTNM classification

Colorectal cancer is classified according to the pTNM system or ypTNM system in a resection specimen after radio-chemotherapy [Compton et al., 2000;Compton, 2003;Quirke and Morris, 2007;Sanjuan et al., 2010].

Primary tumour

TXPrimary tumour cannot be assessed
T0 No evidence of primary tumour
TisIntraepthelial or intamucosal tumour
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the
Subserosa or into the nonperitonealized pericolic or perirectal
tissues
T3a – minimal invasion < 1mm beyond the border of the
muscularis propria
T3b – slight invasion 1-5mm beyond the border of the
muscularis propria
T3c - moderate invasion >5-15mm beyond the border of the

muscularis propria

T3d- extensive invasion >15mm beyond the border of the muscularis propria

T4 Tumour directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b)

Regional lymph nodes

NXRegional lymph nodes cannot be assessed

N0 Noregional lymph nodes metastasis

N1 Metastasis in1-3 lymph nodes

N2 Metastasis in 4 or more lymph nodes

Metastasis in nonregional lymph node will be considered as pM1

Distant metastasis

MXPresence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Assessment of pT1 colorectal tumour

pT1 tumours invade the muscularis mucosa and submucosa without invasion of muscularis propria.

This group of tumours is often encountered in early adenocarcinomas developed in adenomatous polyps or in transanal resection. The histopathology report must include:Histological grade, distance of tumour from the resection margin, vascular or lymphatic invasion and the depth of invasion into submucosa.According to Kikucki levels, the invasion of submucosa is graded in three levels: sm1 (superficial part of submucosa) , sm2 (middle part), sm3 (deep part) [Dworak et al., 1997].

Adenocarcinoma spreading to within 1mm or less of the surgical or endoscopic resection, the presence of lymphatic or vascular invasion and high grade differentiation as well as mid and deep third invasion of the submucosa are findings

suggesting an increased risk for presence of lymph node metastasis [Compton et al., 2000;Compton, 2003;Quirke et al., 2011].

Tumour regression after preoperative treatment (TRG)

Tumour regression after preoperative treatment should be recorded.Preoperative radiation and chemotherapy have been shown to improve outcome in patients with locally advanced rectal adenocarcinoma. There are a number of methods available grading this response which is determined by the amount of residual viable tumour versus the fibrous or fibroinflammatory tissue within the gross tumour mass.One of the methods is the Dworak scoring with five grades: grade 0 no regression, grade 1 minimal regression with obvious fibrosis, grade 2 moderate dominantly fibrotic changes with few tumour cells or groups,grade 4 total regression (1a) In cases of total regression the pathologist is advised to slice and block the whole fibrotic area. In some cases the only finding is the presence of acellular mucin pools within the tumour gross mass and must be regarded as no residual tumour [Compton et al., 2000;Compton, 2003;Rodel et al., 2005;Shia et al., 2004].

Recommendations

- → ***Macroscopic examination of the mesorectal surface helps us evaluate the quality of the surgical specimen.***

- → ***Microscopic description: Should include: Histologic type, Histologic grade [A 2-tiered grading system is used (low and high grade). Low grade has a proportion > 50% glandular formation. In the high grade <50% glandular formation]***

- → ***In patients without preoperative treatment at least 10 lymph nodes (ASCO guidelines)/ 12 lymph nodes (TNM/NICE guidelines) have to be assessed. All identified lymph nodes should be examined. Extramural tumour nodules measured >3mm without evidence of residual lymph node tissue are considered as positive lymph nodes. In the AJCC Manual for staging of cancer a discrete extramural tumour nodul with smooth***

contours irrespective of size is considered as positive lymph node. Number of lymph nodes needed to accurately stage neoadjuvant treated cases is unknown.

- → ***In the histology report it must be specified if there is extramural venous invasion or small vessels in the bowel wall and the presence of perineural invasion. At least 5 blocks from the deepest part of tumour should be examined to confirm the presence or absence of extramural venous invasion.***

- → ***The intratumoral lymphocytic infiltration is associated with MSI and is considered an independent prognostic factor***

- → ***Surgical margin status should be reported. For the resection margins after surgery the R classification system can be used.***

- → ***Rectal cancer is classified according to the pTNM system or ypTNM system in resection specimens after radio-chemotherapy.***
- → ***CRM must be defined, as involved or less than 1 mm from tumour free margin in order to define risk for local recurrence and potentially adjuvant strategy.***
- → ***Surgical quality of TME should be recorded according to the MERCURY classification.***
- → ***Tumor regression after preoperative treatment should be recorded according to the system proposed by Quirke et al.***

2.1 Colon Cancer

2.1.1 Staging

Treatment strategy for colon cancer is guided by adequate staging. Complete colonoscopy and Multi-detector computed tomography (MDCT) scan of the chest, abdomen, and pelvis should be performed. MDCT remains the main imaging modality for preoperative planning, metastatic liver lesion detection and tumour surveillance. Magnetic resonance imaging (MRI) and contrast- enhanced ultrasonography (US) should be considered as problem solving techniques for characterization of indeterminate liver lesions [Ong and Leen, 2007;Floriani et al., 2010].

MDCT is recommended in the initial evaluation of all patients scheduled for colonic carcinoma surgery because of its ability to obtain a rapid global evaluation and demonstrate complications (perforation, obstruction, etc) that may not be clinically apparent. Furthermore, abdominal/pelvic MDCT has a high negative predictive value.

The accuracy rate for assessing lower stage lesions is not as good as that for advanced lesions. This discrepancy relates to the limited ability of MDCT to determine depth of bowel wall penetration.

The specificity for detecting lymph nodes involved with tumor is approximately 50%. As detection of nodes involved with tumor remains a difficult problem, if a colonic resection is planned, local node groups are encompassed in a properly performed cancer operation.

Among patients with potentially resectable liver metastases and a negative initial chest x-ray, additional imaging with a chest CT may detect pulmonary metastases in up to 5% of patients [Kronawitter et al., 1999].

MRI has equal accuracy to MDCT for local staging of colonic neoplasms. Accuracy in identification of lymph node metastases is also equal to MDCT, and slightly superior for detection of liver metastases.

MRI may be beneficial in determining involvement of the adjacent organs. MRI may also be considered in preoperative evaluation of patients with sensitivity to iodinated contrast material, particularly in the evaluation of the liver [Squillaci et al., 2008;Floriani et al., 2010].

Computed tomographic colonography (CTC) can accurately identify all colorectal masses but may overcall stool as masses in poorly distended or poorly prepared colons. CTC has an overall staging accuracy of 81 percent for colorectal cancer and is superior to barium enema in visualizing colonic segments proximal to obstructing colorectal lesions. Furthermore the method can identify synchronous lesions in patients with colorectal masses, and image the proximal colon in patients with obstructing colorectal lesions [Morrin et al., 2000;Floriani et al., 2010].

FDG-PET is not recommended for initial staging. It could be used in patients at high surgical risk when there is a strong probability of metastatic disease invisible on CT or MRI. However, the role of FDG PET/CT is not yet clear owing to the small number of studies [Niekel et al., 2010].

Physical examination and medical and family history of colorectal cancer, polyps and other cancers should be obtained. CEA should be determined before treatment. Additional investigations like virtual colonoscopy or CT colonography could be helpful, even though they are not yet standard procedures. These could be valuable to precisely locate the tumour, which is particularly useful for the surgical approach, especially in patients who are candidates for a laparoscopic resection. They could also help to detect other synchronous colonic lesions or polyps if colonoscopy could not explore the whole colon due to an obstructive tumour.

2.1.2 Pathology

Preparation and assessment of specimen

The surgical specimen should be photographed to document the plane of surgical dissection. The lateral resection margin of the fresh surgical specimen must be inked. The surgical specimen is opened leaving intact the tumour area and 2cm below and above it and is then fixed in formalin solution for 48 hours.

The histology report must include:

A.Gross description: length of surgical specimen, site of tumour (tumour is above/at the peritoneal reflection), tumour size (3 dimensions) distance from proximal or distal margin, depth of invasion, tumour perforation, other lesions not related with the tumour such as (Crohn disease, ulcerative colitis, polyp, familial adenomatous polyposis), number of lymph nodes. The distance of direct tumour spread outside the muscularispropria should be recorded and the area in which tumour spreads closest to the CRM should be identified macroscopically.

B. Microscopic description:

The microscopic description must include

Histologic type

The main histologic types in WHO classification are adenocarcinoma, mucinous adenocarcinoma (>50% mucinous), signet ring carcinoma (>50% signet ring), squamous carcinoma, adenosquamous, small cell, medullary and undifferentiated carcinoma. Although most histological types do not have any proven prognostic significance there are exceptions. The signet–ring carcinoma and small cell carcinoma have poor prognosis. Mucinous carcinoma when associated with microsatellite instability (MSI) has a favourable prognosis. Another carcinoma with favourable prognosis is medullary carcinoma which has a strong relation with MSI [Compton et al., 2000;Compton, 2003].

Histologic grade

A large number of grading systems exist in the literature and most systems in the past used three or four grades (grade 1 / well differentiated, grade 2/ moderately differentiated, grade 3 poorly differentiated, grade 4 undifferentiated).

At present a 2-tiered grading system is used (low and high grade). The system is based on the proportion of gland formation and in this way the interobserver variation is avoided. Low grade has a proportion > 50% glandular formation and in this grade the well and moderately differentiated carcinomas are included. In the high grade category the poorly differentiated and undifferentiated carcinomas are included (<50% glandular formation) [Compton et al., 2000;Compton, 2003;Sanjuan et al., 2010].

Lymph nodes

All lymph nodes found in the surgical specimen should be sampled. It has been shown that a minimum of 12 lymph nodes must be found to predict the real lymph node status.

The interpretation of the discrete nodules of tumour in the adipose tissue on microscopic examination is many times problematic. According to the old guideline extramural tumour nodules that measured > 3mm in diameter but lacked evidence of residual lymph node tissue were considered as positive lymph nodes. According to the updated guideline a discrete extramural nodule with smooth contours irrespective of size is considered as positive lymph node [Compton et al., 2000;Compton, 2003;Maughan and Quirke, 2003;Sanjuan et al., 2010].

Blood, lymphatic vessel invasion and perineural invasion

In the literature there are several studies investigating the prognostic significance of blood or lymphatic vessel invasion. Most of these showed that vascular invasion was prognostically significant, irrespective of the type of vessel involved (blood, lymphatic). Other studies have found a strong prognostic significance for extramural vascular invasion and its association with increased risk of liver metastasis. The prognostic importance of involvement of small vessels in the submucosa has been well documented in the polypectomies for malignant polyps and is associated with risk of lymph node metastasis.

In the histology report it must be specified whether there is extramural venous invasion or small vessels in the bowel wall. Extramural vascular invasion is recorded when tumour is present within a space lined by endothelium and or is surrounded by muscle and when inside the space erythrocytes are observed. Studies have shown that the detection of venous invasion depends on the number of blocks taken from the tumour periphery. The College of American Pathologists recommends three- five blocks from the deepest part of the tumour to be examined.(Compton CC 2000, , Compton CC 2003, Another significant microscopic feature is perineural invasion.

Studies have shown that perineural invasion is an independent indicator of poor prognosis [Compton et al., 2000;Compton, 2003].

Tumour infiltrating lymphocytes (TILs)

The intratumoral lymphocytic infiltration is associated with MSI, medullary architecture and is considered as a favourable prognostic factor. The presence of moderate and severe lymphocytic infiltrates are considered significant [Compton et al., 2000;Compton, 2003].

Residual tumour classification

Surgical margin status should be reported. For the resection margins after surgery the R classification system can be used. The classification has four different grades: Rx (the presence of residual tumour cannot be assessed) R0 (no residual tumour). The distance from the closest margin must be mentioned. R1 (microscopic residual tumour) and R2 (macroscopic residual tumour) [Compton et al., 2000;Compton, 2003;Sanjuan et al., 2010].

pTNM classification

Colorectal cancer is classified according to the pTNM system [Compton et al., 2000;Compton, 2003;Sanjuan et al., 2010].

Primary tumour

TXPrimary tumour cannot be assessed

T0 No evidence of primary tumour

TisIntraepthelial or intamucosal tumour

T1 Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades through the muscularis propria into the Subserosa or into the nonperitonealized pericolic or perirectal tissues

T3a – minimal invasion < 1mm beyond the border of the muscularis propria

T3b – slight invasion 1-5mm beyond the border of the muscularis propria

T3c - moderate invasion >5-15mm beyond the border of the muscularis propria

T3d- extensive invasion >15mm beyond the border of the muscularis propria

T4 Tumour directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b)

Regional lymph nodes

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pT1 tumours invade the muscularis mucosa and submucosa without invasion of muscularis propria.

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Adenocarcinoma spreading to within 1mm or less of the surgical or endoscopic resection, the presence of lymphatic or vascular invasion and high grade differentiation as well as mid and deep third invasion of the submucosa are findings

suggesting an increased risk for presence of lymph node metastasis [Compton et al., 2000;Compton, 2003;Quirke et al., 2011].

Recommendations

→ ***Minimal requirements for staging are complete colonoscopy (either pre- or postoperatively), MDCT of the abdomen and pelvis is the radiological modality of choice, MRI of the abdomen and pelvis is indicated as a problem solving technique (specifically for liver metastases) or if contrast MDCT is contraindicated (LOE I), chest X-ray in all patients or lung CT mainly in patients at high surgical risk and potential lung metastases (LOE III).***

→ ***Laboratory determination of CEA, as well as physical examination, medical and family history of colorectal cancer, polyps and other cancers should be obtained.***

→ ***Virtual colonoscopy or CT colonography (CTC) could be considered for detecting other synchronous colonic lesions or polyps if colonoscopy could not explore the whole colon due to an obstructive tumour (LOE II).***

→ ***FDG-PET should not be used routinely for initial staging (LOE II).***

→ ***Bone scan and brain imaging should only be performed for patients with relevant symptoms.***

→ ***Pathologic assessment should include macroscopic and microscopic assessment, staging for depth of penetration (T), lymph node status (N, min.12 nodes), resection margins (R0 vs. R1/2) and grading (G) (the 2-tiered grading system low and high grade help to avoid interobserver variations: Low grade has a proportion > 50% glandular formation. In the high grade the glandular formation is <50%). In the histology report it must be specified if there is extramural venous invasion or small vessels in the bowel wall and the presence of perineural invasion. At least 5 blocks of tumour should be received for confirm the presence or absence of extramural venous invasion. The intratumoral lymphocytic infiltration is associated with MSI and is considered an independent prognostic factor***

→ ***Surgical margin status should be reported. For the resection margins after surgery the R classification system can be used. The pathology report***

should include the macroscopic assessment of quality of specimen (LOE II; SOR A).

3 Prognostic & predictive markers for staging and treatment for colon and rectal cancer

3.1 Prognostic Marker

Several factors, such as tumour biology and patient related factors influence the prognosis and can modify treatment intervention. The determination of the individual prognostic category is helpful for guiding treatment strategy, e.g. intensity of first line or adjuvant treatment. Some of these factors are combined in prognostic classifications to better define treatment strategy, e.g. Koehne score, although classification is not mandatory and helpful for the clinical routine.

Despite the fact that plentiful potentially prognostic factors have been reported, in the routine use outside clinical trials, only those markerswhich are essential for the selection of treatment and drugs, as well as dosing should be determined.

3.1.1 Early stage colon and rectal cancer

Tumour related prognostic factors

- *MSI status* is the only molecular factor that influences prognosis. Patients with stage II *MSI-H/dMMR* tumors have better prognosis in comparison with those with MSI-L or MSS/MMR proficient tumors.(LOE II, SOR A)
- *KRAS, BRAF or other genes (e.g. PIK3CA, PTEN, etc) do not have a clearly proven prognostic value in stage II or III colorectal cancer.*
- *Genomic signatures* have a potential prognostic value, but are currently not predictive for guiding decision on adjuvant treatment.
- for cancer developing in a polyp (histopathology report must include tumour spread to within 1mm or less of the surgical or endoscopic resection), the presence of lymphatic or vascular invasion and high grade differentiation as well as the depth of invasion into the submucosa all increase the risk of the presence of lymph node metastasis.

- The following factors relating to local tumour stage have a proven prognostic impact and should be mentioned in detail in the histology report:
    - T status
    - N status
    - Histologic grade
    - Extramural invasion
    - Lymphovasculal infiltration
    - Perineural invasion
    - Signet ring histology (worse)
    - Mucinous features (worse)
    - Number of lymph nodes dissected (worse <12)
- Perforation or rupture at surgery has a clear prognostic significance.

Biochemical prognostic factors

- The baseline (before surgery or before chemorediation in case of rectal cancer) CEA level is the only biochemical factor related to a proven prognostic significance. High CEA levels are related to a worse prognosis, however there is no generally accepted cutoff point.

Finally, the number of cases of colon but especially rectal cancer treated in a center is related with patients' outcome in several retrospective studies. However, the cutoff point for the number of cases/year has not been established and the hypothesis has never been tested in a prospective manner.

3.1.2 Advanced colon and rectal cancer

Tumour related prognostic factors

- Detection of *BRAF*^{V600E}is associated with worse prognosis in advanced/metastatic coloretcal cancer regradless of the type of 1st line treatment [Souglakos et al., 2009]. The *BRAF*^{V600E} mutation should be used as stratification factor in future clinical trials.
- It is unnclear whether *KRAS* mutations are associated with worse prognosis [Amado et al., 2008;Karapetis et al., 2008]. The data suggest that *KRAS*^{G13D} is related with worse prognosis while the prognostic significance of the rest of the KRAS mutations is not fully clarified yet.
- Time to recurrence early vs. late (12 months)
- Tumor grading poorly differentiated/undifferentiated (3/4) vs well differentiated (1/2)
- Metachronous (better) matastasis vs. synchronous metastasis
- liver limited disease (+/- lung) vs multiple (lung (better) vs liver)
- presence of peritoneal disease and/or ascites (worse)
- prior adjuvant treatment (worse), in particular if prior oxaliplatin combination exposure

Patients' related prognostic factors

- ECOG ≥2(worse)
- Comorbidities influencing treatment intensity

Biochemical prognostic factors

- leucocytes >10.000 (worse)
- alkaline phospatase exceeding twice the normal value (worse)

- high LDH (worse)
- low hemoglobin (worse)
- baseline CEA level
- low albumin (worse)
- high bilirubin (worse)
- high platelets (worse)

3.2 Predictive markers

The identification of prognostic subgroups by scoring is of norelevance in clinical routine, since currently treatment decision are not based on these scores. However, prognostic subgroups might be of relevance for stratification purposes. Definition of clinical groups according to patient characteristics can be helpful for guiding treatment decision on intensity and selection of drugs/combinations for first line treatment.

3.2.1 Early stage colon and rectal cancer

There is no available marker for predicting the effect of adjuvant chemotherapy for early CRC.

Data on the predictive effect of MSI on efficacy of 5FU or irinotecan are equivocal [Hutchins et al., 2011;Sinicrope et al., 2011;Tejpar et al., 2011].

3.2.2 Advanced/Metastatic Colorectal cancer

KRAS status determination is mandatory before decision for the type 1st line treatment, since *KRAS mutation* precludes efficacy of treatment with anti-EGFR antibodies [Amado et al., 2008;Karapetis et al., 2008;Van Cutsem E. et al., 2009], (LOE I, SOR A). Detection of KRAS mutations (either by RT-qPCR-based techniques

or gene sequencing) can be performed on paraffin embedded tumour block of primary tumour or metastases.

The data regarding the impact of *KRAS codon G13D mutation* (5-8%) are conflicting and non-conclusive(LOE IV, SOR D). One retrospective study suggested that *KRAS codon G13D mutation* do not preclude efficacy of anti-EGFR moAbs treatment [DeRoock et al., 2010], while in the combined analysis of the three randomized studies of panitumumab reported that tumors with *KRAS* codon G13D mutation are resistant to the administration of the antibody.

NRAS, PI3K, PTEN, EGFR mutations, and EGFR ligand (epiregulin, amphiregulin) expression should not guide treatment decision and should not be determined in clinical practice.

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Chemotherapy

Topoisomerase-1 (Topo 1) overexpression was found to be predictive for a benefit of treatment with irinotecan and potentially with oxaliplatin as well in one RCTs but was not confirmed subsequently (LOE IV ; SOR D).

Excision Repair Cross-Complementing gene 1) *ERCC1* expression/polymorphisms, thymidine phosphorylase (TP), or thymidylate synthase (TS) expression or promoter polymorphisms, are associated with efficacy of oxaliplatin or 5FU, however none of these factors should be used for guiding treatment desicions (trials are ongoing).

3.2.3 Prediction of Toxicity

Routine testing for DPD deficiency is not recommended. Testing for DPD deficiency is strongly recommend in case of severe toxicity due to fluoropyrimidines (FP) treatment,before further administration of FP; in case of proven DPD deficiency further exposure to FP (at least in standard doses) must be avoided

Testing for *UGT1A1 Polymorphism should be considered* in cases of severe toxicity resulting from exposure to irinotecan-based regimens.

4 Diagnosis, management, and counseling of hereditary colorectal cancer

Hereditary forms of colorectal cancer show extensive phenotypic and genotypic heterogeneity. In order to establish a diagnosis, direct highly-targeted surveillance and management, and subsequenteffective communication with the molecular geneticist so that at-risk patient's DNA can be tested in accordance with the syndrome of concern. Thus, Lynch syndrome will merit MSI testing and MMR genes testing. A patient with FAP will require APC and MYH testing [Balmana et al., 2010].

Completing a detailed family history will often impart clues to a possible hereditary cancer-prone syndrome should one exist in the family. Information about age at diagnosis, location, histology, and stage, as well as history of concurrent or previous colonic adenomas and other cancers in the family, should be routinely obtained. This will then enable the molecular geneticist to know where to search in the genome for a cancer-causing germ line mutation [ASCO, 2003].

4.1 Familial Polyposis Syndromes

4.1.1 FAP

Hereditary disorders with multiple colonic polyps include FAP, the hamartomatous polyposis syndromes, and hereditary mixed polyposis syndrome (HMPS) inherited by an autosomal dominant pattern.

Genetics

FAP is associated whith germline mutations in APC while the attenuated FAP (AFAP) is associated with germline mutations in the APC exon 9 and MYH, with an autosomal recessive transmission. Gardner syndrome and Turcot syndrome are phenotypic variants of FAP, not separate syndromes [Jasperson et al., 2010].

Extra-Colonic Cancers

Additional cancers also arise in FAP:Gastric, Desmoid, Duotenum, Medulloblastoma [Vasen et al., 2008].

Diagnosis

Clinical diagnosis of classical FAP is based on the identification of >100 colorectal adenomas. Attenuated FAP is characterized by the presence of fewer adenomas and a later onset of the disease; suggested criteria are:

(i) at least two patients with 10–99 adenomas at age >30 years; or

(ii) one patient with 10–99 adenomas at age >30 years, a first-degree relative with CRC and few adenomas, and no family members with >100 adenomas before the age of 30 years

The presence of extra-colonic lesions can also contribute to the initial diagnosis.

Differential diagnosis, based on the genetic testing, should be made between the attenuated form and HNPCC, because as many as 10% of patients with FAP have less than 20 polyps. On the other hand, many patients with HNPCC present with multiple colonic polyps.

Patients with phenotypic FAP and APC/MYH-negative testing comprise about 20% of all cases. They present less frequently with profuse polyposis, as well asCHPRE, desmoid tumors, UGI polyps, and osteomas. By contrast, the presence of tumors other than colorectal is higher in APC/MUTYH-negative families [Bisgaard et al., 2004;Rivera et al., 2011].

The identification of APC or MYH mutations in a proband confirms the diagnosis.

Recommendations-Screening and Prevention

-Detailed family history in directing the work up of hereditary cancer syndromes

-Genetic counseling is clearly important for patients with the FAP phenotype and the APC germline mutation. They show close to 100% lifetime risk for CRC.

-Colonoscopy for screening and surveillance by age for patients with FAP (LOE III, SOR B).

-Prophylactic total colectomy (LOE V, SOR D).

1) Surgery is the first option at the time of diagnosis to minimize the risk of malignancy.

2) Surgical options include subtotal colectomy with ileorectal anastomosis, total proctocolectomy with Brooke ileostomy (or continent ileostomy), and

proctocolectomy with mucosal proctectomy and ileoanal pullthrough (with pouch formation). Colectomy with ileorectal anastomosis (IRA) instead of proctocolectomy with ileal pouch–anal anastomosis (IPAA) could be considered in patients with a mild genotype/phenotype, and with mutations localised at the extreme ends of the gene because of the low risk of developing severe rectal polyposis. IPAA has been related with reduced fertility as compared with IRA in women with FAP, but rectal cancer was only observed in the IRA group (5%) (Aziz, O. et al., 2006).

-For details see Table 1

4.1.2 Hamartomatous polyposis syndromes

Hamartoma refers to an excessive but focal overgrowth of cells and tissues native to the organ in which it occurs. The cellular elements are mature and identical to those found in the remainder of the organ. In the intestinal tract, several discrete familial syndromes characterized by multiple hamartomatous polyps have been described.

Genetics

- Juvenile Polyposis, *SMAG4, BMPR1A*
- Peutz–Jeghers Syndrome (PJS), *STK11 (LKB1)*
- Cowden's, *PTEN*
- Gorlin syndrome, *BCNS*
- and Multiple Endocrine Neoplasia, *MEN II*

Recommendations-Screening and Prevention

-Detailed family history in directing the work up of hereditary cancer syndromes

-Screening and surveillance by age for patients

-Colonoscopy for screening and surveillance by age for patients.

-Prophylactic total colectomy

4.2 Lynch syndrome (hereditary non-polyposis cancer, HNPCC)

Lynch syndrome (hereditary non-polyposis colorectal cancer) is characterised by the development of colorectal cancer, endometrial cancer and various other cancers.

Cardinal Features of Lynch Syndrome:

Earlier average age of CRC onset than in the general population; the average age of CRC onset in Lynch syndrome is 45 years

• Proximal colon cancer involvement

• A significant excess of synchronous and metachronous CRCs

• Autosomal dominant inheritance pattern

• Increased risk for malignancy at certain extracolonic sites, foremost of which is endometrial carcinoma, followed by carcinoma of the ovary, stomach etc

• CRC tumors in Lynch syndrome are more often poorly differentiated.

• They have MSI

• The sensitivity of MSI analysis is slightly higher than that of IHC analysis. In families with a high probability of having a mutation (revised Bethesda criteria), IHC is the best first step because it may direct mutation analysis. In other families, either MSI or IHC analysis might be used as the first step.

Genetics

Lynch syndrome is caused by a mutation in one of the mismatch repair genes: MLH1, MSH2, MSH6 or PMS2.

Recently, germline deletions in the EpCAM gene were found in a subset of families with Lynch syndrome.

A subset of the “Amsterdam positive” cases, estimated at 40% to 70%, do not have MMR deficiency and therefore have been termed ‘familial colorectal cancer type X’ [Bisgaard et al., 2004;Vasen et al., 2007].

Diagnosis

Clinical suspicion is based on fulfillment of clinical criteria. Both the Amsterdam criteria and the revised Bethesda guidelines are used to clinically identify individuals with suspicion of Lynch syndrome or candidates for molecular screening (Table 3). Since >90% of Lynch syndrome CRC cases show MSI and/or loss of the

corresponding protein by IHC, upfront molecular screening is another strategy to identify candidates for germline testing.

If a tumour with MMR or MSI deficiency is detected, germline genetic testing would be indicated. If loss of MLH1/PMS2 expression is observed, methylation of the MLH1 promoter or testing of the somatic BRAF V600E mutation should be performed first to rule out hypermethylation of the MLH1 promoter (10%–15% of sporadic cases are related to this somatic event). The *BRAF* mutation is often present when the promoter region of the *MLH1* gene is methylated (methylation is the most common cause of absent MLH1 staining). When the *BRAF* V600 mutation is present, a deleterious MMR gene mutation has not yet been reported. These characteristics can be useful in determining which patients with absent MLH1 staining should be offered *MLH1* gene sequencing.

-The identification of MLH1, MSH2, MSH6, PMS2 and EpCAM mutation in a proband confirms the diagnosis.

Recommendations

Studies have shown that colorectal surveillance in Lynch syndrome leads to a reduction of CRC and associated mortality. Very few data are available on the effectiveness of surveillance for endometrial cancer [EGAPP, 2009].

-Use the revised Bethesda in selecting families for molecular genetic MSI/IHC analysis of tumours (LOE II; SOR A)

-Use MSI analysis as first step

-Use IHC analysis to direct mutation analysis of MMR Genes.

-Surveillance colonoscopy reduces the risk for developing CRC and the risk of death (LOE II; SOR B). At three year intervals, colonoscopy more than halves the risk of colorectal cancer, prevents deaths from colorectal cancer, and decreases the overall mortality rate by about 65 percent in such families.

Thus, because of missing cancer recurrence with 3-year intervals, colonoscopy for individuals with Lynch syndrome should be performed every 1–2 years, with initiation between ages 20–25 (LOE III, SOR C). An exception involves those families with an MSH6 germline mutation where, due to its more "benign"

features including a later age of onset of CRC, colonoscopic screening could be delayed to the age of 30.

-In families with clustering of CRC but without evidence of MMR deficiency (families without Lynch syndrome), a less intensive surveillance protocol is recommended—that is, colonoscopy at 3–5 year intervals, starting 5–10 years before the first diagnosis of CRC or at 45 years(LOE III, SOR C). -Annual endometrial sampling and transvaginal ultrasound of the uterus and ovaries beginning at ages 30–35 years was indicated in all cases of Lynch Syndrome(LOE III; SOR C)..

-In individuals that developed CRC, evidence favored the efficacy of prophylactic hysterectomy and oophorectomy (LOE III; SOR C). (Vasen, HF., et al., 2007)

Surgical Treatment for a patient who is diagnosed with CRC associated with Lynch syndrome

Regarding the treatment of CRC in patients from families with Lynch syndrome, no controlled trials are available; one decision analysis study has reported an increase in life expectancy with subtotal colectomy compared with partial resection; in view of this study and the high risk of a second CRC, the option of extensive resection should be discussed in young patients (eg, <50 years) ***(LOE III, SOR C)***.

Recommendations: Chemotherapy

-Experimental and clinical studies suggest that MSI-H tumours are resistant to 5-FU-based chemotherapy; however, prospective clinical trials are needed before definitive recommendations can be given (LOE III; SOR a).

Cancer control in Lynch syndrome

.Prophylactic colectomy ?

.Prophylactic gynecologic surgery?

Recommendations: Genetic counseling

-High-risk individuals must receive genetic counseling, so that they understand the pros and cons of cancer genetic testing

Algorithmic guidelines for Lynch syndrome diagnosis and management

They include criteria for selection of subjects for genetic counseling, tumor testing (MSI and/or IHC), mutational testing, surveillance, surgical management, and follow-up surveillance.

Economic and other personal concerns

DNA testing has significant economic dimensions.

Table 1 (Lynch et al., Familial Cancer 7:27-39, 2008)

Table 1 Screening and surveillance recommendations by age for patients with Hereditary Polyposis Syndromes

	FAP	JP	PJS	CS/BRRS PTEN Hamartoma Syndrome
Before age 10	α Fetoprotein and abdominal ultrasound annually from birth to age 10 years			
10–20 years	○ Annual colonoscopy from age 10–12 years	○ Colonoscopy with polypectomy, annually if not all polyps removed, otherwise every 3 years from age 15 years	○ Every 2–3 years, Upper endoscopy (EGD/EGD and enteroscopy), SBFT (? role of capsule endoscopy)	○ Every 2 year colonoscopy, upper endoscopy
	○ Annual upper endoscopy, as soon as colonic polyps appear or 15 years in AFAP	○ Upper endoscopy every 3–5 years from age 15 years; repeated annually if the patient is not polyp free	○ Annual testicular exam, ultrasound if clinically suspected	○ SBFT (? enteroscopy) from age 15 years
	○ (no current consensus on thyroid screening but clinical examination and ultrasound of suspicious lesions needs to be part routine HCM visits)	○ Annual clinical exam and baseline ultrasound of the thyroid from adolescence		○ Monthly breast self exam from age 18 years
				○ Baseline thyroid US at age 18 years, annual neck exam
Older than 20 years	Annual upper and lower endoscopy (including post-colectomy)	○ Monthly breast self-exam, clinical exam every 6–12 months from age 21 years	○ Every 2 year mammography,	○ Annual breast exam, mammography
			○ Annual breast exam, Pap smear, Endometrial biopsy, transvaginal ultrasound	○ Endometrial suction biopsy beginning at 35–40 years
			○ Every 2 year colonoscopy from age 25 years	○ Annual urinalysis (if positive history of renal cancer)
				○ Dermatologic screening exam (melanoma)

Table 2. Vasen FAH et al WWW.jmedgenet.com 2007

Table 2 Surveillance protocol in Lynch syndrome and familial clustering of colorectal cancer

Disorder	Lower age limit (years)	Examination	Interval (years)
Lynch syndrome	20-25	Colonoscopy	1–2
	30-35	Gynaecological examination, transvaginal ultrasound, aspiration biopsy	1–2
	30-35	Gastroduodenoscopy*	1–2
	30-35	Abdominal ultrasound, urinalysis and cytology urine†	1–2
Familial clustering of colorectal cancer without evidence of MSI‡	45-50 or 5–10 before age at diagnosis of first CRC in family	Colonoscopy	3–5

CRC, colorectal cancer; MSI, microsatellite instability.
*If gastric cancer runs in the family or in countries with a high incidence of gastric cancer.
†If urinary tract cancer runs in the family.
‡Amsterdam positive families.

Figure 1. Vasen FAH et al WWW.jmedgenet.com 2007

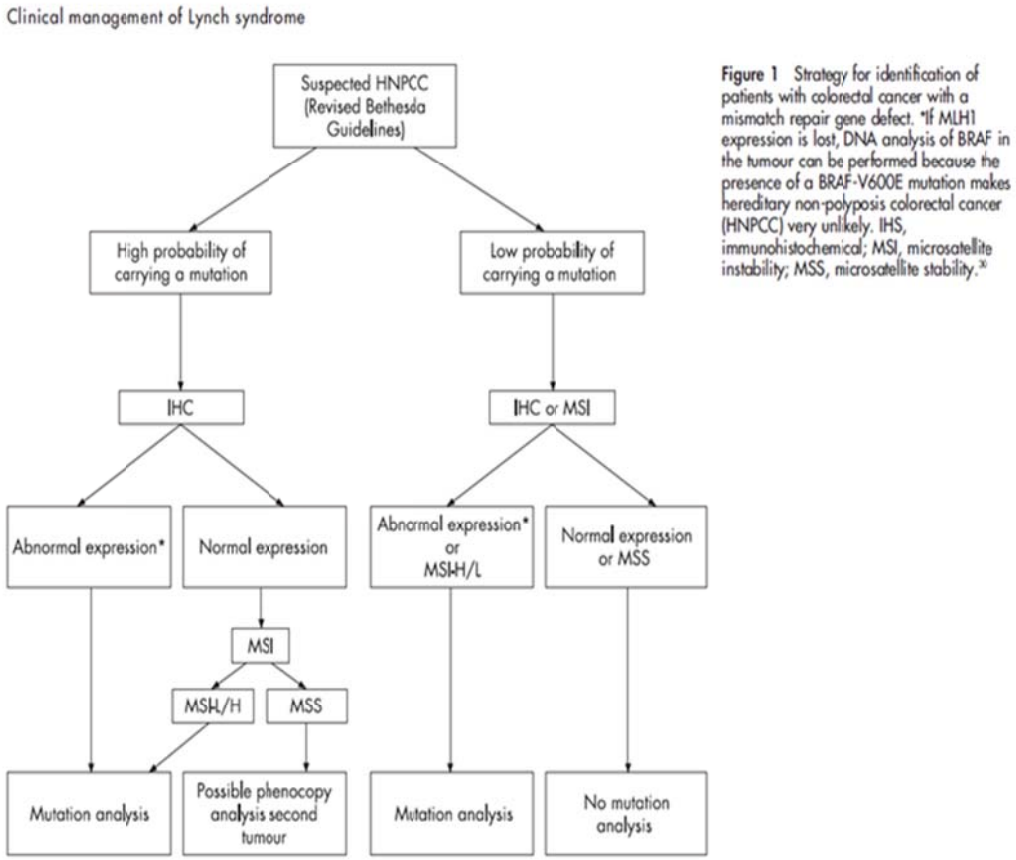


Figure 1 Strategy for identification of patients with colorectal cancer with a mismatch repair gene defect. *If MLH1 expression is lost, DNA analysis of BRAF in the tumour can be performed because the presence of a BRAF-V600E mutation makes hereditary non-polyposis colorectal cancer (HNPCC) very unlikely. IHS, immunohistochemical; MSI, microsatellite instability; MSS, microsatellite stability.*

Table 3 Amsterdam criteria. Vasen FAH et al WWW.jmedgenet.com 2007

Table 3 Amsterdam I and Amsterdam II criteria, and Bethesda guidelines

Amsterdam I criteria:

- At least 3 relatives with histologically verified colorectal cancer:
  1. One is a first-degree relative of the other two;
  2. At least two successive generations affected;
  3. At least one of the relatives with colorectal cancer diagnosed at <50 years. of age;
  4. familial adenomatous polyposis has been excluded.

Amsterdam II criteria:

- At least 3 relatives with an hereditary nonpolyposis colorectal cancer-associated cancer (colorectal cancer, endometrial, stomach, ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract, and skin [sebaceous tumors]):
  1. One is a first-degree relative of the other two;
  2. At least two successive generations affected;
  3. At least one of the hereditary nonpolyposis colorectal cancer-associated cancers should be diagnosed at <50 years. of age;
  4. familial adenomatous polyposis should be excluded in any colorectal cancer cases;

Tumors should be verified whenever possible.

Bethesda Guidelines for testing of colorectal tumors for microsatellite instability:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumors,[a] regardless of age.
3. Colorectal cancer with the MSI-H[b] histology[c] diagnosed in a patient who is less than 60 years of age.[d]
4. Colorectal cancer or HNPCC-associated tumor[a] diagnosed under age 50 years in at least one first-degree relative.[e]
5. Colorectal cancer or HNPCC-associated tumor[a] diagnosed at any age in two first- or second-degree relatives.[e]

[a] Hereditary nonpolyposis colorectal cancer (HNPCC)-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and kerato-acanthomas in Muir–Torre syndrome, and carcinoma of the small bowel

[b] MSI-H = microsatellite instability-high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers

[c] Presence of tumor infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern

[d] There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines

[e] Criteria 4 and 5 have been reworded to clarify the Revised Bethesda Guidelines

5 Management of localized rectal cancer

Localized rectal (cT1-2 N0 crm-) cancers should be treated upfront with either local excision or transabdominal resection (+/-TME). The extent of surgery should be as minimal as possible to maintain function and therefore quality of life. Preoperative treatment with radiotherapy either combined with chemotherapy or not is the standard of care for locally advanced tumours in the lower and middle rectum. Postoperative chemoradiation is reserved for those patients who did not receive preoperative treatment and are at high risk for relapse (stage II/III). Preoperative treatment has to be administered to patients with ≥cT3 and/or N+ disease. Adjuvant chemotherapy should be considered for all patients with high risk characteristics.

5.1 Patient classification for defining treatment strategy

Rectal cancers can be divided into four groups: very early (some cT1), early (cT1–2, some cT3), more advanced (cT3, some cT4) and locally advanced (cT4). Factors other than clinical T-stage, such as tumour height, closeness to the CRM, cN-stage, and vascular and nerve invasion are also relevant. It is presently not possible to give a precise definition of which T and N substages belong to these groups.

The terms ‘favourable or early or good’, ‘intermediate or bad’ and ‘locally advanced or ugly’ can be used for categorizing the rectal cancers into these clinical subgroups. In clinical practice and in many recent studies, the term ‘locally advanced’ has been commonly used for the ‘intermediate/bad’ group, but is best reserved for the truly ‘locally advanced/ugly’ tumours?

Accurate staging is required to determine the need for neoadjuvant therapy or an enhanced surgical procedure. The MERCURY study showed the accuracy, feasibility and reproducibility of MRI in staging rectal cancer. MRI can be used to stratify patients with high accuracy according to TNM and other adverse prognostic factors related to locally advanced rectal cancer and consequently, to target preoperative therapies [MERCURY, 2007]. Most importantly MRI can guide the surgeon to the appropriate plane of excision, in order to obtain a clear resection margin, by providing ‘a road map’ of tumor extension along anatomical structures of the pelvis.

Despite variation in the use of preoperative treatment, there is wide agreement that all patients with potential CRM involvement on MRI should be offered preoperative

chemoradiotherapy because preoperative discussion of MR images in MDT meetings and implementation of this treatment program has led to a decrease in margin positivity rates [Burton et al., 2006]Defined as tumour within 1mm of the mesorectal fascia or T2 tumour arising from below the level of the origin of the levator muscles [Burton et al., 2006].

Treatment stratification of this study was based on evidence of:

a. Five-year survival rates of 85% for rectal cancer patients with T3 tumours < 5mm depth of extramural spread vs 54% survival for cases with T3 >5mm spread [Merkel et al., 2001].

b. Peritoneal involvement is a known poor prognostic factor for rectal cancers [Shepherd et al., 1995].

c. Increasing percentage of nodal disease reduces overall survival in colorectal cancer [Stocchi et al., 2001].

d. EMV has been shown to be an independent poor prognostic factor in colorectal cancer [Conroy et al., 1994].

The CRM positive rate is reducible, but only in the presence of robust MRI staging, preoperative MDT discussion of all the staging investigations, optimal surgery, availability of effective preoperative therapies and standardised histopathology reporting with comprehensive data [Burton et al., 2006].

Recommendations

→ ***For treatment decision, patients should be classified beyond clinical stage TNM and UICC into the following three groups very early (some cT1sm1), early (cT1–2, cT3a/b), locally advanced (cT3c/d/T4 and/or N+)***

5.2 Preoperative treatment

Aim of preoperative treatment is reduction of risk for local relapse, improvement of resectability in terms of function, in particular in low located tumours or enabling R0 resection in crm+ disease.

Recommendations

→ ***Preoperative treatment is recommended in locally advanced tumours (≥cT3, CRM+, emvi and/or N+).***

Radiotherapy

Preoperative treatment options for rectal cancer include radiotherapy alone (short course RT) or a combination of RT with chemotherapy (long course CRT). The potential advantages of preoperative treatment are, potential down-staging and down-sizing, prevention of tumour cell seeding, and increased tumour radio-sensitivity resulting from increased tumour cell oxygenation and decreased toxicity, as compared to postoperative CRT [Sauer et al., 2004]. The main disadvantage of preoperative CRT is overtreatment of patients with early disease (T1-2, N0) as a result of up-staging by conventional imaging modalities. In the German trial [Sauer et al., 2004] 18% of patients who were randomized to receive postoperative CRT and were initially staged to have locally advanced tumors were found to have stage I disease. However, with the implication of endorectal ultrasound and high-resolution phased-array magnetic resonance imaging (MRI), this disadvantage has gradually become of less importance due to the improved accuracy of the evaluation of the local extent of the disease [Valentini et al., 2005]. Moreover MRI evaluates accurately possible involvement of the circumferential resection margin (CRM) [Beets-Tan et al., 2001;Bipat et al., 2004;MERCURY, 2007].

5.2.1 Short course radiotherapy (5x5Gy)

More than 15 randomized studies have evaluated the effectiveness of preoperative RT alone in patients with resectable rectal cancer. In all of these trials moderate RT doses were applied and in most an improvement of local disease control has been shown [Valentini et al., 2005]. Three meta-analyses show that preoperative RT results in a significant decrease in local recurrence at biologically effective doses above 30 Gy. However, results on survival are conflicting [Camma et al., 2000;Colorectal Cancer Collaborative Group, 2001].

The studies that established short course preoperative RT (5x5Gy) are the ones by Folkesson et al [Folkesson et al., 2005] and Kapiteijn et al [Kapiteijn et al., 2001].

Both studies show statistically significant improvements in local control with the addition of RT versus surgery alone. Moreover the Swedish trial [Folkesson et al., 2005] showed a survival benefit that may have been the result of suboptimal surgery that did not implement total mesorectal excision (TME) of the rectum [Folkesson et al., 2005]. It should also be noted that subgroup analysis of the two studies showed that preoperative RT is more effective in patients with stage II and III tumours located in the mid-low rectum and in cases with an uninvolved CRM [Folkesson et al., 2005;Kapiteijn et al., 2001;Marijnen et al., 2003;Peeters et al., 2007].

In a more recent multicentre trial carried out in the UK (MRC CR 07) [Sebag-Montefiore et al., 2009], rectal cancer patients with stage I-III disease were randomized to either receive preoperative short course RT (5x5Gy) followed by TME or TME and selective postoperative CRT in the event of a threatened CRM (<1mm). In this trial a reduction of 61% in the relative risk of local recurrence for patients receiving preoperative RT was seen. Moreover there was a statistically significant improvement in the disease free survival by 24% for the same group of patients. There was however no difference in the overall survival between the two groups.

Preoperative short course RT is administered in five consecutive days up to a total dose of 25Gy (5Gy per fraction). Surgery should take place within one week from the completion of RT [Kapiteijn et al., 2001;Marijnen et al., 2003;Peeters et al., 2007;Sebag-Montefiore et al., 2009]. Due to the short time interval between surgery and RT, no tumor downsizing/staging is expected and therefore short course RT should not be used in cases with a CRM involvement or T4 disease.

Two studies have compared preoperative RT versus long course CRT (5FU based chemotherapy). In the first study [Bujko et al., 2006] patients with resectable T3 or T4 rectal cancer were included, and it was shown that both treatment schemes have similar effectiveness in terms of 4-year survival (67,2% in the RT group versus 66,2% in the CRT group), disease free survival (58,4% versus 55,6% respectively) and local recurrence (9% versus 14.2% respectively). Early toxicity was significantly higher in the CRT group, whereas late toxicity rates between the two groups were comparable.

In the second study by Broendengen et al [16], patients with non resectable rectal cancer received either RT or CRT [Braendengen et al., 2008]. It was shown that CRT was significantly more effective than RT alone in terms of local control (82% versus

67% at 5 years, p=0.03), time to treatment failure (63% versus 44%, p=0.003), cancer specific survival (72%versus 55%, p=0.02) and overall survival (66% versus 53%, p=0.09). Acute toxicity was significantly higher in the CRT group.

RECOMMENDATIONS

- ***Short course RT is effective for resectable rectal tumors with no CRM involvement, where down-sizing is not necessary. Moreover it is more cost effective and time saving as compared to CRT (Evidence level 1, Recommendation A).***
- ***CRT is superior to RT in rectal tumors, where down-sizing and down-staging is necessary (Evidence level 1, Recommendation A).***

5.2.2 LONG-COURSE PREOPERATIVE CRT

Preoperative long course radio-chemotherapy is recommended for locally advanced rectal tumors (cT3-T4 or N+) for which downsizing is desired prior to surgery [Sauer et al., 2004;Valentini et al., 2005]. Long-course preoperative CRT has proved to be equally effective to preoperative RT for patients with resectable rectal cancers in terms of local control and survival [Bujko et al., 2006] but superior to RT in patients with non resectable rectal disease [Braendengen et al., 2008]. It should be noted that an accurate MRI staging may allow a selection of patients with early stage III disease (stage T3a/b) for whom preoperative treatment may not be necessary [Taylor et al., 2011].

The study that established preoperative CRT over postoperative CRT is that by Sauer et al, in which patients with locally advanced rectal tumors (cT3-4, or N+) received either pre-or post-operative CRT [Sauer et al., 2004]. It was shown that preoperative CRT had a significantly decreased local recurrence rate (6% versus 13%, p=0.006) and a significantly decreased rate of both acute (p=0.001) and long term toxicity (p=0.01) [Sauer et al., 2004].

During long-course preoperative CRT a total irradiation dose of 45-46Gy is delivered to the clinical target volume (CTV) (1.8-2.0Gy per fraction). A boost to the gross tumor volume (GTV) can be administrated up to a total dose of 50.4Gy. Higher doses

may be associated with an improved local control but there is a considerable risk for higher complication and toxicity rates. Surgery should follow 6-8 weeks after completion of CRT.

Intraoperative radiotherapy (IORT) up to 10-20Gy can be delivered in a single dose in unresectable or recurrent tumors in order to improve local control [Valentini et al., 2005]. Even though IORT studies show a favorable effect for unresectable patients, the results for recurrent cases are conflicting [Valentini et al., 2005]. In this technique, uninvolved and dose limiting tissues/organs are displaced before irradiation.

In long course CRT, RT can be combined with fluoropirimidines/LV. The following options are available:

5-FU 350mg/m^2 + LV 20mg/m2 d1-5 (Bolus), week 1 and 5

5-FU 1000mg/m^2 d1-5 (CI), week 1 and 5

Capecitabine 850 mg/m^2, twice daily, d1-5

Combination of RT with chemotherapeutics other than fluoropyrimidines or targeted agents should be done only in the context of clinical studies, as early data show no benefit and results from large studies are awaited.

RECOMMENDATIONS

- ***For long term CRT the recommended dose to the CTV is 45-46Gy (1.8-2.0 Gy fractions). A boost to the GTV up to 50.4Gy may be administered. Surgery should follow 6-8 weeks after completion of CRT (LOE I, SOR A).***
- ***Preoperative long-course CRT should be offered to ≥CT3 or N+ rectal tumours or when extramural venous invasion (emvi) is detected.It may be also considered for T2 tumors of the lower rectum (LOE I, SOR A).***
- ***Long-course CRT is the treatment of choice for patients with non resectable rectal cancer or a positive CRM (LOE I, SOR A).***
- ***Preoperative CRT may be omitted in good prognosis patients staged by high resolution magnetic resonance imaging as cT2, T3a/T3b, N0 (LOE II, SOR B).***
- ***For chemotherapy administration during RT either 5FU/LV bolus, 5FU infusion or capecitabine can be used. Combination of RT with chemotherapeutics other than fluoropirimidins or targeted agents should be done only in the context of clinical studies.***

- ***Combination chemotherapy is experimental and cannot be used outside of ongoing clinical trials. Use of targeted agents is not indicated in the neoadjuvant or adjuvant setting.***

5.3 POSTOPERATIVE CRT

Postoperative CRT achieves significant reduction in local recurrence rates after curative resection [Colorectal Cancer Collaborative Group, 2001]. Moreover in 1990 the NCI consensus conference [NIH Consensus, 1990] (analysis of the postoperative North-American chemoradiotherapy studies), it was stated that CRT should be the standard of care for patients with pT3 and/or pN+ disease.

However as already discussed, the German trial [Sauer et al., 2004] showed that preoperative CRT is superior to postoperative CRT both in terms of local control and rates of acute and late toxicity. The recommended dose is 45Gy in 25 fractions to the clinical target volume and a boost of 5,4Gy in 3 fractions to the tumor bed. Fluoropyrimidine based chemotherapy must be administered concurrently. Postoperative CRT should be performed at least 6 weeks after surgery.

RECOMMENDATIONS

- ***Preoperative CRT with concurrent fluoropurimidine-based chemotherapy is superior to postoperative CRT (LOE I, SOR A).***
- ***Post operative CRT must be administed in patients with pT3 or N+ rectal cancers or in cases with positive CRM, perforation in the tumour area or in other cases with high risk of local recurrence. This is only possible in cases where preoperative CRT has not been offered (LOE I, SOR A).***
- ***Patients after local resection of pT1 tumours with adverse factors (involved margins, poor differentiation, SM3 and lymphovascular invasion) or pT2, are at a higher risk of local recurrence and should be offered resectional surgery. Otherwise, adjuvant treatment is indicated (LOE I, SOR A).***

5.4 VOLUMES AND DOSES

The clinical target volume should include the tumour or tumour bed with a 2-5cm margin, the internal iliac nodes upto S1-S2 and the mesorectal lymph nodes. The total dose should be 45-46Gy (1.8-2.0 Gy per fraction).

If the tumour is located >10cm from the anal margin, the obturator nodes can be excluded.

A boost to the tumour bed or GTV with a 2cm margin up to 5.4Gy in 3 fractions is also recommended.

Additional to mesorectal nodes, presacral nodes along to S1-2 level should be included.

External iliac nodes should only be included if an anterior pelvic organ, such as urinary bladder, prostate or female sexual organs are involved.

Fossae ischiorectalis should only be included when the levator muscles and the internal and external sphincters are involved.

The medial inguinal nodes need to be included only when the tumour grows at or below the dentate line.

After abdominoperitoneal resection the perineal wound (scar) should be irradiated as well.

5.4.1 Chemoradiation

Standard preoperative CRT means a dose of 46–50.4 Gy together with 5FU given either as bolus injections with leucovorin at 6–10 times during the radiation (as in the trials proving that CRT provides better local control than the same RT alone), prolonged continuous infusion (likely better than bolus) or oral capecitabine or uracil–tegafur(UFT). The NSABP trial compared 5-FU/LV with capecitabine in the adjuvant setting, giving definitive answers regarding the non inferiority of capecitabine.

- Chemotherapy options for concomitant chemoradiation are:
    - 5-FU 350mg/m2 + LV 20mg/m2 d1-5 (Bolus), week 1 and 5 (EORTC trial)
    - 5-FU 1000mg/m2 d1-5 (CI), week 1 and 5 (CAO/ARO/AIO-94 trial)

- Capecitabine 1650mg/m2 d1-33, 5 days per week, together with radiotherapy (PETACC 6)

- Combination with oxaliplatin or irinotecan have been investigated in phase II and III trials with respect to local response. Despite early promising results for 5-FU/oxaliplatin or capecitabine/oxaliplatin, local complete pathological response is not increased compared to fluoropyrimidines alone. However, the more important results regarding local and distant relapse are pending (data 2011-2013, four large trials). Therefore CRT with fluoropyrimdines alone remains the standard of care. Based on the NSABP trial preliminary data (comparing 5-FU and capecitabine) for practical/logistic reasons capecitabine should/could be preferred.

- Combination with targeted agents (bevacizumab, cetuximab) is still highly investigational. Early promising data have been seen from the addition of bevacizumab, but disappointing results for cetuximab/panitumumab, indicating a potential negative interaction with chemotherapy. Outside clinical trials, targeted drugs should not be used in combination with radiation.

Recommendations

→ ***For long term radio(chemo)therapy the recommended dose is 46 Gy. In large tumours, a boost (GTV) up to a total dose of 55.4 Gy can be administered.***

→ ***For chemotherapy administered concurrently with radiotherapy either 5-FU/LV bolus, 5-FU infusion or capecitabine must be used. Combination chemotherapy is experimental and may not be used out of ongoing clinical trials. Use of targeted agents is not indicated in the setting of neo-adjuvant treatment.***

5.5 Choice of preoperative treatment

Treatment options are radiotherapy alone either short or long course of chemoradiation. The advantage of short course radiation is the short preoperative

treatment phase in comparison to long term radio(chemo)therapy; the disadvantage is, that downsizing of the primary cannot occur if surgery is performed 2-3 days after radiation, however recently it has been shown that after short course radiotherapy downsizing can be expected if surgery is delayed until 6-8 weeks. It should be noted that this approach is still experimental (ongoing trial in the Nordic Group). If long term radiation is used together with concomitant chemotherapy, there is a higher chance for downsizing, improved respectability, potentially maintaining bowel function in case of low located tumours, and reduced relapse rate. Therefore, short course radiotherapy and chemoradiation are equivalent in those tumours where downsizing is not necessary. However, short course is much easier and more cost effective. For low and large tumours and locally advanced tumours (e.g. CRM+) chemoradiation is mandatory.

Recommendations

- → ***Short course radiotherapy is efficatious for tumours where downsizing is not necessary, and more cost effective and time saving.***
- → ***Pre-operative fluoropyrimidine based chemoradiation is recommended for some cT3 or crm+ or cT4 and might be considered for ≥cT2 tumours of the lower rectum.***

5.6 Pre- vs postoperative chemoradiation

It has been shown (CAO/ARO/AIO-94 trial) that preoperative chemoradiation followed by adjuvant chemotherapy compared to postoperative adjuvant chemoradiation significantly reduces local recurrence, has less acute and long term toxicity and in addition enables a higher rate of sphincter saving surgery by downsizing and thus improves functional outcome in low located tumours. However, distant relapse rate and overall survival were similar for both approaches.Preoperative chemoradiation is the treatment of choice for all patients at higher risk for relapse considered for chemoradiation (clinical stage II/III).

Recommendations

→ ***Preoperative chemoradiation is the standard treatment. Postoperative adjuvant chemoradiation is indicated whenever i) there is an increased risk of local recurrence following surgery and ii) neo-adjuvant treatment was indicated but not given.***

5.7 New concepts

Chemotherapy +/- preoperative chemoradiation is an investigational but highly effective approach. In locally advanced tumours the value of upfront induction chemotherapy +/- targeted drugs followed by local treatment with chemoradiation and subsequent surgery and adjuvant chemotherapy is currently investigated.

As a step further, for patients with limited tumours (T3 crm-) combination chemotherapy with FOLFOX+bevacizumab, however without chemoradiation, achieved a pCR-Rate of 27%. Both approaches are still investigational.

Recommendations

→ ***Induction combination chemotherapy before definitive local treatment (radiotherapy amd surgery) in patients without distant metastases and R0 resectable primary tumour (after preoperative treatment) should not be given out of a clinical trial. This approach is still experimental.***

→ ***Induction chemotherapy as front line treatment (e.g. FOLFOX bevacizumab) and single modality before surgery, without local radio (chemo)therapy may not be given out of a clincial trial.***

6 Rectal Cancer: Definitive local treatment (surgery)

6.1 RESECTABLE NON-OBSTRUCTING LESION

6.1.1 GENERAL CONSIDERATIONS

Because oncological outcomes strongly depend on accurate diagnosis, staging and pursuing of the optimal therapeutic strategies, patients with rectal cancer should be treated in specialized centers with high volume of referred cases and by a multidisciplinary team which involves surgeons, histopathologist, radiologists, medical and radiation oncologists.

Prioperative assessment of the general condition and base-line tumor markers, as well as preparation of the patient, is similar to that for colon cancer (see in colon cancer chapter). Although bowel mechanical preparation prior to surgery is not recommended in resections of the colon with primary anastomosis, in rectal cancer cases where resection of the rectum with low colo-anal anastomosis is planned to be covered by a defunctioning stoma, bowel cleansing is recommended.

There is substantial evidence that application of enhanced recovery programmes in rectal cancer surgery is associated with reduced stress, reduced duration of postoperative ileus, better physical performance, less morbidity and faster recovery [Delaney et al., 2003;Gouvas et al., 2009a]. Although limited, there is also evidence that enhanced recovery programmes work with laparoscopy in rectal cancer surgery, similarly offering faster recovery and better outcomes [King et al., 2006;Schwenk et al., 2006]. Therefore, implementation of “fast-track” is strongly recommended in rectal cancer surgery.

RECOMMENDATIONS

- ***Patients with rectal cancer should be treated in specialized centers by a multi-disciplinary team (MDT)***
- ***Bowel mechanical preparation is recommended if a diverting stoma is planned (SOR C).***
- ***Implementation of enhanced recovery programmes should be enhanced (LOE II, SOR B).***

6.1.2 SURGICAL TREATMENT

Transabdominal resection of the rectum is the standard treatment of rectal cancer. A large range of surgical procedures aiming to cure rectal cancer is applied. The exact type of procedure depends on the location and histological characteristics of the tumor. In any case surgical resection should be curative (R0). It is of paramount importance to locate exactly the position of the tumor (distance form anal verge - anterior, lateral or posterior location), and this is achieved with rigid proctoscopy. The procedures available include high anterior resection of the rectum (HARR), lower anterior resection of the rectum (LARR), ultra-LARR, intersphincteric resection of the rectum (IS-LARR), different types of abdominoperineal resection of the rectum (APR) and local excision of the tumour (open transanal or transanal endoscopic microsurgery-TEM).

In case of neo-adjuvant treatment in the form of short course radiotherapy, the time interval of surgery is 1-2 weeks [Bujko et al., 2006;Folkesson et al., 2005;Kapiteijn et al., 2001]. Following a long course of chemoradiotherapy, the exact time interval to surgery has not been defined, and varies from 6 to 12 weeks [Bosset et al., 2006;Sauer et al., 2004]. This depends on the grade of tumour response to neo-adjuvant treatment. Even if a complete response is detected on pelvic MRI at 6 weeks after the end of treatment, this should be followed by resection of the rectum. Deferral of surgery in case of complete response is only allowed within the frame of a research protocol (“wait and watch” policy).

- ***Transabdominal resection is the standard treatment irrespective of stage of tumour. Resectional surgery should be curative (R0) (SOR A).***
- ***The type of surgery depends on the exact tumour location (SOR A).***
- ***The interval between the end of neo-adjuvant short course of radiation and surgery is 1-2 weeks (LOE I, SOR A).***
- ***The interval between the end of neo-adjuvant chemoradiation treatment and surgery varies between 6 and 12 weeks, depending on the grade of response (LOE II, SOR B).***

- ***In cases of complete response to neo-adjuvant treatment, as assessed by high resolution MRI 4-6 weeks after end of treatment, transabdominal resection is again the standard treatment. Deferral of surgery and "wait and watch policy" could be followed only within the context of research protocols.***

TRANSABDOMINAL RESECTION - SURGICAL PRINCIPLES

The surgical principles of radical transabdominal resection for rectal cancer include: central ligation and division of the inferior mesenteric artery (IMA), ligation and division of the inferior mesenteric vein (IMV) just below the pancreas, mobilization of the splenic flexure if necessary, and total mesorectal excision (TME) which involves en bloc removal of the package of the rectum and mesorectum covered by their intact embryologic envelop, that is the posterior mesorectal fascia and the Denonvillier' s fascia. This is achieved by sharp dissection in the well confined embryological planes and by preserving the autonomic pelvic nerve plexuses [Heald et al., 1982;Heald et al., 2004]. The macroscopic assessment of the quality of the resected specimen according to specific definitions [Nagtegaal et al., 2002b;Nagtegaal et al., 2002a;Quirke et al., 1986] is mandatory. A complete TME specimen with intact fasciae and no coning towards the bowel wall (intramesorectal or muscularis dissection) is a strong positive prognostic factor of local recurrence prevention [Quirke et al., 2009], as is the negative by 1-2mm circumferential resection margin (CRM) [Nagtegaal et al., 2002a]. The distal to the tumor transsection of the rectum is achieved either transabdominally or transanally, and the colo-anal anastomosis is fashioned with the use of a circular stapling device or by hand respectively.

A temporary defunctioning stoma to protect the anastomosis is strongly recomended, particularly in case of a very low colo-anal anastomosis, an anastomosis in the obese male patient, and after neo-adjuvant treatment [Huser et al., 2008;Tan et al., 2009b]. Defunctioning stoma can be closed 3 to 6 months later, provided anastomosis is complete and leak is not identified by proctoscopy or double contrast imaging.

UPPER THIRD OF RECTUM

For tumors located at the upper third of the rectum and the rectosigmoid junction a high anterior resection of (HARR) is recommended. The procedure involves the aforementioned described central to the tumor dissection of the bowel and a clear distal margin of transection of at least 5cm. TME is recommended, although partial mesorectal excision (PME) is an alternative option. A stapled colo-rectal anastomosis is preferable. A diverting stoma is also recommended in case of neo-adjuvant chemo-radiation.

MIDDLE THIRD OF RECTUM

For tumors located in the middle rectum (6-10cm from the anal verge) the low anterior resection of rectum (LARR) with TME, and preservation of the pelvic nerve plexuses is indicated. A clear distal bowel margin of at least 1cm is required. A stapled colo-rectal anastomosis is preferable. A diverting stoma is also recommended invariably.

LOWER THIRD OF RECTUM

For T1, N0 tumors or T2-3, N0 subjected and responding to neo-adjuvant treatment and in which a distal bowel clearance >1cm does not involve a major part of the external anal sphincter, a LARR with TME and intersphincteric distal dissection with hand-sewn colo-anal anastomosis is recommended [Han et al., 2009;Tilney and Tekkis, 2008;Yamada et al., 2009]. For those cases with the above tumor characteristics, but in whom a colo-anal anastomosis is expected to be associated with poor functional results, an intersphincteric abdominoperineal resection of rectum (APR) is recommended [Hohenberger et al., 2006].

For low rectal tumors in which distal bowel clearance of >1cm involves the major part of the external anal sphincter, an abdominoperineal resection of the rectum (APR) is indicated. Recent data from the Swedish registry [Pahlman et al., 2007] and a review [den Dulk M. et al., 2009] show that standard APR for T3,4 rectal cancers is associated with higher local recurrence rate and a worse overall survival as compared to LARR. This difference could be at first attributed to the fact that patients subjected to APR have tumors that are more advanced and exhibit different patterns of recurrence [Kusters et al., 2010;Shirouzu and Ogata, 2009]. However, it is supported that standard APR achieves a suboptimal resected specimen with commonly threatened CRM at the level of the levator ani, and that this translates to increased recurrence rates [Shihab et al., 2010]. For this reason a more extended form of APR

is recommended: the so called “extralevator” or “cylindrical” APR [Holm et al., 2007] by which a complete resected specimen is acquired [West et al., 2010a]. The procedure is completed with a terminal colostomy.

It has been hypothesized that the increased local recurrence after APR for low rectal cancer is the result of lateral, in addition to the upward, lymphatic drainage. On the contrary, upward lymphatic drainage characterizes rectal tumors located at the middle and upper rectum [Steup et al., 2002]. For this reason, an extended lateral pelvic lymphadenectomy in addition to TME is advocated. However, a recent meta-analysis showed no difference in recurrence and survival rates between extended lymphadenectomy and standard TME for low rectal cancer. Moreover, the former procedure is associated with higher rate of urinary and sexual dysfunction [Georgiou et al., 2009]. Lateral lymphadenectomy should be only preserved for those with obviously involved lateral pelvic nodes.

RECOMMENDATIONS

- ***The main principles of curative surgery include i) central ligation of inferior mesenteric artery (IMA), ii) resection of the sigmoid colon and iii) dissection of rectum and mesorectum along their embryological planes (fasciae propriae), thus achieving a total mesorectal excision (TME) (LOE III).***
- ***For tumours of the upper third of rectum, a high anterior resection of the rectum (HARR) with a partial (PME) or total (TME) mesorectal excision and a distal clear bowel margin of at least 5cm are indicated. Addition of a diverting stoma in case of neo-adjuvant chemo-radiation is recommended (LOE I).***
- ***For tumours of the middle third of rectum a low anterior resection of the rectum (LARR) with TME and a distal clear bowel margin of at least 1cm are recommended. Pelvic nerve plexuses should be preserved during dissection. Fashioning of a stapled anastomosis, if technically feasible, is preferable. Pull-through technique and hand-sewn anastomosis is an alternative technique. Addition of a diverting stoma is mandatory in all cases (LOE I).***
- ***For tumours of the lower third of rectum in which distal bowel clearance of at least 1cm involves removal of the major part of the external anal sphincter, the abdominoperineal resection of the rectum (APR) with TME and***

permanent colostomy is recommended. The cylindrical type or extralevator APR instead of the standard APR which results to a specimen waist at the level of puborectalis muscle and impaired CRM is also recommended (LOE III).

- ***For tumours of the lower third of rectum in which distal bowel clearance of at least 1cm does not involve the external anal sphincter, an intersphincteric LARR with TME, stapled or hand-sewn anastomosis and covering stoma are recommended (LOE I).***
- ***For very low T1-3 tumours of the rectum in which distal bowel clearance of at least 1cm does not involve the external anal sphincter, ultra-low intersphincteric LARR with TME after neo-adjuvant chemo-radiation is recommended. A stapled colo-anal or transanal colo-anal hand-sewn anastomosis and a diverting stoma complete the procedure (LOE II).***

LAPAROSCOPIC-ASSISTED COLECTOMY

Unlike colon cancer, evidence on the laparoscopic approach for the surgical treatment of rectal cancer is at present limited. According to one multicenter "CLASICC" trial [Guillou et al., 2005;Jayne et al., 2007] and three meta-analyses of studies of limited quality [Aziz et al., 2006;Breukink et al., 2006;Ma et al., 2010], laparoscopic TME is as safe and effective as the open approach, both in terms of immediate postoperative outcomes and of oncological results. Moreover, laparoscopy is associated with faster recovery [Gouvas et al., 2009c]. Also, quality of surgery and acquired specimen is comparable between the two approaches [Gouvas et al., 2009b;Pechlivanides et al., 2007].

However, specific to the laparoscopic approach are some technical problems. Dissection of the rectum in obese male patients is problematic because of limited view deep into the pelvis. Also, transection of the rectum distal to the tumor upon the pelvic aspect of the levator ani and a stapled colo-anal anastomosis are technically difficult, particularly in the obese male patient. These difficulties translate to increased conversion and anastomotic leak rates as compared to the open approach [Laurent et al., 2007]. For the above reasons, laparoscopic TME surgery for rectal cancer should

only be performed by experienced surgical groups and at present within the frame of research protocols.

- ***The laparoscopic approach for the surgical treatment of rectal cancer should be strictly performed by a very experienced surgical team. The principles of resection are the same as in the open approach. The approach is contraindicated in locally advanced, perforating or obstructing tumours (LOE II).***
- ***Predicting factors for conversion to open should be identified preoperatively, because under specific circumstances conversion may be associated with impaired short- and long- term outcomes (LOE II).***
- ***Obesity and male sex are factors associated with increased conversion and morbidity as a result of technical difficulties with distal transection of the rectum and stapled anastomosis. In these cases alternative techniques such as hybrid laparoscopic-open approach or transanal transection and hand-sewn anastomosis are recommended (LOE III).***

Transanal excision is recommended for T1, N0-x or T2, N0-x lesions, the latter after neo-adjuvant chemoradiation, that are small (<3cm), involve less than 30 percent of the lumen circumference, and are preferably located laterally or posteriorly and within 8cm from the anal verge. With the application of transanal endoscopic microsurgery (TEM), even tumors located higher than 8cm from the anal verge can be resected successfully. Local excision should be of full thickness and perpendicular to the rectal wall, including adjacent perirectal fat with clear rectal wall and fat margins of at least 3mm. It is important to orient the specimen and fix it on a cork board prior to be sent to the pathology department. If pathologic examination shows positive margins, poor tumor differentiation, perineural invasion, extramural vein invasion or lymphovascular invasion, a transabdominal radical resection is recommended.

Transanal excision carries the advantages of sphincter preservation, minimal morbidity, no mortality and fast recovery [Middleton et al., 2005]. The disadvantage of the procedure is lack of pathological staging of regional lymph nodes and lack of information about lymph node micrometastases that tend to be more common in early

lesions [Landmann et al., 2007]. As far as long-term oncological results are concerned, reports from studies of rather poor quality are conflicting. Some authors claim that local excision of T1, N0 tumors and T2,N0 after neo-adjuvant treatment is associated with recurrence rate similar to radical resection [Borschitz et al., 2008;Duek et al., 2008;Lezoche et al., 2005]. Opposite are the results reported by others [Nash et al., 2009], who showed a recurrence rate of 13.2 percent after local excision as compared to 2.7 percent after radical resection in 282 patients with T1 rectal tumor. They also found a 20 percent nodal involvement in patients subjected to radical resection. These results depict the inability to accurately stage the disease after local excision. Waiting for the results of several ongoing trials which test the oncological safety of local excision, the procedure is not recommended even for T1, with exception of patients who refuse a radical resection or those with a poor general condition [Suppiah et al., 2008].

RECOMMENDATION

- ***In patients with cT1 tumors with microscopic characteristics of good prognosis refusing transabdominal surgery, transanal resection or TEM could be considered (LOE III).***

6.2 RECURRENT RECTAL CANCER

After introduction of neo-adjuvant treatment and implementation of TME with clear circumferential resection margin (CRM), local recurrence of rectal cancer dropped from around 30 percent to below 10 percent [Heriot and Kumar, 2000].

Predictive factors for local recurrence of rectal cancer are a surgeon's experience to perform TME and adequate volume of cases, completeness of TME with clear CRM and distal margin, and specific tumour characteristics such as differentiation and lymphatic invasion [Birbeck et al., 2002;Dent et al., 2007;Heald et al., 1982;Moore et al., 2003;Nagtegaal et al., 2002a;Stocchi et al., 2001;Tilney and Tekkis, 2008]. History, physical examination and increase in CEA raise suspicion for local recurrence which is confirmed by imaging of the pelvis (CT, MRI, PET/CT) and positive biopsy of the mass [Mirnezami et al., 2010].

Only fit patients should be subjected to further investigation for the assessment of local extent of the disease and the identification of possible distant recurrence. This procedure should be undertaken only by a multidisciplinary team in highly specialized referral centres [Dresen et al., 2008;Tilney and Tekkis, 2008]. There are several classifications of recurrent rectal cancer based on imaging. The one proposed by the panel is that of the Memorial Sloan Kattering Group [Moore et al., 2004], according to which local recurrence is classified as central-axial (anastomotic, mesorectal, perineal), anterior (involvement of genitourinary pelvic system), posterior involvement of presacral fascia and sacrum and lateral (involvement of lateral pelvic soft tissues, and lateral osseous pelvis).

If neo-adjuvant treatment has not been given at primary surgery, it should be administered prior to attempting resection of recurrent disease. Even if neo-adjuvant treatment has been given at primary surgery, an additional 30-40Gy could be administered [Glimelius, 2003]. Also, if available, intraoperative radiation of the pelvis can be considered [Haddock et al., 2001].

The only curative treatment of locally recurrent rectal cancer is a complete R0 resection which is possible in less than 50 percent of the cases. The surgical team should include colorectal surgeons, orthopaedic spine surgeon, surgeon of the genitourinary system and plastic surgeons. Absolute contraindications for resection are involvement of the external ileac vessels, tumour extention to the sciatic notch, oedema of the lower limb resulting from venous or lymphatic occlusion and poor general status of the patient. Relative contraindications for resection are distant metastasis, primary stage IV disease, extensive involvement of the lateral pelvic wall, tumour extension to S2 vertebra and above and predicted R1 or R2 resection [Mirnezami et al., 2010]. Chemotherapy after curative surgery is recommended, although there is no sound evidence. Immediate postoperative morbidity and mortality are 15-80 percent and 0-8 percent, respectively. After R0 resection, five-year survival rates are reportedly around 35 percent [Dresen et al., 2008].

In inoperable recurrent rectal cancer the therapeutic target is palliation. Palliative surgery is not recommended, as it carries increased morbidity and mortality [Belluco et al 2002]. Systemic chemotherapy should be considered. Additional palliative interventional options may include i) radiotherapy to control local pain and bleeding

[Farouk et al., 1997;Pacini et al., 1986], ii) thermo-coagulation, laser application, arterial embolisation and stenting of obstructing lesions to improve local symptoms [Khot et al., 2002], iii) proximal colostomy to relieve obstruction, and iv) isolated hypoxic chemotherapeutic perfusion in selected cases [Guadagni et al., 2001;Wanebo et al., 2003].

RECOMMENDATIONS (level 3)

- ***Patients with recurrent or locally advanced primary rectal cancer should be treated in highly specialized centers by a multi-disciplinary team (MDT).***
- ***Staging of the disease involves pelvic MRI, abdominal and chest CT and PET/CT.***
- ***Chemoradiation should be given as neo-adjuvant treatment if not offered prior to initial surgery.***
- ***Only curative surgery is justified (R0), the extent of which varies according to the location of the tumour in fit patients. Adjuvant chemotherapy is indicated.***
- ***If curative surgery cannot be achieved palliative measures such as chemotherapy, radiotherapy, could be offered.***

6.3 LOCALLY ADVANCED PRIMARY RECTAL CANCER

Similar to recurrent rectal cancer, a multimodality approach by a highly specialised multidisciplinary team is recommended for the treatment of locally advanced primary rectal cancer. Accurate staging of the disease and identification of tumour anatomical relationship to the pelvic organs by image modalities is the primary step. Neo-adjuvant chemoradiation aims to downsize and downstage the local disease [Sun et al., 2011]. If response is favourable as assessed by pelvic imaging, curative resection (R0) can be achieved. Type of resection depends on the extent of local disease, and varies from TME with LARR or APR to pelvic exenteration or/and sacral bone excision, similar to recurrent rectal cancer. If a R0 resection is not possible palliative measures can be undertaken [Liska and Weiser, 2010].

RECOMMENDATION

If neo-adjuvant chemoradiation succeeds to downsize and downstage the locally advanced primary rectal cancer, surgery is the standard option of treatment, provided that a curative (R0) resection can be achieved. The extent of resection depends on the local extension of the tumour (LOE III).

6.4 Postoperative adjuvant treatment

6.4.1 Postoperative chemoradiation

Postoperative CRT and chemotherapy is administered for 6 months, consisting of 6 cycles of 5-FU chemotherapy (bolus or continuous infusion) with concomitant radiotherapy (e.g. 50 Gy, 1.8–2.0 Gy/fraction) either during cycles 1 and 2 or 3 and 4. During radiotherapy 5-FU should be give as continuous infusion. Apparently the main advantage of the postoperative approach is the better selection of patients based on pathologic staging; disadvantages include increased toxicity related to parts of the small bowel or the perineal scar after APR in the radiation field and a potentially more radio-resistant hypoxic postsurgical area.

Recommendations

- → ***Postoperative CRT (e.g. 50 Gy, 1.8–2.0 Gy/fraction) with concomitant fluoropyrimidine-based chemotherapy instead of preoperative CRT is no longer recommended.***
- → ***Postoperative CRT with concomitant fluoropyrimidine-based chemotherapy must be administered in patients with a cT3 or N+ tumor, or positive circumferential margins or perforation in the tumour area or in other cases with high risk of local recurrence, if preoperative radio(chemo)therapy has not been given.***
- → ***Patients after local resection of pT1 tumours with adverse factors (involved margins, poorly differentiation, sm3 and lymphovascular invasion) or pT2 are at a higher risk for local recurrence should be offered resectional surgery. Otherwise, adjuvant treatment is indicated.***

6.4.2 Postoperative (adjuvant) chemotherapy

In contrast to colon cancer the available data from randomized trials for rectal cancer investigating the value of adjuvant chemotherapy in addition to preoperative radio(chemo)therapy and surgery are very limited (only one underpowered trial,

EORTC). However, the benefit of adjuvant single agent 5-FU after upfront surgery in combination with postoperative radiation have clearly shown that adjuvant 5-FU improves survival, which is consistent with the results of the QUASAR trial rectal cancer subgroup, showing a significant superiority of about 50% reduction for any recurrence. The EORTC trial showed a non significant trend for improved DFS after long term follow up, which is consistent with the QUASAR observation, but with less patient numbers. A definite answer like in colon cancer will not be achieved, since all ongoing or closed trials large trials (STAR, PRODIGE, NSABP, CAO/ARO, PETACC 6) have no control arm without adjuvant chemotherapy, but using single agent 5-FU or capecitabine as control, with the exception of the SCRIPT trial, which compares no adjuvant chemotherapy vs. single agent capecitabine after short course radiation and TME. (probably underpowered, results earliest 2013).

In the US, standard adjuvant treatment for locally advanced rectal cancer is 5-FU/LV or capecitabine or FOLFOX). The ongoing Intergroup trial which compares FOLFOX or FOLFIRI with 5-FU/LV is not recruiting. Only PETACC 6 and CAO/ARO trial will be able to give clear information about the value of FOLFOX (CAO/ARO) or XELOX (PETACC 6). However, data will not be available before 2012 and 2013, respectively.

Recommendations

- → ***Adjuvant chemotherapy could be considered for stage II/III patients.***
- → ***Perioperative chemotherapy, when indicated, should be administered for a total of 6 months.***
- → ***If adjuvant chemotherapy is indicated, the same as colon cancer principle should be followed***

6.5 Strategy and management of synchronous metastatic rectal cancer

Treatment strategy for synchronous metastatic rectal cancer should be based on achievability of R0 resection (either initially or after induction treatment) for systemic disease and local stage of the primary tumour (PT).

For initially resectable disease preoperative chemotherapy might be a possible approach. Chemotherapy () should also be administered to patients with initially unresectable disease. Resection of the primary rectal cancer with curative intent should only be considered in case of potentially R0-resectable systemic disease, either initially or after chemotherapy Preoperative treatment for the primary should be based on the algorithm for M0 disease. Therefore, either preoperative chemoradiation or short course radiotherapy for localized or preoperative chemoradiation for unresectable rectal cancer could be considered to reduce local failure. Staged or synchronous surgery should be performed for resectable disease either initially or after treatment. In case of R0 resection of the primary tumour and metastases postoperative, adjuvant chemotherapy for 6 months should be considered. Palliative surgery, stenting or (chemo) radiation in case of unresectable disease, even after systemic treatment should be as minimally invasive as possible..

Recommendations

→ For R0 resectable primary tumour and liver+/-lung metastases, upfront chemotherapy for 3 months and local treatment according to stage for RT followed by resection (staged or synchronous) followed by postoperative chemotherapy for 3 months.

→ For initially unresectable, but potentially resectable after induction chemotherapy liver+/-lung metastases upfront chemotherapy should be as active as possible. If systemic disease becomes resectable, primary tumour should be treated according to stage, followed by resection of metastatic disease and if feasible adjuvant treatment.

→ In case of liver+/-lung metastases, which will never become resectable, palliative chemotherapy should be administered. Local treatment of the primary tumour will be confined to bleeding or obstructing tumours (stent, laser ablation, short course radiotherapy).

→ Chemotherapy options for induction tretament in synchronous metastatic disease are:

- ***for resectable liver+/-lung metastases: FOLFOX (3 months)***
- ***for liver+/-lung metastases not R0 resectable: FOLFOX +bevacizumab, FOLFOX+anti-EGFR-moAB (only KRAS wt) or FOLFOXIRI***

Strategy and treatment algorithm for rectal cancer with synchronous metastatic disease (stage IV)

7 Peri-operative management of Stage 0 - III colon cancer

Colon cancer is classified according to the TNM classification (UICC 2002). Primary treatment is based on upfront surgery, followed by adjuvant chemotherapy according to stage.

7.1 Surgical treatment of the primary tumor in resectable colon cancer

7.1.1 DETERMINATION OF FBC, CLOTTING MECHANISMS, BIOCHEMISTRY PARAMETERS, LFTs, CEA

A full blood count (FBC) is necessary to determine levels of hemoglobin. If hemoglobin is less than 8gr/100ml increased postoperative morbidity is expected. A hemoglobin level of above 10gr/100ml prior to surgery is desirable. This can be achieved either with blood transfusion at least 2-3 days prior to surgery or with the administration of erythropoietin and iron intravenous infusion at least two weeks preoperatively. There is evidence that blood transfusion impairs immune response of the patient to malignant process of the disease which may translate to worse long-term oncological outcomes [Cella et al., 2003;Heiss et al., 1996]. For this reason erythropoietin and iron infusion is recommended as the safest choice in oncological terms, although relative evidence is not sound and recommendation level is low [Bokemeyer et al., 2007]. Defective clotting mechanisms should be corrected accordingly before surgery.

A base-line determination of serum carcinoembryonic antigen (CEA) level is necessary for the indirect detection of completeness of surgery, namely increased preoperative CEA levels should be normalized after curative surgery. Also according to a recent review [Tan et al., 2009a], postoperative increase of serum CEA is a highly specific but insufficiently sensitive factor for the detection of local or distant recurrent colorectal cancer. A cut-off value of 2.2ng/ml may provide the ideal balance of sensitivity and specificity. Therefore, serial serum CEA determination is highly recommended as a first-line surveillance test.

7.1.2 ASSESSMENT OF GENERAL STATUS

Arterial blood hypertension, cardiac failure or arrhythmias should be corrected to the best possible level prior to surgery. Also, acute respiratory infection should be treated with antibiotics and pulmonary insufficiency with bronchodilation. ASA III or IV condition is not an absolute contraindication for surgery, provided there is continuous invasive monitoring and the patient is admitted to the ICU immediately after surgery.

RECOMMENDATIONS

- ***Maximum improvement of the patient's general status (cardiopulmonary) and blood and coagulation profile is mandatory (SOR A).***
- ***Preoperative base-line determination of serum CEA levels is recommended as a first-line surveillance test (LOE, SOR A).***

7.1.3 BOWEL PREPARATION

There is substantial evidence that mechanical bowel preparation prior to elective colectomy does not offer any advantage over surgery without bowel preparation [Bucher et al., 2004;Guenaga et al., 2009;Slim et al., 2009]. As a matter of fact and according to a recent meta-analysis, mechanical bowel preparation may be associated with increased rate of anastomotic leak and wound infection [Bucher et al., 2004].

RECOMMEDATION

- ***Mechanical bowel preparation is not indicated, as there is evidence that it may increase anastomotic leak (LOE I, SOR A).***

7.1.4 ENHANCED RECOVERY PROGRAMMES

Implementation of enhanced recovery programmes, so called "fast-track", in colorectal surgery for both benign and malignant diseases reduces physiological and psychological stress, accelerates normalization of gastrointestinal function, improves postoperative physical status, and most importantly is associated with less morbidity

and shorter postoperative hospital stay. In addition, implementation of those programmes does not necessitate specific equipment nor does it require increased costs. Therefore, implementation of “fast-track” is strongly recommended in units with motivated and adequately trained personnel [Delaney et al., 2003;Gouvas et al., 2009a;Kehlet and Dahl, 2003].

RECOMMENDATION

- ***Implementation of enhanced recovery programmes is strongly recommended, because it is associated with less postoperative morbidity and faster recovery (LOE I, SOR A).***

7.1.5 RESECTABLE NON-OBSTRUCTING LESION

For early cancer stage 0 or partly stage I (T1) local excision by means of the colonoscope could be considered, particularly in patients with increased co-morbidities. If histology shows clear margins of resection, well differentiated tumour (G1, G2) and no lymphatic invasion, an expectant policy is recommended, as local recurrence is not very likely and lymph node metastasis may occur in only up to 4 percent. In case histology shows incomplete resection margins, a poorly differentiated lesion (G3, G4) or lymphatic invasion, surgical curative resection should follow, as local recurrence is very likely and lymph node metastasis may occur in up to 20 percent of the cases [Levin et al., 2008].

For resectable colonic carcinoma, the oncologically optimal surgical procedure is a curative (R0) colectomy with adequate proximal and distal resection bowel margins, and en bloc complete removal of the respective to the resected segment mesocolon (CME) with all regional lymph nodes [Cohen, 1991;Hohenberger et al., 2006;West et al., 2010b]. Adequate removal of proximal and distal resection bowel margins ensures complete removal of the pericolic lymph nodes which are located along the marginal vessels. Based on the fact that potential involvement of pericolic lymph nodes does not extend the 8cm proximal and distal to the tumor baring bowel segment, bowel resection margins should be at least 10cm, unless this is restricted by the exact location of the tumor or/and type of colectomy [Goligher, 1985;Toyota et al., 1995]. As

a general rule proximal ligation and division of the vascular stems supplying the specimen to be resected (central vascular ligation - CVL) ensures CME and the highest possible retrieved number of lymph nodes [Hohenberger et al., 2009;West et al., 2010b].

For tumors situated at the cecum and ascending colon, CVL involves the ileocolic vessels and the right branches of the middle colic vessels. For tumors situated at the right side of the transverse colon, CVL involves the ileocolic and the middle colic vessels. For tumors situated at the middle and left transverse colon, and the upper descending colon, CVL involves the middle colic vessels, the ascending branches or the stalk of the ileocolic vessels and the ascending branches of the left colic vessels.

For tumors situated at any site from the descending colon to the rectosigmoid junction CVL involves the division of the inferior mesenteric artery at 1cm distal to its origin from the aorta and the inferior mesenteric vein just below the lower border of the pancreas [Hohenberger et al., 2009;West et al., 2010b].

Resection should be complete in terms of removal of all regional to the resected bowel segment lymph nodes. A resection is considered incomplete (R2) if involved lymph nodes are not removed. The number of the lymph nodes removed depends on the location of the tumor [Bilimoria et al., 2008]. In general, right colon segments tend to contain much higher numbers than the left ones. According to UICC recommendations [Compton and Greene, 2004] at least 12 lymph nodes are required to be examined for the staging of the disease. If all lymph nodes examined are negative but <12 in number, staging is not optimal and safe. The accuracy of staging of colorectal cancer parallels the number of removed lymph nodes [Joseph et al., 2003]. There are two additional reasons emphasizing the significance of the number of removed lymph nodes: i) increased number of removed lymph nodes is associated with improved survival, irrespective of the nodal status [Le Voyer et al., 2003], and ii) the ratio of the metastatic to total number of removed nodes is inversely related to recurrence and overall survival [Berger et al., 2005]. The latter one stands true only when the number of examined nodes is >12 [Bilimoria et al., 2008;Johnson et al., 2006;Wong et al., 2007].

Laparoscopic colectomy is nowadays the alternative to the open approach. There is substantial evidence based on several comparative studies that the laparoscopic

approach for colon cancer surgery is as effective and as safe as the open one. Several meta-analyses and systematic reviews [Bonjer et al., 2007;Kuhry et al., 2008;Soop and Nelson, 2008] including among others three large multicentric randomized comparative trials: the COST trial in the USA involving 872 patients [COST Study Group, 2004;Fleshman et al., 2007;Weeks et al., 2002], the CLASICC trial in the UK involving 794 patients [Guillou et al., 2005;Jayne et al., 2007] and the COLOR trial in Northern Europe involving 1248 patients with colon cancer [Buunen et al., 2009;Veldkamp et al., 2005]) and several other single-center comparative randomized trials [Franklin, Jr. et al., 1996;Lacy et al., 2002;Leung et al., 2004;Milsom et al., 1998] clearly show that the laparoscopic approach is associated with faster recovery, less postoperative pain and use of narcotic analgesics and less immediate postoperative morbidity as compared to the open approach. Furthermore, quality of surgery, as depicted in the percentage of involved resected margins and the number of retrieved lymph nodes, is similar between the two approaches. Also, local recurrence and overall and disease-related survival are similar between the two approaches. Finally, and in the long run, there is less readmission rate due to obstructive ileus [Rosin et al., 2007] and less incidence of incisional hernias [Laurent et al., 2008;Yamamoto et al., 2008] after the laparoscopic than the open approach. It has been recently shown that laparoscopic colectomy works perfectly with enhanced recovery programmes, offering even better faster recovery and less immediate postoperative morbidity [Wind et al., 2006].

It is recommended that laparoscopic colectomy for cancer should be performed by experienced surgical teams with adequate case volume, a necessary factor for improved outcomes [Kuhry et al., 2005]. Conversion to open, particularly when performed at a late stage of the procedure, may be associated with increased postoperative morbidity as compared to both the laparoscopically completed and the open approach. The main predictive factors for conversion are the T4 large tumors, the increased ASA condition of the patient, obesity and surgeon's limited experience [Tekkis et al., 2005]. Preoperative image staging is mandatory to identify T4 tumor or tumors >8cm which should be amenable only to the open approach. Previous surgery and advanced age are not contraindications to laparoscopy. Also it should be considered that obesity, although not an absolute contraindication, is associated with

increased rate of conversion. Tumors not invading the bowel wall and unlikely to be visually identified at laparoscopy should be marked with indian ink prior to surgery or localized with an on the table colonoscopy. The laparoscopic approach is not recommended for carcinomas located at the transverse colon, because dissection of the middle colic vessels is very difficult and laborious and quality of specimen is not optimal [Gouvas et al 2012]. The laparoscopic approach is not recommended in acutely perforated or obstructing colonic tumors.

RECOMMENDATIONS

- ***For stage 0 (Tis N0 M0) and T1, N0, M0 low risk tumours, local excision or simple polypectomy with clear margins by colonoscopy could be performed, preferably in patients with increased co-morbidities (SOR A).***
- ***The non-obstructing colonic cancer should be treated by surgical resection, irrespective of stage (SOR A).***
- ***A curative resection (R0) of the non-obstructing colonic cancer involves removal of the tumour baring colonic segment with adequate proximal and distal margins, central ligation and division of the supplying vessels and removal of the attached mesocolon (complete mesocolon excision –CME). The exact length of bowel removed, vessels ligated and divided and mesocolon removed depends on the exact location of the tumour (LOE I, SOR A).***
- ***The quality of the resected specimen should be macroscopically assessed and photographed prior to fixation (SOR A).***
- ***For adequate staging of the disease, at least 12 lymph nodes should be found in the resected specimen (LOE, SOR A).***
- ***Removal of the highest possible number of lymph nodes is encouraged, as it is associated with better oncological outcomes in both stage II and III disease (LOE I, SOR A).***
- ***Laparoscopic surgery for uncomplicated cancer of the right and left colon offers faster recovery and less morbidity as compared to the open approach. Oncological results are similar between the two approaches, provided the surgical team involved is well trained and serves a large volume of cases***

(LOE I, SOR A).

- ***Laparoscopic resection of tumours of the transverse colon may be technically demanding and quality of specimen may not be optimal due to difficult dissection ligation and division of the middle colic vessels at their origin (LOE II, SOR B).***
- ***Laparoscopic approach is not indicated for bulky and advanced colon carcinomas, where curative resection can be achieved by open surgery (LOE I, SOR A).***
- ***Small lesions not visible by laparoscopy should be marked prior to surgery (LOE I, SOR A).***
- ***As conversion may be associated with increased morbidity as compared both to laparoscopically completed and to open approach, predictive factors for conversion, such as obesity or ASA III- IV cases, should by identified prior to attempt laparoscopy (LOE II, SOR B).***

7.1.6 RESECTABLE NON-OBSTRUCTING SYNCHRONUS BOWEL LESIONS

Synchronous carcinomas of the colon are resected in the form of one specimen and one anastomosis is established. Segmental colonic resection with multiple anastomoses should be avoided, as they are associated with increased morbidity. When one of the carcinomas is located at the right colon an extended right hemicolectomy is recommended. Similarly, when two lesions are located at the left colon a left hemicolectomy is recommended [Corman, 2005].

RECOMMEDATION

- ***Extended colectomy with CME and CVL is indicated for synchronous non-obstructing colon lesions. Segmental colon resections with more than one colo-colonic anastomosis are not indicated. Extended colectomy may be achieved by laparoscopy in selected cases (LOE III, SOR C)***

7.1.7 OBSTRUCTING LESION

For resectable colon cancer causing acute complete obstruction, resection with one

or two stage anastomosis is recommended [Gastinger et al., 2004;Patriti et al., 2005;SCOTIA Study Group, 1995;Seah et al., 2005;Villar et al., 2005]. If the condition of the patient does not permit surgery, stenting for the alleviation of the obstruction first and curative resection after two weeks time is the management of choice [Meisner et al., 2004;Regimbeau et al., 2004;Syn et al., 2005].

If the obstructing carcinoma is unresectable, palliative surgery in the form of defunctioning proximal stoma or insertion of a stent is recommended. If the general condition of the patient permits, chemotherapy and/or radiotherapy could be added [Fiori et al., 2004]

RECOMMENDATIONS

- ***Obstructing resectable colonic tumours are treated with one- or two- stage curative colectomy, with colo-colonic anastomosis depending on the option (LOE II, SOR B)***
- ***Alternative to immediate surgery for obstructing resectable colonic tumours is stenting of the lesion. Elective curative surgery follows at a later stage (LOE II, SOR B)***
- ***Obstructing unresectable colonic tumours are palliated by chemotherapy, stenting of the obstructing lesion and supportive care (LOE II, SOR B)***

7.1.8 COLON CARCINOMA IN HNPCC

Considering that HNPCC patients are younger in age than those with sporadic disease and probability to develop metachronous lesions is very high, an extended colectomy is recommended [Box et al., 1999;Lee et al., 2001;Rodriguez-Bigas et al., 1997;Rodriguez-Bigas and Petrelli, 2002].

RECOMMENDATION

- ***For colon cancer on the basis of HNPCC extended colectomy is indicated, particularly in the young patient, where metachronous lesions are highly likely to develop (RG A).***

7.2 Postoperative treatment

Adjuvant therapy after primary tumour resection is aimed at reducing the risk of relapse and death by eliminating residual micrometastatic disease. It should be considered for all patients with stage III and high risk stage II disease (defined by the presence of at least one of the following risk factors: lymph nodes sampling <12, poorly differentiated tumour, vascular. lymphatic or perineural invasion, obstruction, perforation or pT4 stage). The various therapeutic options need to be discussed with the patient on an individual basis taking into account performance status, age, comorbidities and patient preferences, as well as tumour characteristics (pathological stage, grading, and overall risk of relapse).

Combination chemotherapy with a backbone of fluoropyrimidine and oxaliplatin (FLOX, FOLFOX, XELOX) are superior when compared to single agent 5-FU in terms of disease free survival and overall survival (FLOX, FOLFOX) for stage III patients. However, a recent analysis from the ACCENT database published only in abstract form suggests that patients over 70 years of age may not receive additional benefit from combination chemotherapy as opposed to single agent fluoropyrimidine; XELOX on the other hand has shown benefit independently of sex and age. However, even with XELOX the improvement in patients >70 is also diminished with HR for survival exceeding 0.9 and the data only go up to 3 years; in the MOSAIC and NSABP C-07 studies follow up is upto 5 years and inevitably there are more recurrences and deaths .

It is uncertain whether modest benefits from adjuvant chemotherapy in stage II colorectal cancer justify the toxicity, cost, and inconvenience.When all patients with stage II disease were looked at, DFS and OS did not differ significantly with the addition of oxaliplatin, although for high risk stage II patients there was a clear trend for improved DFS which however did not translate into an improved OS, presumably due to deaths from other causes and smaller numbers.

The available data so far available from a number of retrospective studies strongly support the assessment of microsatellite instability testing to become routine clinical practice. Some 25% of tumors proximal to the splenic flexure will be dMMR and knowing

that such tumors have a 50% lower risk of primary tumor recurrence will help guide the use of chemotherapy in this group of patients. While many patients with dMMR tumors would not be offered chemotherapy given their greatly reduced recurrence risk, such patients should not be excluded from receiving chemotherapy if this is otherwise indicated (eg, for high-risk pathology such as T4 stage). In addition, routine testing would aid identification of insidious hereditary nonpolyposis colorectal cancer in individuals showing loss of staining of hMSH2 or hMLH1 in the absence of *BRAF* mutations.

Therefore, most benefit of fluoropyrimidine/oxaliplatin combination is seen in stage III patients, particularly those who are under70 years.
Adjuvant therapy should not be routinely offered for unselected stage II colon cancer patients. However, because of a possible small absolute benefit with single agent fluoropyrimidines, chemotherapy can be considered for medically fit high-risk stage II patients. Combination chemotherapy with oxaliplatin can also be discussed for selected cases with high-risk features.

Infusional 5-FU should be preferred compared to bolus 5-FU due to better tolerability, although the need for a port device and its potential associated complications (thrombosis, lung embolism, infection) should be borne in mind. The use of capecitabine in combination with oxaliplatin which does not require central venous access, is another option.

Adjuvant chemotherapy has to be started ideally within 6-8 weeks from surgery and is given for 6 months. Shorter adjuvant treatment duration (3 months) is currently under prospective evaluation.

Options for adjuvant chemotherapy are:

5-FU/LV infusional (de Gramont or AIO) or bolus regimens (Mayo or Roswell Park)

Capecitabine

FOLFOX

Patient follow up depends on stage, perioperative treatment, and amenability for intervention with either resection of recurrent disease or consideration of further systemic therapy.

Generally valid assessments are three monthly clinical visits for the first three years, followed by six monthly visits for further two years with clinical examination, evaluation of long term toxicities (polyneuropathy after oxaliplatin), and CEA testing.

Complete colonoscopy must be performed at initial diagnosis, after three and afterwards every five years. If the diagnostic colonoscopy was incomplete, this should be repeated within the first 12 months after surgery.

In patients with high risk disease, CT scan of the chest and abdomen every 6-12 months could be considered, although such close follow up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence. Follow up CT scans should be performed with the same imaging protocols and contrast phases of enhancement. If MRI was used for the initial staging, MRI should also be used for the follow up. CT images can not be compared to MRI images due to different sensitivity/specificity.

Recommandations

→ Adjuvant chemotherapy should be recommended to all patients with stage III and high risk stage II disease (LOE I, SOR A).

→ Adjuvant chemotherapy has to be started within 6-8 weeks after surgery. It is questionable whether adjuvant chemotherapy commenced beyond 12 weeks is of any benefit (LOE II, SOR B).

→ Infusional 5-FU should be preferred over bolus 5-FU (LOE II, SOR B).

→ Stage III patients should receive fluoropyrimidine and oxaliplatin based adjuvant chemotherapy for a duration of 6 month (LOE I, SOR A). Whenever this combination is contraindicated, single agent fluoropyrimidine can be considered.

→For stage II patients MSI testing should be strongly considered as it can have a significant impact on prognosis and outcome (LOE II, SOR B)

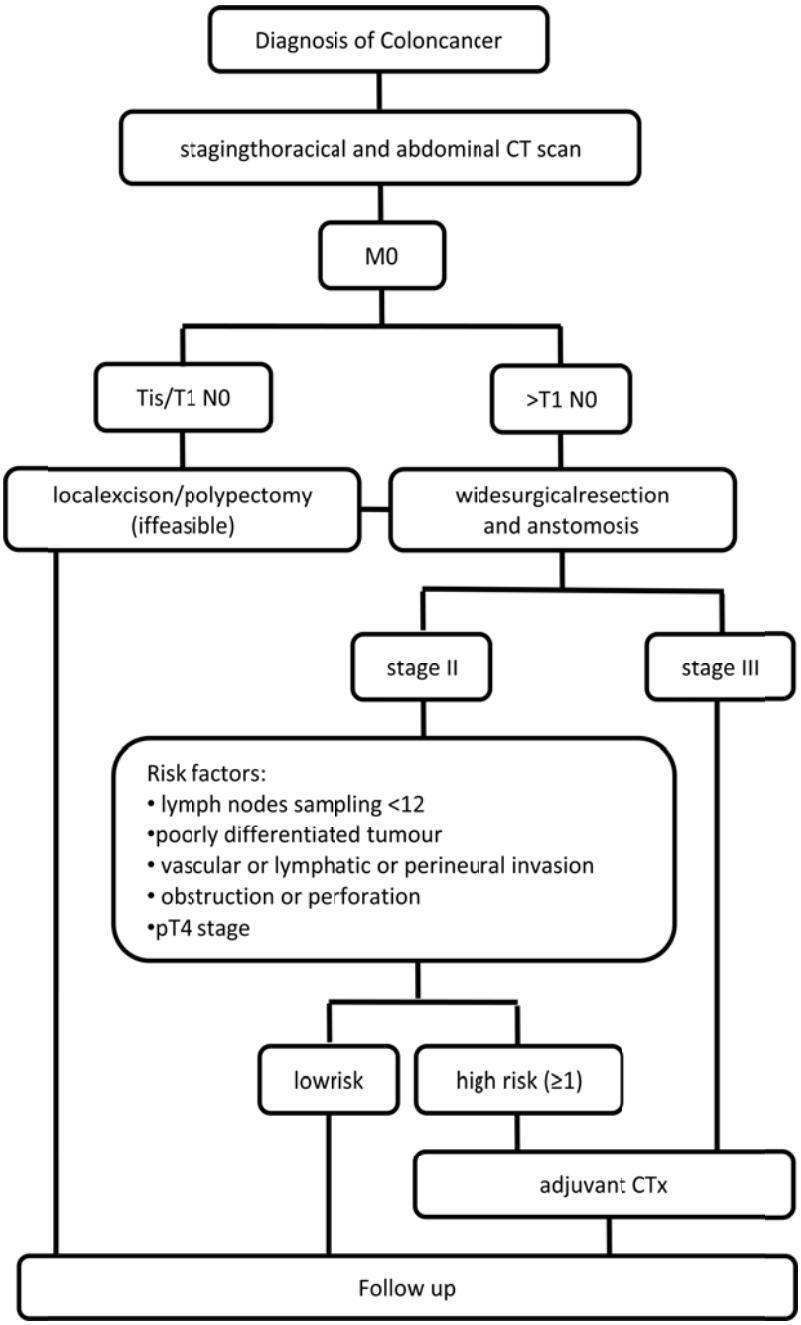
→For Low risk stage II disease single agent fluoropyrimidine can be considered, but bearing in mind that it achieves relatively limited absolute risk reduction for recurrence (LOE II, SOR B).

→ High risk stage II patients should be considered for adjuvant chemotherapy with single agent fluoropyrimidine or FOLFOX for a duration of 6 months (LOE II, SOR B).

→ Patients older than 70 years of age who are thought to be at high risk for recurrence, can be considered for adjuvant chemotherapy with single agent fluoropyrimidine for a duration of 6 months. Although combination treatment with oxaliplatin is an option for stage III disease, it should be noted that the additional benefit conferred is questionable for this age group….

→ Irinotecan combinations and monoclonal antibodies (bevacizumab or cetuximab/panitumumab) cannot be recommended for use in the adjuvant setting.

Strategy and treatment algorithm



8 Management of resectable liver/lung metastases

All patients with metastatic disease from colorectal cancer should be discussed in the context of a multidisciplinary team, especially cases that are candidates for resection [Nordlinger et al., 2007]. Such a team should comprise the necessary medical and non-medical team members (Diagnostic: radiology, pathology – Therapeutic: surgery, medical oncologgy, radiotherapy, palliative care medicine – others: nursing)

It has been documented that liver surgery in high volume centers has been associated with better outcomes including morbidity, perioperative mortalitry and survival.

8.1 Definition of resectability

The criteria for resectability of liver metastases are not standardized and have evolved over the last years. They are clearly related to the experience of the surgeon and of the multidisciplinary team.

Reccomendations

- ***Age, number of lesions and extrahepatic disease (if resectable) are not contraindications for surgery. . (LOE III; SOR C)***
- ***Multiple resections can also be performed, provided there is sufficient remnant liver (>30%) and surgery is not too risky due to the location. Other considerations must include the presence of questionably resectable extrahepatic disease and poor tumour biology.***
- ***The aim of liver resection (resectability) is to remove all macroscopic disease with clear (negative) margins and leave sufficient functioning liver. (LOE II; SOR B)***
- ***The ability to achieve clear margins (R0 resection) should be determined by the radiologist and surgeon in the regional hepatobiliary unit. (LOE III; SOR C)***
- ***The surgeon in collaboration with the radiologist should define the acceptable residual functioning volume, approximately one third of the***

volume in healthy liver, and preservation of at least two contiguous segments. (LOE III; SOR C). MDCT-volumetry is considered as the method of choice to estimate remaining liver volume.

- ***MRI is recommended for further evaluation in equivocal liver lesions. PET-CT may provide additional information about extrahepatic disease; therefore it can be useful in helping surgeons to decide against operating, by detecting distant metastases in high-risk patients. It has been proven to be very useful in patients with rising CEA and normal anatomic imaging. Intraoperative US is the only method capable to detect the smallest liver metastases that may be missed by other imaging modalities. If deemed medically unfit for surgery, patients should be considered for ablative therapy (RFA) (LOE IV; SOR D).***

8.2 Prognostic factors

Based on data fron old series patients have been considered to have non resectable disease in the presence of (1)> than four metastatic lesions (2) bilobar disease (3) extrahepatic disease and (4) resection margins <1 cm. None of these factors are considered now as absolute contraindication for surgery, however patients with these characteristics are those who have a worse prognosis

8.3 Management of Resectable Liver Metastases

The optimal treatment strategy of patients with resectable metastatic disease should be discussed in a multidisciplinary team.

For patients with resectable liver metastases surgical resection offers the best chance of long-term survival with actuarial 5 year survival rates ranging from 30% to 50% in some selected series.

Unfortunately 60%-75%of these patients will suffer relapse, with the majority occurring in the liver.

The role of adjuvant chemotherapy after metastasectomy is still unclear, in particular incorporating modern chemotherapy, including targeted agents.

Underpowered trials with 5-FU +LV or intrahepatic arterial (HIA) chemotherapy with FUDR + systemic chemotherapy with 5-FU+LV have shown some advantage, although no study has shown a clearly significant survival benefit [Kemeny et al., 2002;Portier et al., 2006].

Nevertheless, postoperative adjuvant systemic chemotherapy is recommended (as in stage III colon cancer) in Europe and USA, despite lack of level 1,2 evidence.

Currently the value of bevacizumab in addition to adjuvant XELOX, after liver metastasectomy, is investigated in the Netherlands. Another trial (NSABP C-09) comparing adjuvant systemic Oxaliplatin plus Capecitabine alone or with HIA FUDR, is underway.

Another approach for patients with resectable disease is the use of perioperative chemotherapy. An EORTC trial using perioperative chemotherapy with FOLFOX (3 months before and 3 months after metastasectomy) showed superior PFS for the perioperative treatment group [Nordlinger et al., 2008]. Thus, this approach represents (despite final survival data still lacking) a current standard with level 2 evidence. There is no evidence yet that adding a biologic to a cytotoxic doublet improves the outcome in resectable metastases compared with a cytotoxic doublet alone,. Intensification of induction chemotherapy is currently under investigation (FOLFOX beva/anti EGFR, FOLFOXIRI +/-beva/anti EGFR). The optimal sequencing of chemotherapy in patients with resectable liver metastases (perioperative versus postoperative) is the subject of an ongoing NCI-sponsored trial (NSABP-C-11).

Reccomendations

- ***Primarily resectable patients should receive treatment with FOLFOX for 3 months preoperatively, followed by resection, followed by 3 months FOLFOX postoperatively (LOE II;SOR A). (For solitary metastatic tumor with a diameter <5cm maybe, the need for pre-op chemotherapy is unclear).***
- ***During preoperative treatment thorough evaluation for complete remission has to be performed, after 6 weeks of treatment.***

- ***If preoperative chemotherapy was not applied, in case of R0 resection, adjuvant chemotherapy, as in stage III colon cancer, for 6 months can be considered (LOE III;SOR A).***
- ***Timing interval from chemotherapy to surgery should be 4-6 weeks, as well as from surgery to adjuvant chemotherapy.***
- ***For patients with resectable disease and insufficient response on preoperative chemotherapy immediate metastasectomy may be considered.***
- ***In case of progressive disease during preoperative chemotherapy second line systemic chemotherapy should be administered.***
- ***An other option is the use intrahepatic arterial (HIA) plus IV chemotherapy, but only at very experienced Institutions.(SOR B)***
- ***Ablation is generally inferior to resection. However, it can be used (preferably with radiofrequency or microwaves) in patients unfit for surgery, or as bridge to resection, or in combination with resection (if liver remnant is threatened)***

8.4 Management of resectable lung metastases

Patients with limited lung metastases have a very good prognosis with 5 year survival rate of 25-35%.

Recommendations

Despite the lack of data regarding perioperative treatment an approach similar to the management of resectable liver metastases, should be considered.

Alternatively an initial resection without perioperative treatment followed by postoperative chemotherapy can be carried out.

9 Treatment of advanced disease

9.1 Selection criteria for 1st line treatment

9.1.1 Molecular factors

With the exception of *KRAS* mutation which excludes patients from treatment with anti-EGFR antibodies no further prognostic/predictive molecular marker is relevant for routine 1st line treatment decision outside clinical trials [Amado et al., 2008;Karapetis et al., 2008;Van Cutsem E. et al., 2011].

9.1.2 Clinical factors

The optimal treatment strategy of patients with metastatic CRC should be discussed in a multidisciplinary tream. The aim of the 1st line treatment depends on the clinical presentation and biology of the tumour (metastases limited to liver or lung or both, or peritoneum; dynamics of progression; symptoms) and patient factors (comorbidities, age, potential to undergo secondary resection). In case of major response to induction chemotherapy of liver, lung (or even peritoneal) R0/R1 resection can result in long term survival and potentially cure in a minority of patients.
With this respect, patients can be individually divided into the following three clinical groups, by parameters describing localization and extent of disease, tumour dynamics, comorbidities, potential of the patient to tolerate chemotherapy and surgical treatment.

1. Liver (± lung) metastases only
Might become resectable after induction chemotherapy
± limited/localized metastases to other sites
Physically able to undergo major surgery (biological age, heart/lung condition)
2. Multiple metastases
Rapid progression
Tumour-related symptoms/Risk of rapid deterioration
Comorbidity allows aggressive treatment

Or group 3 without severe comorbidity
3. Unresectable metastases
Never suitable for resection
No major symptoms or risk of rapid deterioration, or
Severe comorbidity (excluding from surgery and/or intensive systemic treatment)

Although never prospectively proven, the achievement of a disease-free status after chemotherapy and surgery is the only means to give the potential for long term survival or cure in an otherwise incurable/palliative situation. For this aim, the most active induction chemotherapy which is able to induce downsizing as much as possible in as many patients as possible should be selected for group 1.
For the intermediate group, , the aim is a rapid regression of metastases – in particular in cases of imminent tumour associated complications –an escalation strategy (single agent followed by combination) is risky in that switch to a more effective second line treatment may be too little too late. Therefore, the most active 1st line treatment is more appropriate for most of these patients.
Patients in the third group are treated mostly with a palliative intent. Therefore, an escalation strategy seems be appropriate. However, some patients with excellent responses might also become candidates for secondary surgery with further escalation.

9.2 Choice of treatment

Available chemotherapeutic agents are fluoropyrimidines (5-Fluorouracil modulated by folinic acid (5-FU/FA) or capecitabine), irinotecan and oxaliplatin.
Capecitabine can be safely substituted by 5-FU/FA in combination with oxaliplatin [Arkenau et al., 2008] and in combination with irinotecan after the necessary dose adjustment of both drugs. However, FOLFIRI should be the preferred option over XELIRI as it is associated with less GI toxicity [Montagnani et al., 2010].
Possible chemotherapeutic regimens are listed below:

- FOLFOX [Tournigand et al., 2004]/XELOX
- FOLFIRI [Douillard et al., 2000;Tournigand et al., 2004]/XELIRI

- FOLFOXIRI [Falcone et al., 2007;Souglakos et al., 2006]
- Fluoropyrimidine monotherapy (5-FU/FA, capecitabine)
- Irinotecan monotherapy or IROX only in case of fluoropyrimidine contraindications [Goldberg et al., 2006].

Monoclonal antibodies are the VEGF targeting bevacizumab and the anti-EGFR antibodies cetuximab and panitumumab. Anti-EGFR-antibodies have no activity in KRAS mutant tumours. The combination of capecitabine, oxaliplatin with cetuximab (and panitumumab as well) seem to have no additional benefit over capecitabine and oxaliplatin alone and should be avoided at present [Maughan et al., 2011].

Possible combination regimens are listed below:

- FOLFOX + moAB (bevacizumab or anti-EGFR in KRAS wt) [Bokemeyer et al., 2009;Saltz et al., 2008;Douillard et al., 2010]
- XELOX + bevacizumab [Saltz et al., 2008]
- FOLFIRI/XELIRI + moAB (bevacizumab or anti-EGFR in KRAS wt) [Fuchs et al., 2008;Moosmann et al., 2011;Van Cutsem E. et al., 2009]
- Fluoropyrimidine mono (5-FU/FA, capecitabine) + bevacizumab [Kabbinavar et al., 2005]

The first line regimen depends on the chosen treatment strategy. For potentially resectable and/or symptomatic disease first line treatment should ideally be a chemotherapy doublet in combination with a monoclonal antibody or a triplet. If tumor shrinkage is desirable, treatment with FOLFIRI and cetuximab for KRAS wt or FOLFOXIRI should be considered. First line treatment with monotherapy [Seymour et al., 2007] or doublet (either chemotherapy or chemotherapy with moAB) could be a valid option for patients, for whom a secondary resection is not feasible, and who have no symptoms or risk for deterioration of their disease.

9.3 Timing for assessment of response and treatment duration

The selected induction chemotherapy should be given for at least 8 weeks when the first reassessement will be performed, in order to avoid unnecessary chemotherapy application in case of early progression.

If the treatment aim is pure palliation, the timing of first evaluation is of less importance. An interval of 12 weeks might be more appropriate.

The treatment duration is dependent on the treatment aim. If secondary surgery is attempted, induction chemotherapy should be continued until R0 resectability might be achieved, with the first evaluation after 8 weeks (to evaluate whether the chosen regimen is active at all), 4 months, and if resectability is still not achievable, 6 months. Further treatment (more than 6 months) with the same regimen is not recommended.

If the aim of secondary resection cannot be achieved as well as in patients where resection is not the aim of treatment this should be continued according to the individual's situation, patients' needs, cumulative toxicity (in particular oxaliplatin) and aggressiveness of the disease.

Survival will not be significantly impaired if first line treatment is not given continuously until progression (including stop of oxaliplatin due to cumulative neurotoxicity) in most patients.

Drug and treatment holidays are acceptable options in selected patients after initial periods of treatment [Chibaudel et al., 2009;Tournigand et al., 2006].

Recommendation

Treatment strategy is selected according to categorization in the three different defined goups. Patients in the two first groups are candidates for aggressive treatment.

Group 1: Aggressive treatment

FOLFOXIRI (IIC) or Cetuximab (KRAS wt)+FOLFIRI (IB),

FOLFOX (Level IB)

FOLFOX+Cetuximab or Panitumumab (KRAS wt) or Bevacizumab (Level IIB)

XELOX+Bevacizumab (IIC)

Group 2: Aggressive treatment

As per group 1

XELOX+/- Bevacizumab (IIB)

mXELIRI+/-Bevacizumab or Cetuximab (KRAS wt) (IIC)

FOLFOX+Panitumumab/cetuximab (KRAS wt) (IIB)

Group 3: Palliative treatment

Fluoropyrimidine +/-Bevacizumab (sequential treatment)(IIB)

Doublets chemotherapy (IA)

Doublets chemotherapy+antiEGFR (KRAS wt) (IIB)

9.4 Management of unresectable liver/lung metastases

9.4.1 Choice of Induction Chemotherapy

Standard combination chemotherapy regimens comprising 5-FU/LV in combination with either irinotecan, typically FOLFIRI, or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 7%–40% of patients with initially unresectable metastases depending upon the initial selection of patients [Nordlinger et al., 2008]. However, 75%–80% of these patients experience cancer relapse within 2 years of resection. Data emerging from randomized trials suggest that the addition of a targeted agent (bevacizumab or cetuximab) or even scarce data of phase II trials on the combination with a third cytotoxic plus or minus a targeted agent, might be even more effective, although concerns about toxicity limit the use of this triplet to highly selected cases. The combination of a chemo-doublet plus cetuximab has led to higher resection rates (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wild-type CRC. The combination of FOLFOX/cetuximab and FOLFIRI/cetuximab has led to similar response rates and resection rates in KRAS wild-type tumours [Bokemeyer et al., 2009;Van Cutsem E. et al., 2009].

The combination of a fluoropyrimidine/oxaliplatin/bevacizumab has led to a non-significant trend in an increased resection rate compared with the chemo-backbone alone, although no increase in response rate was shown [Saltz et al., 2008]. There are no data available from randomized studies comparing a chemo-doublet plus bevacizumab with a chemo-doublet plus cetuximab.

Limited data for the three-drug combination FOLFOXIRI indicating that this could be an alternative option to FOLFIRI/FOLFOX + cetuximab with probably more toxicity, is

probably the preferred option if targeted drugs, in particular cetuximab, are not available or are contraindicated [Falcone et al., 2007;Souglakos et al., 2006].

Recommendation

For KRAS wt tumours, induction treatment with FOLFIRI/FOLFOX + cetuximab appears to be more effective in terms of major tumour shrinkage and secondary resectability, than bevacizumab based combinations, for which less data are available. (LOE II; SOR B)

FOLFOXIRI should be considered as a treatment option especially for patients with KRAS mutant tumors.(LOE II; SOR C).

9.4.2 Timing of surgery

Surgery can be performed safely after 4 weeks from the last cycle of chemotherapy plus or minus cetuximab, and 5–8 weeks following chemotherapy plus bevacizumab. Resection of the metastases should be performed as soon as the metastases are resectable, since unnecessary prolonged administration of chemotherapy may lead to a higher postoperative morbidity. The postoperative morbidity is more related to the duration of the chemotherapy than to the type of chemotherapy that is administered, although oxaliplatin and irinotecan may cause different histological changes in liver parenchyma: oxaliplatin is related to sinusoidal liver lesions and irinotecan to steatohepatitis [Aloia et al., 2006;Karoui et al., 2006;Nakano et al., 2008].

Recommendation

Surgery can be performed safely after 4 weeks from the last cycle of chemotherapy and 5–8 weeks following bevacizumab containing treatment. (LOE IV; SOR D)

9.4.3 Extent of Surgery

Recommendation

- ***If possible all residual tumour lesions should be resected. Additional measures like prior portal vein embolization to enable resection of otherwise non-resectable lesions, RFA, etc. might be used.***

- ***Lesions with complete regression mostly contain residual viable tumours cells. However, it is not clear whether all initially involved sites should be resected irrespective of response or whether only visible residual (preop imaging or intraoperative) lesions should be resected.***

9.5 Synchronous metastatic colon cancer

Recommendation

- ***Initially resectable synchronous disease should be treated preoperatively with FOLFOX for 3 months, followed by resection of the primary tumour and metastases either staged or synchronous and postoperatively 3 months FOLFOX. (LOE II; SOR C)***
- ***In case of symptomatic primary and resectable systemic disease, resection of the primary tumour (and the metastases if possible) should be performed upfront, followed by "adjuvant"chemotherapy for 6 months.(LEO IV; SOR C)***
- ***In case of symptomatic primary and unresectable systemic disease, resection of the primary tumour should be performed, followed by induction chemotherapy and further treatment according to response. (LEO IV; SOR D)***
- ***Upfront surgery of the primary tumour for an asymptomatic primary in case of unresectable systemic diseasedoes not have to be performed. However, upfront systemic chemotherapy should be started. (LOE IV; SOR D)***
- ***In case of secondary resectability of metastatic disease after induction chemotherapy, resection of the primary tumour and metastases either staged or synchronous should be performed. (LOE IV; SOR D)***

9.6 Role of surgery in disease still unresectable after induction chemotherapy

Recommendation

In case of insufficient response of liver metastases to induction chemotherapy, surgical resection may not be performed, since tumour debulking is an inappropriate method to improve survival

9.7 Non-surgical management of liver metastases (RFA, SIRT, TACE, stereo tactic radiation)

The gold standard in the management of colon cancer metastatic to the liver is resection [Gravante et al., 2011;Mulier et al., 2008]. Most of these patients are not candidates for surgery due to either disease bulk or the presence of non-resectable extrahepatic metastases. This group of patients should be treated with systemic chemotherapy. A subgroup of patients with liver metastases will progress after chemotherapy options, are exhausted or have toxicity from systemic therapy that limits chemotherapy options. These patients are potential candidates for palliative ablative or arterial interventions.

9.7.1 Radiofrequency ablation (RFA)

The decision to offer ablative therapy to patients with hepatic metastases should be made by the regional hepatobiliary unit. Patients whose tumors have been downsized by chemotherapy but are not resectable may also be considered for ablative therapy.
RFA is accepted as preferable to other ablative techniques for treating colorectal metastases. Factors determining success are lesion size, the number of lesions and location [Van Tilborg et al., 2011]. Ablation should be reserved for patients with a limited number of smaller tumors. Local recurrence is significantly higher when colorectal metastases larger than 3-5 cm are treated, while prognosis is worse when more than five tumors are present at the time of ablation (LOE II). Larger tumors may be treated with a combination of ablation and arterial embolization or chemoembolization [Gillams and Lees, 2009;Lencioni et al., 2004].
Radiofrequency ablation may be performed intraoperatively, laparoscopically, or percutaneously. The percutaneous approach is associated with the least procedural risk and may be performed under local anesthesia. Percutaneous RFA should be considered a primary treatment option for patients with unresectable hepatic tumors or conditions that prohibit general anesthesia or abdominal surgery [Gillams and Lees, 2004;Guenette and Dupuy, 2010].

9.7.2 Selective internal radiation therapy (SIRT)

SIRT of liver metastases from primary colorectal cancer often results in a high rate of tumor regression. All patients indicated for a SIR-treatment must not have widespread metastases - ruled out by PET-CT or whole body CT/MRI. Current evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate. For patients who have previously been treated with chemotherapy, there is evidence that SIRT can achieve control of hepatic metastases but the evidence of its effects on survival and on quality of life is inadequate (NICE consultation document [2011]).

The response rate based only on changes in tumor volume according to the CT scans (RECIST) is often poor due to no significant change of tumor size. However, after SIRT there is a significant decrease of tumor markers and FDG-uptake proving that tumor nodules are no longer viable. Patient selection, is also a key issue because there are considerations that a subgroup of patients with huge metastases or pre-existing extrahepatic manifestations seem to benefit less from this therapeutic modality.

9.7.3 Transarterial Chemoembolization (TACE)

TACE using Irinotecan loaded beads is safe and effective in the treatment of patients following failure of standard systemic chemotherapy. Patients may receive repeat embolizations (max 100 mg per embolization). The technique shows minimal complication rate and acceptable tumor response [Martin et al., 2009a;Martin et al., 2009b]. Neither number of liver lesions, size of liver lesions or extent of liver replacement (<or= 25% vs >25%) are predictors of overall survival. TACE may also achieve downsizing of metastases so that they can be treated by thermal ablation [Vogl et al., 2007].

This treatment by TACE shows a significant benefit for patients who have failed first and second line therapy and is potentially an effective therapy when compared to the historical response rates to third and fourth line systemic chemotherapy. The fact that substantial extrahepatic progression is often observed after regional treatment for liver metastases further suggests that systemic chemotherapy should be added to chemoembolization (LOE III).

10 Management of peritoneal disease / ascites (Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC))

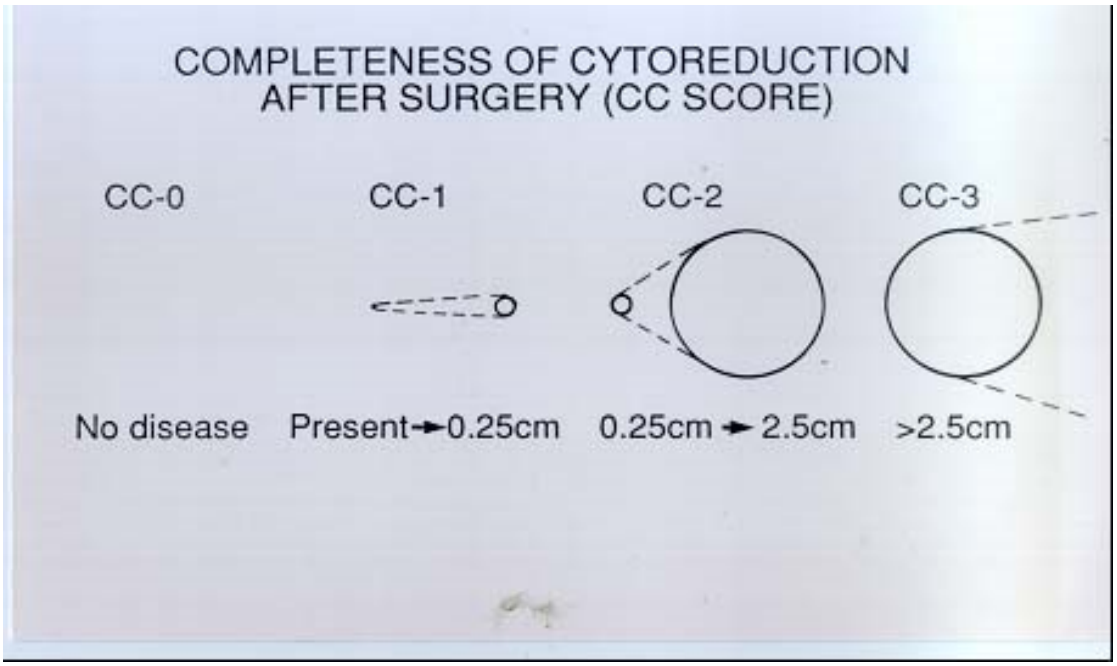
Peritoneal carcinomatosis was considered until recently a terminal disease and patients were treated palliatively [Koppe et al., 2006]. The incidence of peritoneal carcinomatosis of colorectal cancer is around 11% [Jayne et al., 2002]. Large studies that included between 50 and 392 patients with peritoneal carcinomatosis who were treated with systemic chemotherapy showed that the median survival was between 5.2 and 12.6 months [Jayne et al., 2002;Sargent et al., 2010;Verwaal et al., 2003]. In the majority of these studies only 5-FU based chemotherapy regimens were used and as a consequence the medical community is still unaware of the efficacy of modern drug treatment for this subgroup of patients.

Maximal cytoreductive surgery using standard peritonectomy procedures [Sugarbaker, 1995] combined with perioperative intraperitoneal chemotherapy either as hyperthermic intraoperative (HIPEC) or as early postoperative under normothermia (EPIC) has demonstrated that survival is significantly improved in selected patients. One retrospective multi-institutional study with 506 patients showed that the median survival after cytoreductive surgery and intraperitoneal chemotherapy was 19.2 months and 3 and 5 year overall survival was 39% and 19% respectively [Glehen et al., 2004]. Prospective studies with small number of patients had already shown that cytoreductive surgery combined with intraperitoneal chemotherapy improved survival in properly selected patients as compared to historical data [Elias et al., 2001;Sugarbaker et al., 1996]. The same results have been conducted by other studies [Elias et al., 2004a;Kecmanovic et al., 2005;Mahteme et al., 2004;Pilati et al., 2003;Shen et al., 2004;Sugarbaker et al., 1996;Verwaal et al., 2003;Witkamp et al., 2001]. One prospective non-randomized trial [Mahteme et al., 2004], and two [Elias et al., 2004a;Verwaal et al., 2003] prospective randomized trials showed clearly that the survival of patients with peritoneal carcinomatosis of colorectal origin was significantly improved by cytoreductive surgery and intraperitoneal chemotherapy as compared to

cytoreductive surgery and systemic chemotherapy. The Dutch prospective randomized trial was prematurely abandoned because patients who underwent cytoreductive surgery combined with HIPEC had significantly improved long-term survival compared to those who underwent cytoreductive surgery combined with systemic chemotherapy [Verwaal et al., 2003]. The long-term follow-up of these patients reconfirmed the same results [Verwaal et al., 2008]. One meta-analysis has shown that patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy are offered significant survival benefit [Cao et al., 2009]. Another retrospective study showed that the median survival in patients undergoing cytoreductive surgery and HIPEC with oxilaplatin which was potentiated by systemic infusion of 5-FU+leucovorin was significantly improved compared to survival of patients that underwent cytoreductive surgery and systemic chemotherapy with the same drugs [Elias et al., 2010]. There is accumulating evidence that cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is associated with improved survival as compared to systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal origin [Yan et al., 2006].

Cytoreductive surgery with perioperative intraperitoneal chemotherapy does not offer benefit to all patients with peritoneal carcinomatosis of colorectal origin and proper patient selection is required. The completeness of cytoreduction which is assessed by the CC-score is the most important variable of long-term survival [Sadeghi et al., 2000;Elias et al., 2001;Elias et al., 2010;Glehen et al., 2004;Kecmanovic et al., 2005;Mahteme et al., 2004;Pilati et al., 2003;Shen et al., 2004;Sugarbaker et al., 1996;Verwaal et al., 2003;Witkamp et al., 2001]. The extent of peritoneal involvement which is assessed by the calculation of the Peritoneal Cancer Index is another important prognostic variable [Elias et al., 2001;Elias et al., 2010;Glehen et al., 2004;Mahteme et al., 2004;Pilati et al., 2003;Shen et al., 2004;Sugarbaker et al., 1996;Verwaal et al., 2003;Yan and Morris, 2008].

10.1 Assessment of the completeness of cytoreduction



Complete cytoreductive surgery for colorectal cancer with peritoneal carcinomatosis is considered only a CC-0 surgery

10.2 Calculation of the Peritoneal Cancer Index (I would probably remove the whole of this section)

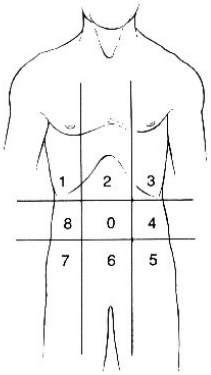
The calculation of the peritoneal cancer index is possible with the division of the abdomen and pelvis in 13 different regions. Two transverse and two sagittal planes are used to divide the abdomen and pelvis in nine regions. The upper transverse plane is the lowest part of the costal margin and the lower plane is the anterior superior iliac spine. The sagittal planes divide the abdomen in three equal sectors. The abdominopelvic region 0 (AR-0) includes the midline incision, the greater omentum and the transverse colon. The abdominopelvic region 1 (AR-1) includes the superior surface of the right lobe of the liver, the undersurface of the right hemidiaphragm, and the right retrohepatic space. The epigastric fat, the left lobe of the liver, the lesser omentum and the falciform ligament are included in the

abdominopelvic region 2 (AR-2). The abdominopelvic region 3 (AR-3) includes the undersurface of the left hemidiaphragm, the spleen, the tail of the pancreas, as well as the anterior and posterior surface of the stomach. The descending colon and the left abdominal gutter are included in abdominopelvic region 4 (AR-4). The left pelvic side wall and the sigmoid colon are included in the abdominopelvic region 5 (AR-5). The abdominopelvic region 6 (AR-6) includes the internal female genitalia, the cul-de-sac of Douglas, and the rectosigmoid colon. The abdominopelvic region 7 (AR-7) includes the right pelvic side wall, the base of the cecum, and the appendix. The abdominopelvic region 8 (AR-8) includes the ascending colon and the right paracolic gutter. The small bowel and its mesentery are divided in four additional regions in upper jejunum (AR-9), lower jejunum (AR-10), upper ileum (AR-11), and lower ileum (AR-12). The peritoneal cancer index is the summation of the tumor volume in each one of the 13 different regions in which the abdomen and the pelvis are divided.

Although the inclusion of the anatomic structures in the abdominopelvic regions is arbitrary the assessment of the distribution and extent of the peritoneal dissemination is detailed.

The tumor volume is assessed as LS-0 (lesion size) when no visible tumor is detected, as LS-1 when tumor nodules are < 0.5 cm in their largest diameter, as LS-2 when tumor nodules are 0.5-5 cm in their largest diameter, and as LS-3 when tumor nodules are > 5 cm in their largest diameter, or there are confluent any size nodules. LS-0, LS-1, and LS-2 are considered small volume tumors, and LS-3 large volume tumors.

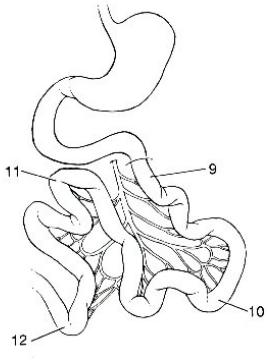
Peritoneal Cancer Index



Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____
PCI	☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



10.3 Eligibility criteria for maximal cytoreductive surgery and perioperative intraperitoneal chemotherapy of colorectal origin

1. Performance status > 50% (according to Karnofsky performance scale)
2. Normal hematological profile (WBC>4000/dl, platelets>150.000)
3. Normal renal (blood urea<50mg/dl, creatinine<1.5/dl) and liver function
4. No evidence of distant and irresectable metastatic lesions (liver, bone marrow, lung, brain).
5. No evidence of a second malignancy at risk for recurrence except for skin basal carcinoma or in situ carcinoma of the cervix properly treated
6. No evidence of ureteral or biliary obstruction
7. No evidence of disease at remote lymph nodes
8. Patients capable to tolerate major surgery (no evidence of recent myocardial disease or pulmonary disease)
9. Limited peritoneal carcinomatosis (PCI<13)

Ineligibility criteria for cytoreductive surgery and perioperative intraperitoneal chemotherapy

1. Performance status < 50% (according to Karnofsky performance scale)
2. WBC count <4000/dl, and platelet count <150.000/dl
3. Blood urea level >50mg/dl, and creatinine level >1.5mg/dl
4. Abnormal liver function
5. Presence of another malignant tumor at risk for recurrence (except for skin basal carcinoma or in situ carcinoma of the cervix properly treated)
6. Ureteral or biliary obstruction
7. Disease at remote lymph nodes that have no relation to the primary site (these are considered metastases from metastases)
8. Severe myocardial failure, recent myocardial infarction, chronic obstructive pulmonary disease, recent pulmonary infection
9. Extensive peritoneal spread (PCI>13)
10. Presence of peritoneal nodule with a diameter>5cm at the ligament of Treitz
11. Multiple segmental obstruction of the small bowel
12. Presence of tumor nodules greater than 5 cm in diameter on small bowel surfaces or directly adjacent to small bowel mesentery in the jejunum or upper ileum
13. Pregnancy
14. Age less than 16 years (?)

10.4 Cytoreductive surgery

Cytoreductive surgery is possible using standard peritonectomy procedures [6]. Initially 6 different peritonectomy procedures had been described. Currently the peritonectomy procedures include 1) the epigastric peritonectomy procedure, 2) the right subdiaphragmatic peritonectomy procedure, 3) the left subdiaphragmatic peritonectomy procedure, 4) greater omentectomy±splenectomy, 5) lesser omentectomy, 6) cholecystectomy with resection of the omental bursa, 7) right lateral peritonectomy procedure, 8) left lateral peritonectomy procedure, 9) pelvic peritonectomy procedure, and 10) resection of other organs.

Perioperative intraperitoneal chemotherapy

Even if the macroscopically visible tumor has been completely removed after maximal cytoreductive surgery the microscopic residual tumor will possibly be present at the

peritoneal surfaces. The disseminated cancer cells adhere to the peritoneal surfaces and are covered by fibrin, platelets, polymorphonuclear cells, and monocytes that infiltrate fibrin during the healing process. Growth factors released in large amounts stimulate fibroplast proliferation and local collagen production, eventually modulating wound healing, promote cancer proliferation, and give rise to secondary tumors within 2-3 years after initial surgery.

The concept about the use of intraperitoneal chemotherapy is based upon the properties of the peritoneal-plasma barrier. Peritoneal plasma barrier is an anatomical and functional structure. It is consisted by the fluid in the abdominal cavity, the mesothelium, the intervening interstitium, and the blood vessel wall. Most of the cytostatic drugs are large molecular weight substances that are confined for long at the peritoneal surfaces and exert intensively their pharmacologic properties before their absorption into the systemic circulation. The penetration of intraperitoneal chemotherapy is limited to approximately 1-2 mm into tissues and may result in the eradication of the microscopic residual tumor.

10.5 Hyperthermic Intraperitoneal Intraoperative Chemotherapy (HIPEC)

Hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC) enhances cytotoxicity and improves drug penetration. The heat itself has potential antitumor properties. If HIPEC is performed with the open abdominal technique (Coliseum technique) the surgeon may distribute uniformly the heat and the cytotoxic drugs to the entire peritoneal cavity manually. Renal toxicity of intraperitoneal chemotherapy is avoided by careful monitoring of urine output during perfusion. Side-effects of systemic chemotherapy (nausea, vomiting) are avoided because the patient is under general anesthesia. The time that elapses during hyperthermic perfusion normalizes a number of parameters (hemodynamics, hemostasis, temperature etc). The most frequently used cytotoxic drugs are mitomycin-C, cis-platin, doxorubicin, and oxaliplatin.

10.6 Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Early postoperative intraperitoneal chemotherapy under normothermia (EPIC) is used with the same intent as HIPEC before intra-abdominal adhesions are formed. The method is used during the first five postoperative days, because the formation of adhesions after days 7-8 does not permit uniform distribution of the cytostatic drugs. The distribution of cytostatic drugs is imperfect with EPIC because the undersurface of the right hemidiaphragm, the corresponding surface of the right lobe of the liver, the anterior surface of the stomach, the folds of small bowel mesentery, and adherent bowel surfaces, the male pelvis, and the abdominal wall are not adequately exposed to cytostatic drugs. The effectiveness of the peritoneal-plasma barrier persists despite extensive stripping of the peritoneal surfaces and the pharmacokinetics of intraperitoneal drug delivery is not changed. In the early postoperative period, drugs that require cell replication are most appropriate. These drugs are administered in a large volume of fluid for the first 5 to 7 days postoperatively and include 5-fluorouracil, paclitaxel, and docetaxel.

10.7 Morbidity and hospital mortality of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy

The hospital mortality of patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy is low varying from 0-4% [Stephens et al., 1999;Sugarbaker and Jablonski, 1995;Glehen et al., 2004]. The hospital morbidity is high ranging from 20-54% [Elias et al., 2004b;Stephens et al., 1999;Sugarbaker and Jablonski, 1995;Glehen et al., 2004], implying that the method must currently be performed in specifically organized peritoneal surface malignancy centers.

10.8 Long-term survival of patients with peritoneal carcinomatosis of colorectal origin

Reports from five institutions with at least 25 patients treated, for a total of 333 patients, show that with a mean follow-up of 33 months (range=6 to 99 months), the

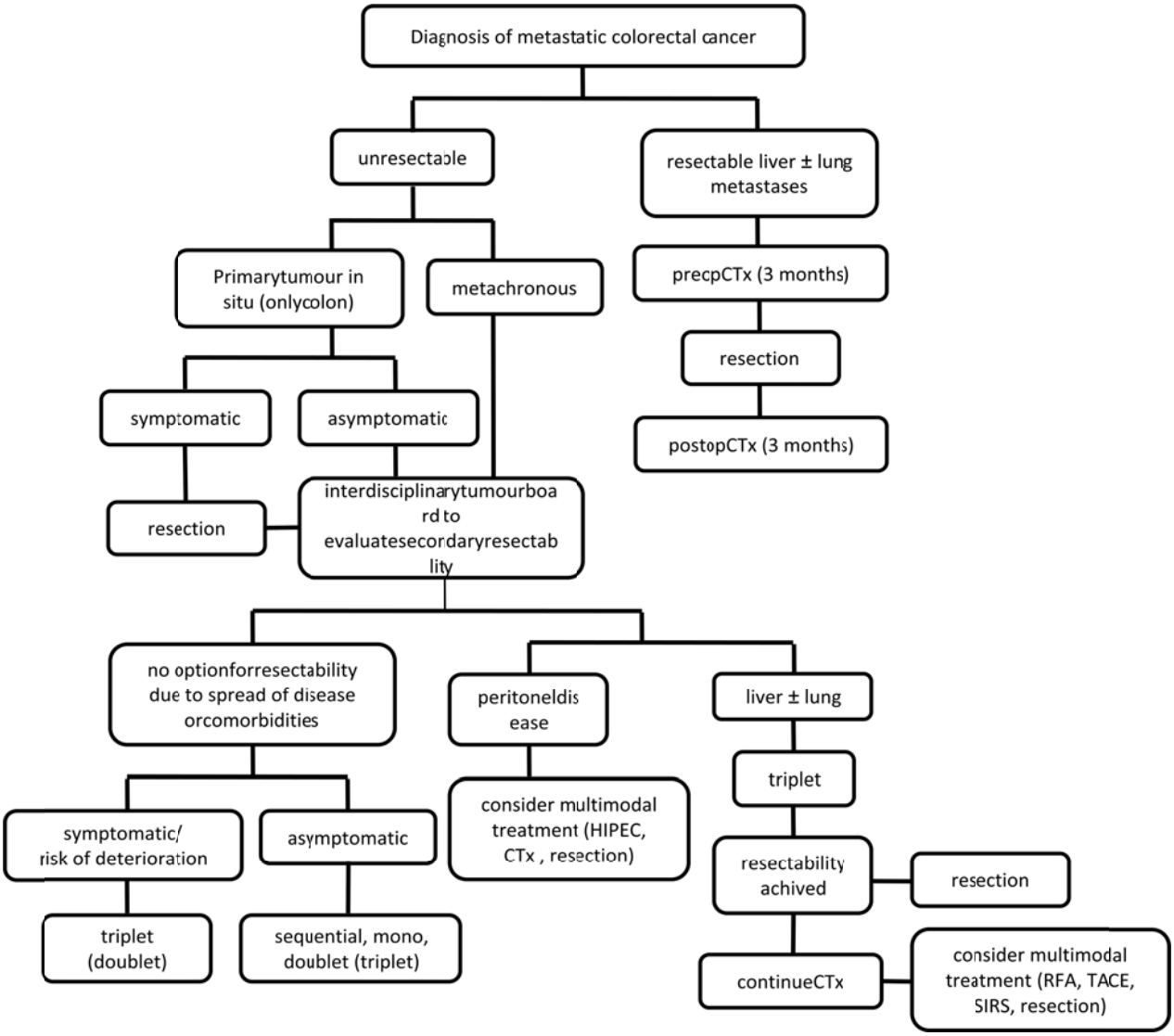
mean survival of all patients at 3 years was 31% (range=23% to 47%). In all these reports, patients in whom complete cytoreductive surgery was possible had a median survival that far exceeded the survival in patients who had incomplete cytoreductive surgery [Glehen et al., 2003;Pestieau and Sugarbaker, 2000;Shen et al., 2003;Witkamp et al., 2001;Elias et al., 2001;Glehen et al., 2004].

One multi-intitutional retrospective study showed that the positive independent prognostic indicators by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of peritoneal carcinomatosis, age younger than 65 years, and use of systemic chemotherapy. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were negative independent prognostic indicators. The therapeutic approach combining cytoreductive surgery with perioperative intraperitoneal chemotherapy achieved long-term survival in a selected group of patients with peritoneal carcinomatosis of colorectal origin and the completeness of cytoreduction was the most important prognostic indicator [Glehen et al., 2004].

Recommendations

In patients with peritoneal carcinomatosis of colorectal origin the option of being treated with maximal cytoreductive surgery combined with perioperative intraperitoneal chemotherapy followed by systemic chemotherapy in organized peritoneal surface malignancy centers and after multi-disciplinary discussion should be offered to carefully selected patients.

10.9 Strategy and treatment algorithm



11 Choice of Salvage treatment

By the term salvage treatment we refer to different types of treatments that we can offer our patients, when the disease has progressed or recurred after the 1st line setting. Salvage treatment aims mainly to improve the quality of life and if possible to prolong life.

Second and after-line treatments may not have a strong prognostic utility and they concern lesser numbers of patients [LOE II, SOR B] [Brouquet et al., 2011]. Management of these patients should be based on the "continuum of care" principle [Grothey et al., 2008;Koopman et al., 2007;Seymour et al., 2007].

The intensity of the 2nd line treatment depends on the number of sites of disease progression, the biology of the tumour and the patient's performance status (metastases limited to liver or lung or both, or peritoneum; dynamic of progression; symptoms, comorbidities, age, potential to undergo secondary resection) [LOE III, SOR C].

In case of major response to induction chemotherapy for liver, lung (or even peritoneal) disease, R0 resection should be considered, as it may result in long term survival and potentially cure in a small number of patients -although this is based on lower-level evidence than in the first-line setting [Adam et al., 2004].

With this respect, patients can be individually divided into the following three clinical groups, by parameters describing localisation and extent of disease, tumour dynamics, and patient's performance status [LOE III, SOR C].

1. patients potentially eligible for secondary surgical cytoreduction
2. fit patients with rapid tumour turnover, high disease volume, symptoms that need palliation
3. unfit patients or patients with slow tumour turnover, low disease volume, no/low symptoms in need for less aggressive palliative treatment

Available chemotherapeutic agents are fluoropyrimidines (5-Fluorouracil modulated with folinic acid (5-FU/FA), capecitabine and UFT), irinotecan and oxaliplatin [Rougier et al., 1998;Tournigand et al., 2004].

Although never prospectively proven, the achievement of a disease free status after chemotherapy and surgery is the only way to give long term survival or cure in an otherwise incurable/palliative situation [LOE III, SOR C]. For this purpose, the

most active induction chemotherapy which is able to induce downsizing as much as possible in as many patients as possible, should be selected.

For the intermediate group, , rapid regression of metastases is desirable – in particular when symptoms are either imminent or present. Therefore, the most active 2nd line treatment seems to be appropriate.

For the the third group of patients , monotherapy, low toxicity combination chemotherapy or an escalation strategy as well as observation periods seem more appropriate [LOE II, SOR B] [Chibaudel et al., 2009].

For the second and third group of patients optimal duration of therapy after response to induction therapy has not been established. The usual way is to introduce treatment when disease progression is confirmed during follow-up, and to alternate treatment with the longest possible observational periods. If chemotherapy is well tolerated the usual period of treatment is about 6 months.

Monoclonal antibodies used in colorectal cancer are the VEGF targeting agent bevacizumab which has been tested in the second-line setting and the anti-EGFR-antibodies cetuximab and panitumumab [Cunningham et al., 2004;Giantonio et al., 2007;Van Cutsem E. et al., 2007]. Anti-EGFR-antibodies have no activity in KRAS mutant tumours [LOE I, SOR A] [Amado et al., 2008;Karapetis et al., 2008]. Preliminary data on the KRAS codon 13 G13D mutation that is associated with response to anti-EGFR antibodies need further validation. Data from cross-trial comparisons suggest that cetuximab and panitumumab have similar efficacy [Grothey, 2010a]. However there are certain differences that may lead to the selection of one over the other agent. Such differences are:

1. schedule of administration
2. toxicity profile
3. combinations with certain chemotherapy drugs i.e. Irinotecan
4. magnitude of response
5. allergic reactions

If disease progression occurs during treatment with an EGFR inhibitor, then the disease is considered resistant to all EGFR inhibitors.

Some of the combinations of cytotoxic agents with targeted compounds have high-level evidence of activity in the first-line or third-line setting only [LOE II, SOR B].

In such cases, these therapies could also be considered for administration as second-line therapy taking into account individual patient and tumour characteristics as well as the absence of relevant trials. Bevacizumab efficacy is supported by data from prospective RCT in the first-line and second-line setting (E3200) [LOE II, SOR B] [Giantonio et al., 2007]. No data exist on its use in the third line setting for patients who had not received it in first or second line. As it is not feasible to test all combinations in all lines of therapy, extrapolation of safety and efficacy data from relevant trials in other lines of therapy seems scientifically justified but should be used with caution.

Table. Salvage therapy options for patients with advanced colorectal cancer (read as columns, not sequentially as rows)

Second-line therapy	**Third-line therapy**	**Further salvage therapies**
FOLFOX +/- Bevacizumab [LOE I, SOR A]	FOLFOX[II, B]	Mitomycin-C +/- Fluoropyrimine[III,C]
CapOx +/- Bevacizumab [LOE III, SOR C]	CapOx[II, B]	Re-introduction of previously administered chemotherapy [III, C]
FOLFIRI +/- Bevacizumab or Cetuximab [LOE I, A for FOLFIRI, LOE III, SOR C for combinations]	Irinotecan + Cetuximab [II, B]	Gemcitabine combinations [III, D]
FOLFIRI +/- Panitumumab [LOE I, SOR B]	Cetuximab[II, A]	Best Supportive Care
Irinotecan +/- Cetuximab [LOE I, SOR B]	Panitumumab[II, B]	IrOx[III, C]

	Mitomycin-C +/- Fluropyrimidine[III, C]	Best Supportive Care
		Clinical trials

The second line regimen depends on the chosen treatment strategy, prior first line therapy as well as patient characteristics. For potentially resectable and/or symptomatic disease, second line treatment should be a chemotherapy doublet with a monoclonal antibody or cytotoxic monotherapy with a monoclonal antibody [LOE II, SOR B].

Salvage therapy with monotherapy or doublet (either chemotherapy or chemotherapy with moAb or moAb) could be a valid option for patients, who are not feasible for secondary resection and have no symptoms or risk for deterioration of their disease [LOE II, SOR B].

Mitomycin C is generally not recommended as first, second or third line therapy when new generation compounds are available as treatment options as it is inferior to these therapies[LOE I, SOR A]. It could be a treatment option for patients with Irinotecan and platinum refractory disease fit enough to receive mitomycin with or without a fluoropyrimidine in the third line or further lines of therapy with the aim of symptom control and modest survival prolongation when no other alternative exist [LOE III, SOR C] [Dimou et al., 2010].

Maintenance therapy refers to treatment that is used following initial therapy, when disease is stable and not exhibiting signs of progression. The role of maintenance therapy and its optimal scheduling for metastatic colorectal cancer is under review. Researchers have been evaluating the optimal role of maintenance therapy among patients with colorectal cancer. Because chemotherapy is associated with side effects, researchers are interested in finding the optimal scheduling of therapy; such a program would reduce side effects while maintaining survival benefits.

The OPTIMOX2 trial evaluated continuous maintenance therapy among patients with metastatic colorectal cancer [Chibaudel et al., 2009]. This trial included 202 patients with metastatic colorectal cancer who were initially treated with oxaliplatin-based

chemotherapy. One group of patients was then treated with continuous maintenance chemotherapy (same as initial chemotherapy without oxaliplatin) while the other group had a break from chemotherapy and was treated again once their disease progressed.

- Overall survival was 26 months for those treated with maintenance therapy compared with 19 months for those not treated with maintenance therapy.
- Progression-free survival was improved for patients treated with maintenance therapy.
- During maintenance therapy fewer than 10% of patients experienced severe side effects

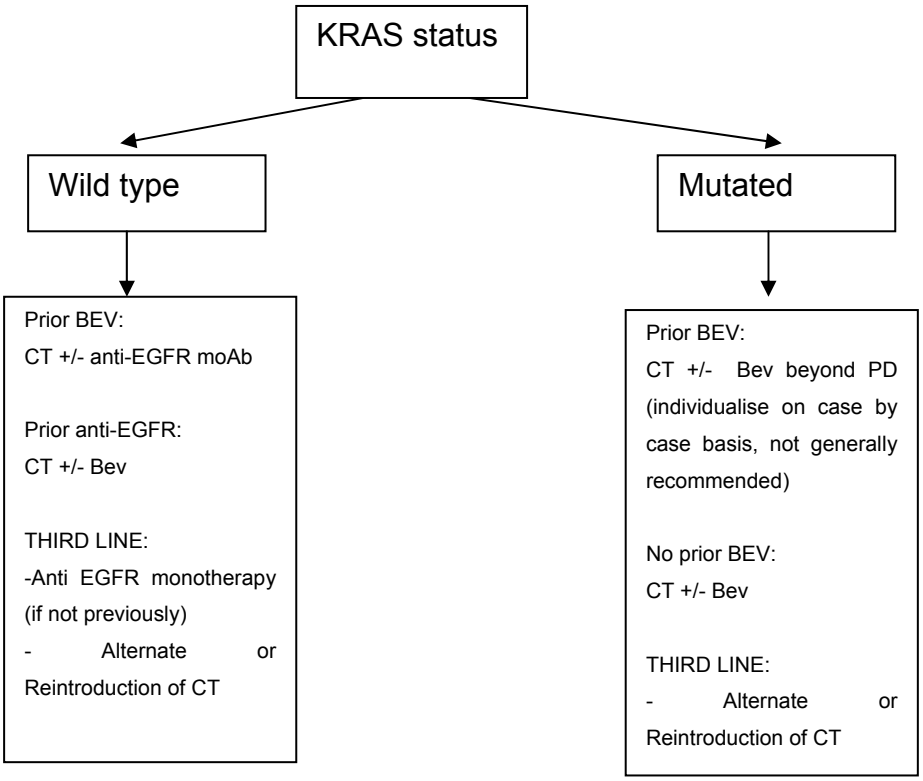
The researchers concluded that maintenance therapy may improve survival for patients with metastatic colorectal cancer as compared with re-introduction of chemotherapy at disease progression. There are some other studies (MACRO trial COIN-B trial) that suggest maintainance treatment with either chemotherapy or using monoclonal antibodies such as bevacizumab or cetuximab [Tabernero et al 2010]. Despite all the above information, presently maintenance treatment is not considered standard.

There is no data supporting continuation of anti-EGFR moAbs or bevacizumab beyond progression. Regarding bevacizumab administration beyond disease progression with use of a different chemotherapeutic regimen, there is low level evidence to support survival improvement from this strategy [LOE III, SOR C]. However, the data from retrospective cohort studies may include several biases [Grothey, 2010b]. Studies of maintenance bevacizumab following induction chemotherapy are underway (eg, DREAM, CAIRO-3).
No data from prospective randomised studies exist on the repeated use of previous chemotherapeutic combinations after their failure. Still, re-introduction of previously administered chemotherapeutic regimens as a therapeutic trial in patients without other therapeutic alternatives has biological rationale in view of preclinical evidence of unstable, reversible resistance of cancer cells. A progression-free interval of >6 months after chemotherapy has been advocated by some investigators to be indirect

evidence that the disease is still sensitive and on that basis the same chemotherapy could be re-introduced either immediately or after further lines of therapy[LOE IV, SOR C] [Grothey, 2010b].

Follow-up of patients that have completed 2nd or further line, treatment should be carried out (if patient well and asymptomatic) every 8-12 weeks with clinical examination, blood tests, tumour markers and imaging (either CT scan or MRI).

SALVAGE TREATMENT ALGORITHM



Recommendations

- ***Relevant for treatment strategy is the aim of 2nd line treatment which is dependent on the clinical presentation and biology of the tumour (tumour volume; dynamic of progression; symptoms), patient factors (comorbidities, age, potential to undergo secondary resection) and prior first-line therapy [LOE II, SOR B].***

- ***Second line treatment should be a cytotoxic monotherapy or doublet with or without a monoclonal antibody [LOE II, SOR B].***

- ***Third-line therapy options comprise anti-EGFR antibody therapy (KRAS wild type tumours) [LOE II, SORA], alternative chemotherapy single-agents or combinations [LOE II, SOR A], or re-introduction of previously administered chemotherapeutic combinations [LOE IV, SOR c].***

- ***Maintenance treatment with either chemotherapy or targeted agents is not currently recommended as standard.***

- ***Continuing targeted agents beyond disease progression is not recommended.***

- ***Consideration could be given to options that do not include chemotherapeutic agents such as stereotactic Radiation Therapy, RFA, TACE, or stenting for palliation in selected patients with good PS and controlled/minimal extrahepatic disease.***

- ***Patient participation in clinical trials should be strongly encouraged.***

12 Follow up

12.1 Rectal Cancer

Follow-up of patients with rectal cancer depends on stage, kind of surgery, perioperative treatment, and amenability for resection of recurrent disease. It also serves to identify and prevent second colorectal cancers.

Although there is not strong proof that intensive follow-up in patients with rectal cancer improves outcome, it is suggested that a similar approach to that used for colon cancer patients, is undertaken with the addition of proctoscopy.

Generally valid assessments are three monthly clinical visits for the first three years followed by six monthly visits for two more years with clinical examination, evaluation of long term toxicities (bowel or genitourinary function), and CEA testing (in patients possibly amenable to resection of hepatic or pulmonary recurrence) (LOE V, SOR D).

Complete colonoscopy must be performed at initial diagnosis, at 1 year after resection and after three and subsequently every five years. In case that a colonoscopy could not be performed prior to surgery because of an obstructing lesion, it is recommended that full colonoscopy is performed at 6 months after resection. If follow-up colonoscopy shows advanced adenoma it should be repeated in 1 year.

Patients receiving local excision and/or no perioperative radiotherapy should be closely monitored for local recurrence with digital rectal examination and sigmoidoscopy every three months for the first three years, afterwards every six months for two years. In patients who have undergone a low anterior resection, sigmoidoscopy is recommended every 6 months for 5 years.

Pelvic imaging, with either CT, MRI or ERUS should be done biannually for the first three years.

In patients with high risk disease (stage II and III) CT scan of the chest and abdomen every 6-12 months could be considered, although such close follow up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence.

Surveillance for multimodally treated rectal cancers should be considered beyond five years, as perioperative treatment might delay recurrence beyond this point in time.

12.1.1 Surveillance schedule

		3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
	CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	colonoscopy				x										x		
	Clinical examination (digital rectal examination and rigid rectoscopy)	(x)	x	(x)	x	(x)	x	(x)	x	(x)	x	(x)	x	x	x	x	x
High Risk St II/III	Abdominal/pelvic/ thoracic CT scan		(x)		x		(x)		x		(x)		x		(x)		(x)

12.2 Colon cancer

Patients follow up depends on stage, perioperative treatment, and amenability for resection of recurrent disease. In the past there were no solid data showing that intensive follow-up of patients with curatively resected colon cancer, improved survival. Four recent meta-analyses have shown that intensive follow-up improves overall survival by 7-13% and is now considered standard (LOE I, SOR A).

Generally valid assessments are three monthly clinical visits for the first three years followed by six monthly for two additional year visits with clinical examination, evaluation of long term toxicities (polyneuropathy after oxaliplatin), and CEA testing (in patients possibly amenable to resection of hepatic or pulmonary recurrence).

Complete colonoscopy must be performed at initial diagnosis, at 1 year after resection and after three and subsequently every five years (Level III, grade B). In case that a colonoscopy could not be performed prior to surgery because of an obstructing lesion, it is recommended that full colonoscopy is performed at 6 months after resection. If follow-up colonoscopy shows advanced adenoma it should be repeated in 1 year.

In patients with high risk disease CT scan of the chest and abdomen every 6-12 months could be considered, although such close follow up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence (LOE II, SOR B).

Follow up CT scans should be performed with the same imaging protocols and contrast phases of enhancement. If MRI was used for the initial staging MRI should also be used for the follow up. CT images can not be compared to MRI images due to different sensitivity/specificity.

Liver CEUS could substitute for abdominal CT scan regarding follow up of liver metastases specifically in young patients with no evidence of extrahepatic disease (LOE III, SOR C).

Routine PET-CT scanning is not recommended as a preoperative study or for surveillance.

12.2.1 Surveillance schedule

Colon cancer																	
		3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
	CEA	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	colonoscopy												x				
	abdominal ultrasound		x		x		x		x		x		x		x		x
high risk (stage III)	abdominal/thoracic CT scan		(x)		x		(x)		x		(x)		x		(x)		(x)

13 Appendices

13.1 Staging-TNM system

TNM	Stage	Extension to	
Tis N0 M0	0	Carcinoma *in situ*: intraepithelial or invasion of lamina propria	
T1 N0 M0	I	Submucosa	
T2 N0 M0	I	Muscularis propria	
T3 N0 M0	IIA	Subserosa/perirectal tissue	
	Substaging[a]	T3a	<1 mm
		T3b	1–5 mm
		T3c	5–15 mm
		T3d	15+ mm
T4 N0 M0	IIB	Perforation into visceral peritoneum (b) or invasion to other organs (a)[b]	
T1–2 N1 M0	IIIA	1–3 regional nodes involved	
T3–4 N1 M0	IIIB	1–3 regional nodes involved	
T1–4 N2 M0	IIIC	≥4 regional nodes involved	
T1–4 N1–2 M1	IV	Distant metastases	

Stage	T	N	M
0	Tis	N0	M0
I	T1,2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1,2	N1	M0
IIIB	T3,4	N1	M0
IIIC	any	N2	M0
IV	any	any	M1

Grading of surgical TME specimen (M.E.R.C.U.R.Y. criteria)
Good (grade 1): intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defects larger than 5 mm; no coning on specimen; smooth CRM on slicing
Moderate (grade 2): moderate bulk to mesorectum but irregularity of the mesorectal surface; moderate coning of the specimen towards the distal margin; at no site is the muscularis propria visible with the exception of the area of insertion of levator muscles; moderate irregularity of the CRM
Poor (grade 3): little bulk of mesorectum with defects down into muscularis and/or very irregular CRM

tumor regression grading systems
0 = complete histomorphologic regression
1 = major histomorphologic regression with few hard to find scattered microscopic foci <2 mm
2 = minor histomorphologic regression with fibrosis outweighing residual cancer cells
3 = minimal histomorphologic regression with no/ negligible evidence of any tumor response

13.2 Pathology Report

Surname **Report No**

Forenames **Date of receipt**

Data of birth **Department, Surgeon**

Sex

Gross Description

Site of tumour

Dimensions of the tumour

Distance of tumour of the nearer margin

Presence of the tumour perforation (pT4) ☐ Yes ☐ No

Depth of tumour invasion

For rectal tumours

Tumour is ☐ above ☐ at ☐ below
the peritoneal reflection

Distance from the dentate line

Microscopic

Type of adenocarcinoma

Other type of carcinoma

Differentiation (histologic grade)

Low grade ☐

High grade ☐

Local invasion

pT1 Tumor invades submucosa ☐

pT2 Tumor invades muscularis propria ☐

pT3 Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized pericolic or perirectal tissues ☐

pT4 Tumour directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b) ☐

Small vessel invasion

Lymphatic ☐ Yes ☐ No

Blood ☐ Yes ☐ No

Extramural Venous invasion ☐ Yes ☐ No

Perineural invasion ☐ Yes ☐ No

Tumour infiltrating lymphocytes ☐ Yes ☐ No

Resection margins

R0 (no residual tumour) ☐

Final document ☐

R1 (microscopic residual tumour)

R2 (macroscopic residual tumour) ☐

For rectal tumour

Circumferential margin involvement (CRM)

Histological measurement from tumour to CRM ..... mm

Lymph nodes

N0 No regional lymph nodes metastasis ☐

N1 Metastasis in 1-3 lymph nodes ☐

N2 Metastasis in 4 or more lymph nodes ☐

Distant metastasis

MX Presence of distant metastasis cannot be assesed

M0 No distant metastasis

M1 Distant metastasis

Tumour regression after preoperative treatment

grade 0 no regression ☐

grade 1 minimal regression with obvious fibrosis ☐

grade 2 moderate dominantly fibrotic changes with few tumour cells or groups ☐

grade 4 total regression ☐

TNM

T ☐ N ☐ M ☐

Signature

Is based on "Reporting colorectal cancer" by P.Quirke and E Morris

Histopathology 2007

14 References

Reference List

NICE consultation document. 2011.
Ref Type: Internet Communication

Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H (2004) Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg* **240**: 1052-1061

Akasu T, Sugihara K, Moriya Y, Fujita S (1997) Limitations and pitfalls of transrectal ultrasonography for staging of rectal cancer. *Dis Colon Rectum* **40**: S10-S15

Aloia T, Sebagh M, Plasse M, Karam V, Levi F, Giacchetti S, Azoulay D, Bismuth H, Castaing D, Adam R (2006) Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* **24**: 4983-4990

Amado RG, Wolf M, Peeters M, Van CE, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* **26**: 1626-1634

Arkenau HT, Arnold D, Cassidy J, az-Rubio E, Douillard JY, Hochster H, Martoni A, Grothey A, Hinke A, Schmiegel W, Schmoll HJ, Porschen R (2008) Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. *J Clin Oncol* **26**: 5910-5917

ASCO (2003) American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* **21**: 2397-2406

Aziz O, Constantinides V, Tekkis PP, Athanasiou T, Purkayastha S, Paraskeva P, Darzi AW, Heriot AG (2006) Laparoscopic versus open surgery for rectal cancer: a meta-analysis. *Ann Surg Oncol* **13**: 413-424

Balmana J, Castells A, Cervantes A (2010) Familial colorectal cancer risk: ESMO Clinical Practice Guidelines. *Ann Oncol* **21 Suppl 5**: v78-v81

Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van BH, De BA, von Meyenfeldt MF, Baeten CG, van Engelshoven JM (2001) Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet* **357**: 497-504

Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, MacDonald JS, Catalano PJ, Haller DG (2005) Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* **23**: 8706-8712

Bilimoria KY, Palis B, Stewart AK, Bentrem DJ, Freel AC, Sigurdson ER, Talamonti MS, Ko CY (2008) Impact of tumor location on nodal evaluation for colon cancer. *Dis Colon Rectum* **51**: 154-161

Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J (2004) Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology* **232**: 773-783

Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, Abbott CR, Scott N, Finan PJ, Johnston D, Quirke P (2002) Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* **235**: 449-457

Bisgaard ML, Ripa R, Knudsen AL, Bulow S (2004) Familial adenomatous polyposis patients without an identified APC germline mutation have a severe phenotype. *Gut* **53**: 266-270

Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, Repetto L, Soubeyran P (2007) EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* **43**: 258-270

Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de BF, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* **27**: 663-671

Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhrij E, Haglind E, Pahlman L (2007) Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. *Arch Surg* **142**: 298-303

Borschitz T, Wachtlin D, Mohler M, Schmidberger H, Junginger T (2008) Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. *Ann Surg Oncol* **15**: 712-720

Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* **355**: 1114-1123

Box JC, Rodriguez-Bigas MA, Weber TK, Petrelli NJ (1999) Clinical implications of multiple colorectal carcinomas in hereditary nonpolyposis colorectal carcinoma. *Dis Colon Rectum* **42**: 717-721

Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, Wiig JN, Bystrom P, Bujko K, Glimelius B (2008) Randomized phase III study comparing

preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* **26**: 3687-3694

Breukink S, Pierie J, Wiggers T (2006) Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* CD005200

Brouquet A, Overman MJ, Kopetz S, Maru DM, Loyer EM, Andreou A, Cooper A, Curley SA, Garrett CR, Abdalla EK, Vauthey JN (2011) Is resection of colorectal liver metastases after a second-line chemotherapy regimen justified? *Cancer* **117**: 4484-4492

Brown G, Kirkham A, Williams GT, Bourne M, Radcliffe AG, Sayman J, Newell R, Sinnatamby C, Heald RJ (2004) High-resolution MRI of the anatomy important in total mesorectal excision of the rectum. *AJR Am J Roentgenol* **182**: 431-439

Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, Williams GT (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology* **227**: 371-377

Bucher P, Mermillod B, Gervaz P, Morel P (2004) Mechanical bowel preparation for elective colorectal surgery: a meta-analysis. *Arch Surg* **139**: 1359-1364

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* **93**: 1215-1223

Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D (2006) MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? *Br J Cancer* **94**: 351-357

Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ (2009) Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* **10**: 44-52

Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M (2000) Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *JAMA* **284**: 1008-1015

Cao C, Yan TD, Black D, Morris DL (2009) A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* **16**: 2152-2165

Capirci C, Rubello D, Chierichetti F, Crepaldi G, Carpi A, Nicolini A, Mandoliti G, Polico C (2004) Restaging after neoadjuvant chemoradiotherapy for rectal adenocarcinoma: role of F18-FDG PET. *Biomed Pharmacother* **58**: 451-457

Cella D, Dobrez D, Glaspy J (2003) Control of cancer-related anemia with erythropoietic agents: a review of evidence for improved quality of life and clinical outcomes. *Ann Oncol* **14**: 511-519

Chibaudel B, Maindrault-Goebel F, Lledo G, Mineur L, Andre T, Bennamoun M, Mabro M, Artru P, Carola E, Flesch M, Dupuis O, Colin P, Larsen AK, Afchain P, Tournigand C, Louvet C, de GA (2009) Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* **27**: 5727-5733

Cho YB, Chun HK, Kim MJ, Choi JY, Park CM, Kim BT, Lee SJ, Yun SH, Kim HC, Lee WY (2009) Accuracy of MRI and 18F-FDG PET/CT for restaging after preoperative concurrent chemoradiotherapy for rectal cancer. *World J Surg* **33**: 2688-2694

Cohen AM (1991) Surgical considerations in patients with cancer of the colon and rectum. *Semin Oncol* **18**: 381-387

Colorectal Cancer Collaborative Group (2001) Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* **358**: 1291-1304

Compton CC (2003) Colorectal carcinoma: diagnostic, prognostic, and molecular features. *Mod Pathol* **16**: 376-388

Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M, Willett C (2000) Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* **124**: 979-994

Compton CC, Greene FL (2004) The staging of colorectal cancer: 2004 and beyond. *CA Cancer J Clin* **54**: 295-308

Conroy T, Guillemin F, Stines J, Denis B (1994) [Diagnosis and staging of colorectal cancers]. *Rev Prat* **44**: 2706-2713

Corman ML (2005) Carcinoma of the colon. In *Colon and Rectal Surgery*, Corman ML (ed) pp 767-903. Lippincott Williams & Wilkins: Philadelphia

COST Study Group (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* **350**: 2050-2059

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van CE (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* **351**: 337-345

Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW (2003) Prospective, randomized, controlled trial between a pathway of controlled

rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* **46**: 851-859

den Dulk M., Putter H, Collette L, Marijnen CA, Folkesson J, Bosset JF, Rodel C, Bujko K, Pahlman L, van d, V (2009) The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. *Eur J Cancer* **45**: 1175-1183

Dent OF, Haboubi N, Chapuis PH, Chan C, Lin BP, Wong SK, Bokey EL (2007) Assessing the evidence for an association between circumferential tumour clearance and local recurrence after resection of rectal cancer. *Colorectal Dis* **9**: 112-121

DeRoock W, Jonker DJ, Di NF, Sartore-Bianchi A, Tu D, Siena S, Lamba S, Arena S, Frattini M, Piessevaux H, Van CE, O'Callaghan CJ, Khambata-Ford S, Zalcberg JR, Simes J, Karapetis CS, Bardelli A, Tejpar S (2010) Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* **304**: 1812-1820

Detry RJ, Kartheuser AH, Lagneaux G, Rahier J (1996) Preoperative lymph node staging in rectal cancer: a difficult challenge. *Int J Colorectal Dis* **11**: 217-221

Dimou A, Syrigos KN, Saif MW (2010) Is there a role for mitomycin C in metastatic colorectal cancer? *Expert Opin Investig Drugs* **19**: 723-735

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* **355**: 1041-1047

Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocakova I, Ruff P, Blasinska-Morawiec M, Smakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J (2010) Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* **28**: 4697-4705

Dresen RC, Beets GL, Rutten HJ, Engelen SM, Lahaye MJ, Vliegen RF, de Bruine AP, Kessels AG, Lammering G, Beets-Tan RG (2009) Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part I. Are we able to predict tumor confined to the rectal wall? *Radiology* **252**: 71-80

Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, niels-Gooszen AW, van den Brule AJ, van den Berg HA, Rutten HJ (2008) Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol* **15**: 1937-1947

Duek SD, Issa N, Hershko DD, Krausz MM (2008) Outcome of transanal endoscopic microsurgery and adjuvant radiotherapy in patients with T2 rectal cancer. *Dis Colon Rectum* **51**: 379-384

Dworak O, Keilholz L, Hoffmann A (1997) Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis* **12**: 19-23

EGAPP (2009) Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med* **11**: 35-41

Elias D, Blot F, El OA, Antoun S, Lasser P, Boige V, Rougier P, Ducreux M (2001) Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* **92**: 71-76

Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, Giovannini M, Lasser P (2004a) Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* **11**: 518-521

Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dube P, Glehen O (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* **28**: 63-68

Elias D, Matsuhisa T, Sideris L, Liberale G, Drouard-Troalen L, Raynard B, Pocard M, Puizillou JM, Billard V, Bourget P, Ducreux M (2004b) Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: pharmacokinetics, tissue distribution and tolerance. *Ann Oncol* **15**: 1558-1565

Engelen SM, Beets-Tan RG, Lahaye MJ, Lammering G, Jansen RL, van Dam RM, Konsten J, Leijtens JW, van d, V, Beets GL (2010) MRI after chemoradiotherapy of rectal cancer: a useful tool to select patients for local excision. *Dis Colon Rectum* **53**: 979-986

Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crino L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* **25**: 1670-1676

Farouk R, Nelson H, Gunderson LL (1997) Aggressive multimodality treatment for locally advanced irresectable rectal cancer. *Br J Surg* **84**: 741-749

Fiori E, Lamazza A, De CA, Bononi M, Volpino P, Schillaci A, Cavallaro A, Cangemi V (2004) Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer Res* **24**: 265-268

Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Jr., Hellinger M, Flanagan R, Jr., Peters W, Nelson H (2007) Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* **246**: 655-662

Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, Giovagnoni A (2010) Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging* **31**: 19-31

Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U (2005) Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* **23**: 5644-5650

Franklin ME, Jr., Rosenthal D, brego-Medina D, Dorman JP, Glass JL, Norem R, Diaz A (1996) Prospective comparison of open vs. laparoscopic colon surgery for carcinoma. Five-year results. *Dis Colon Rectum* **39**: S35-S46

Fuchs CS, Marshall J, Barrueco J (2008) Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol* **26**: 689-690

Gastinger I, Marusch F, Koch A, Meyer F, Nestler G, Schmidt U, Meyer J, Eggert A, Albrecht R, Kockerling F, Lippert H (2004) [Hartmann's procedure indication in colorectal carcinoma]. *Chirurg* **75**: 1191-1196

Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, Tekkis P (2009) Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. *Lancet Oncol* **10**: 1053-1062

Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB, III (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* **25**: 1539-1544

Gillams AR, Lees WR (2004) Radio-frequency ablation of colorectal liver metastases in 167 patients. *Eur Radiol* **14**: 2261-2267

Gillams AR, Lees WR (2009) Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. *Eur Radiol* **19**: 1206-1213

Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De SM, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AA, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P (2004)

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* **22**: 3284-3292

Glehen O, Mithieux F, Osinsky D, Beaujard AC, Freyer G, Guertsch P, Francois Y, Peyrat P, Panteix G, Vignal J, Gilly FN (2003) Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. *J Clin Oncol* **21**: 799-806

Glimelius B (2003) Recurrent rectal cancer. The pre-irradiated primary tumour: can more radiotherapy be given? *Colorectal Dis* **5**: 501-503

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts S (2006) Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J Clin Oncol* **24**: 3347-3353

Goligher JA (1985) Incidence and pathology of carcinoma of the colon and rectum. In *Surgery of the Anus, Rectum and Colon.*, pp 445. Balliere Tindale: London

Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP (2009a) Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis* **24**: 1119-1131

Gouvas N, Tsiaoussis J, Pechlivanides G, Tzortzinis A, Dervenis C, Avgerinos C, Xynos E (2009b) Quality of surgery for rectal carcinoma: comparison between open and laparoscopic approaches. *Am J Surg* **198**: 702-708

Gouvas N, Tsiaoussis J, Pechlivanides G, Zervakis N, Tzortzinis A, Avgerinos C, Dervenis C, Xynos E (2009c) Laparoscopic or open surgery for the cancer of the middle and lower rectum short-term outcomes of a comparative non-randomised study. *Int J Colorectal Dis* **24**: 761-769

Gravante G, Overton J, Sorge R, Bhardwaj N, Metcalfe MS, Lloyd DM, Dennison AR (2011) Radiofrequency ablation versus resection for liver tumours: an evidence-based approach to retrospective comparative studies. *J Gastrointest Surg* **15**: 378-387

Grothey A (2010a) EGFR antibodies in colorectal cancer: where do they belong? *J Clin Oncol* **28**: 4668-4670

Grothey A (2010b) Reintroduction of oxaliplatin: a viable approach to the long-term management of metastatic colorectal cancer. *Oncology* **79**: 389-399

Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, Kozloff M (2008) Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol* **26**: 5326-5334

Guadagni S, Fiorentini G, Palumbo G, Valenti M, Russo F, Cantore M, Deraco M, Vaglini M, Amicucci G (2001) Hypoxic pelvic perfusion with mitomycin C using a

simplified balloon-occlusion technique in the treatment of patients with unresectable locally recurrent rectal cancer. *Arch Surg* **136**: 105-112

Guenaga KK, Matos D, Wille-Jorgensen P (2009) Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* CD001544

Guenette JP, Dupuy DE (2010) Radiofrequency ablation of colorectal hepatic metastases. *J Surg Oncol* **102**: 978-987

Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* **365**: 1718-1726

Haddock MG, Gunderson LL, Nelson H, Cha SS, Devine RM, Dozois RR, Wolff BG (2001) Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. *Int J Radiat Oncol Biol Phys* **49**: 1267-1274

Han JG, Wei GH, Gao ZG, Zheng Y, Wang ZJ (2009) Intersphincteric resection with direct coloanal anastomosis for ultralow rectal cancer: the experience of People's Republic of China. *Dis Colon Rectum* **52**: 950-957

Heald RJ, Husband EM, Ryall RD (1982) The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* **69**: 613-616

Heald RJ, Moran BJ, Brown G, Daniels IR (2004) Optimal total mesorectal excision for rectal cancer is by dissection in front of Denonvilliers' fascia. *Br J Surg* **91**: 121-123

Heiss MM, Tarabichi A, Delanoff C, Allgayer H, Jauch KW, Hernandez-Richter T, Mempel W, Beck KG, Schildberg FW, Messmer K (1996) Perisurgical erythropoietin application in anemic patients with colorectal cancer: A double-blind randomized study. *Surgery* **119**: 523-527

Heriot AG, Kumar D (2000) Prospective audit following the introduction of short course preoperative radiotherapy for rectal cancer. *Br J Surg* **87**: 965

Hohenberger W, Merkel S, Matzel K, Bittorf B, Papadopoulos T, Gohl J (2006) The influence of abdomino-peranal (intersphincteric) resection of lower third rectal carcinoma on the rates of sphincter preservation and locoregional recurrence. *Colorectal Dis* **8**: 23-33

Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis* **11**: 354-364

Holm T, Ljung A, Haggmark T, Jurell G, Lagergren J (2007) Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. *Br J Surg* **94**: 232-238

Hughes R, Glynne-Jones R, Grainger J, Richman P, Makris A, Harrison M, Ashford R, Harrison RA, Livingstone JI, McDonald PJ, Meyrick TJ, Mitchell IC, Northover JM, Phillips R, Wallace M, Windsor A, Novell JR (2006) Can pathological complete response in the primary tumour following pre-operative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for sterilisation of pelvic lymph nodes, a low risk of local recurrence and the appropriateness of local excision? *Int J Colorectal Dis* **21**: 11-17

Huser N, Michalski CW, Erkan M, Schuster T, Rosenberg R, Kleeff J, Friess H (2008) Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. *Ann Surg* **248**: 52-60

Hutchins G, Southward K, Handley K, Magill L, Beaumont C, Stahlschmidt J, Richman S, Chambers P, Seymour M, Kerr D, Gray R, Quirke P (2011) Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol* **29**: 1261-1270

Janssen MH, Ollers MC, Riedl RG, van den BJ, Buijsen J, van Stiphout RG, Aerts HJ, Lambin P, Lammering G (2010) Accurate prediction of pathological rectal tumor response after two weeks of preoperative radiochemotherapy using (18)F-fluorodeoxyglucose-positron emission tomography-computed tomography imaging. *Int J Radiat Oncol Biol Phys* **77**: 392-399

Jasperson KW, Tuohy TM, Neklason DW, Burt RW (2010) Hereditary and familial colon cancer. *Gastroenterology* **138**: 2044-2058

Jayne DG, Fook S, Loi C, Seow-Choen F (2002) Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* **89**: 1545-1550

Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM (2007) Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* **25**: 3061-3068

Johnson PM, Porter GA, Ricciardi R, Baxter NN (2006) Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol* **24**: 3570-3575

Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, MacDonald JS, Catalano PJ, Haller DG (2003) Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. *Ann Surg Oncol* **10**: 213-218

Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* **23**: 3706-3712

Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van d, V (2001) Preoperative

radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* **345**: 638-646

Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* **359**: 1757-1765

Karoui M, Penna C, min-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B (2006) Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* **243**: 1-7

Kecmanovic DM, Pavlov MJ, Ceranic MS, Sepetkovski AV, Kovacevic PA, Stamenkovic AB (2005) Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy. *Eur J Surg Oncol* **31**: 147-152

Kehlet H, Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* **362**: 1921-1928

Kemeny MM, Adak S, Gray B, MacDonald JS, Smith T, Lipsitz S, Sigurdson ER, O'Dwyer PJ, Benson AB, III (2002) Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. *J Clin Oncol* **20**: 1499-1505

Khot UP, Lang AW, Murali K, Parker MC (2002) Systematic review of the efficacy and safety of colorectal stents. *Br J Surg* **89**: 1096-1102

Kim SH, Lee JM, Hong SH, Kim GH, Lee JY, Han JK, Choi BI (2009) Locally advanced rectal cancer: added value of diffusion-weighted MR imaging in the evaluation of tumor response to neoadjuvant chemo- and radiation therapy. *Radiology* **253**: 116-125

King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH (2006) Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* **93**: 300-308

Koh DM, Brown G, Husband JE (2006) Nodal staging in rectal cancer. *Abdom Imaging* **31**: 652-659

Koh DM, Chau I, Tait D, Wotherspoon A, Cunningham D, Brown G (2008) Evaluating mesorectal lymph nodes in rectal cancer before and after neoadjuvant chemoradiation using thin-section T2-weighted magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* **71**: 456-461

Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van BA, Sinnige HA, Creemers GJ,

Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ (2007) Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* **370**: 135-142

Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP (2006) Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* **243**: 212-222

Kronawitter U, Kemeny NE, Heelan R, Fata F, Fong Y (1999) Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. *Cancer* **86**: 229-235

Kuhry E, Bonjer HJ, Haglind E, Hop WC, Veldkamp R, Cuesta MA, Jeekel J, Pahlman L, Morino M, Lacy A, Delgado S (2005) Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. *Surg Endosc* **19**: 687-692

Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ (2008) Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* CD003432

Kusters M, Marijnen CA, van d, V, Rutten HJ, Lahaye MJ, Kim JH, Beets-Tan RG, Beets GL (2010) Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. *Eur J Surg Oncol* **36**: 470-476

Kwok H, Bissett IP, Hill GL (2000) Preoperative staging of rectal cancer. *Int J Colorectal Dis* **15**: 9-20

Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* **359**: 2224-2229

Lahaye MJ, Beets GL, Engelen SM, Kessels AG, de Bruine AP, Kwee HW, van Engelshoven JM, van d, V, Beets-Tan RG (2009) Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part II. What are the criteria to predict involved lymph nodes? *Radiology* **252**: 81-91

Lahaye MJ, Engelen SM, Kessels AG, de Bruine AP, von Meyenfeldt MF, van Engelshoven JM, van d, V, Beets GL, Beets-Tan RG (2008) USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. *Radiology* **246**: 804-811

Lambregts DM, Maas M, Riedl RG, Bakers FC, Verwoerd JL, Kessels AG, Lammering G, Boetes C, Beets GL, Beets-Tan RG (2011a) Value of ADC measurements for nodal staging after chemoradiation in locally advanced rectal cancer-a per lesion validation study. *Eur Radiol* **21**: 265-273

Lambregts DM, Vandecaveye V, Barbaro B, Bakers FC, Lambrecht M, Maas M, Haustermans K, Valentini V, Beets GL, Beets-Tan RG (2011b) Diffusion-weighted

MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. *Ann Surg Oncol* **18**: 2224-2231

Landmann RG, Wong WD, Hoepfl J, Shia J, Guillem JG, Temple LK, Paty PB, Weiser MR (2007) Limitations of early rectal cancer nodal staging may explain failure after local excision. *Dis Colon Rectum* **50**: 1520-1525

Larsen SG, Wiig JN, Dueland S, Giercksky KE (2008) Prognostic factors after preoperative irradiation and surgery for locally advanced rectal cancer. *Eur J Surg Oncol* **34**: 410-417

Laurent C, Leblanc F, Bretagnol F, Capdepont M, Rullier E (2008) Long-term wound advantages of the laparoscopic approach in rectal cancer. *Br J Surg* **95**: 903-908

Laurent C, Leblanc F, Gineste C, Saric J, Rullier E (2007) Laparoscopic approach in surgical treatment of rectal cancer. *Br J Surg* **94**: 1555-1561

Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, MacDonald JS, Catalano PJ, Haller DG (2003) Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* **21**: 2912-2919

Lee JS, Petrelli NJ, Rodriguez-Bigas MA (2001) Rectal cancer in hereditary nonpolyposis colorectal cancer. *Am J Surg* **181**: 207-210

Lencioni R, Crocetti L, Cioni D, Della PC, Bartolozzi C (2004) Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. *Invest Radiol* **39**: 689-697

Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY (2004) Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. *Lancet* **363**: 1187-1192

Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ (2008) Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* **134**: 1570-1595

Lezoche E, Guerrieri M, Paganini AM, Baldarelli M, De SA, Lezoche G (2005) Long-term results in patients with T2-3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. *Br J Surg* **92**: 1546-1552

Liska D, Weiser MR (2010) Optimal surgical treatment of locally advanced low rectal cancer. *Minerva Chir* **65**: 181-196

Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez-Sainz J, Gomez-Rio M, Bellon-Guardia M, Ramos-Font C, Rebollo-Aguirre AC, Cabello-Garcia D, Ferron-Orihuela A

(2007) Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. *Eur J Nucl Med Mol Imaging* **34**: 859-867

Ma Y, Yang Z, Qin H, Wang Y (2010) A meta-analysis of laparoscopy compared with open colorectal resection for colorectal cancer. *Med Oncol*

Mahteme H, Hansson J, Berglund A, Pahlman L, Glimelius B, Nygren P, Graf W (2004) Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study. *Br J Cancer* **90**: 403-407

Maizlin ZV, Brown JA, So G, Brown C, Phang TP, Walker ML, Kirby JM, Vora P, Tiwari P (2010) Can CT replace MRI in preoperative assessment of the circumferential resection margin in rectal cancer? *Dis Colon Rectum* **53**: 308-314

Marijnen CA, Nagtegaal ID, Kapiteijn E, Kranenbarg EK, Noordijk EM, van Krieken JH, van d, V, Leer JW (2003) Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* **55**: 1311-1320

Martin RC, Joshi J, Robbins K, Tomalty D, O'Hara R, Tatum C (2009a) Transarterial Chemoembolization of Metastatic Colorectal Carcinoma with Drug-Eluting Beads, Irinotecan (DEBIRI): Multi-Institutional Registry. *J Oncol* **2009**: 539795

Martin RC, Robbins K, Tomalty D, O'Hara R, Bosnjakovic P, Padr R, Rocek M, Slauf F, Scupchenko A, Tatum C (2009b) Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. *World J Surg Oncol* **7**: 80

Maughan NJ, Morris E, Forman D, Quirke P (2007) The validity of the Royal College of Pathologists' colorectal cancer minimum dataset within a population. *Br J Cancer* **97**: 1393-1398

Maughan NJ, Quirke P (2003) Modern management of colorectal cancer--a pathologist's view. *Scand J Surg* **92**: 11-19

Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP (2011) Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* **377**: 2103-2114

Meisner S, Hensler M, Knop FK, West F, Wille-Jorgensen P (2004) Self-expanding metal stents for colonic obstruction: experiences from 104 procedures in a single center. *Dis Colon Rectum* **47**: 444-450

MERCURY (2007) Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology* **243**: 132-139

Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P (2001) The prognostic inhomogeneity in pT3 rectal carcinomas. *Int J Colorectal Dis* **16**: 298-304

Middleton PF, Sutherland LM, Maddern GJ (2005) Transanal endoscopic microsurgery: a systematic review. *Dis Colon Rectum* **48**: 270-284

Milsom JW, Bohm B, Hammerhofer KA, Fazio V, Steiger E, Elson P (1998) A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. *J Am Coll Surg* **187**: 46-54

Mirnezami AH, Sagar PM, Kavanagh D, Witherspoon P, Lee P, Winter D (2010) Clinical algorithms for the surgical management of locally recurrent rectal cancer. *Dis Colon Rectum* **53**: 1248-1257

Montagnani F, Chiriatti A, Licitra S, Aliberti C, Fiorentini G (2010) Differences in efficacy and safety between capecitabine and infusional 5-fluorouracil when combined with irinotecan for the treatment of metastatic colorectal cancer. *Clin Colorectal Cancer* **9**: 243-247

Moore HG, Riedel E, Minsky BD, Saltz L, Paty P, Wong D, Cohen AM, Guillem JG (2003) Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. *Ann Surg Oncol* **10**: 80-85

Moore HG, Shoup M, Riedel E, Minsky BD, Alektiar KM, Ercolani M, Paty PB, Wong WD, Guillem JG (2004) Colorectal cancer pelvic recurrences: determinants of resectability. *Dis Colon Rectum* **47**: 1599-1606

Moosmann N, von Weikersthal LF, Vehling-Kaiser U, Stauch M, Hass HG, Dietzfelbinger H, Oruzio D, Klein S, Zellmann K, Decker T, Schulze M, Abenhardt W, Puchtler G, Kappauf H, Mittermuller J, Haberl C, Schalhorn A, Jung A, Stintzing S, Heinemann V (2011) Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104--a randomized trial of the German AIO CRC study group. *J Clin Oncol* **29**: 1050-1058

Morrin MM, Farrell RJ, Raptopoulos V, McGee JB, Bleday R, Kruskal JB (2000) Role of virtual computed tomographic colonography in patients with colorectal cancers and obstructing colorectal lesions. *Dis Colon Rectum* **43**: 303-311

Mulier S, Ni Y, Jamart J, Michel L, Marchal G, Ruers T (2008) Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol* **15**: 144-157

Nagtegaal ID, Marijnen CA, Kranenbarg EK, van d, V, van Krieken JH (2002a) Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* **26**: 350-357

Nagtegaal ID, van d, V, van der WE, Kapiteijn E, Quirke P, van Krieken JH (2002b) Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* **20**: 1729-1734

Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P, Jaeck D (2008) Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* **247**: 118-124

Nash GM, Weiser MR, Guillem JG, Temple LK, Shia J, Gonen M, Wong WD, Paty PB (2009) Long-term survival after transanal excision of T1 rectal cancer. *Dis Colon Rectum* **52**: 577-582

Niekel MC, Bipat S, Stoker J (2010) Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* **257**: 674-684

NIH Consensus (1990) NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* **264**: 1444-1450

Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van CE, Scheithauer W, Gruenberger T (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* **371**: 1007-1016

Nordlinger B, Van CE, Rougier P, Kohne CH, Ychou M, Sobrero A, Adam R, Arvidsson D, Carrato A, Georgoulias V, Giuliante F, Glimelius B, Golling M, Gruenberger T, Tabernero J, Wasan H, Poston G (2007) Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* **43**: 2037-2045

Ong KO, Leen E (2007) Radiological staging of colorectal liver metastases. *Surg Oncol* **16**: 7-14

Pacini P, Cionini L, Pirtoli L, Ciatto S, Tucci E, Sebaste L (1986) Symptomatic recurrences of carcinoma of the rectum and sigmoid. The influence of radiotherapy on the quality of life. *Dis Colon Rectum* **29**: 865-868

Pahlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjodahl R, Ojerskog B, Damber L, Johansson R (2007) The Swedish rectal cancer registry. *Br J Surg* **94**: 1285-1292

Park MJ, Kim SH, Lee SJ, Jang KM, Rhim H (2011) Locally advanced rectal cancer: added value of diffusion-weighted MR imaging for predicting tumor clearance of the

mesorectal fascia after neoadjuvant chemotherapy and radiation therapy. *Radiology* **260**: 771-780

Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, Quirke P, Sebag-Montefiore D, Moran B, Heald R, Guthrie A, Bees N, Swift I, Pennert K, Brown G (2011) Magnetic Resonance Imaging-Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience. *J Clin Oncol* **29**: 3753-3760

Patriti A, Contine A, Carbone E, Gulla N, Donini A (2005) One-stage resection without colonic lavage in emergency surgery of the left colon. *Colorectal Dis* **7**: 332-338

Pechlivanides G, Gouvas N, Tsiaoussis J, Tzortzinis A, Tzardi M, Moutafidis M, Dervenis C, Xynos E (2007) Lymph node clearance after total mesorectal excision for rectal cancer: laparoscopic versus open approach. *Dig Dis* **25**: 94-99

Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, Rutten H, Pahlman L, Glimelius B, Leer JW, van d, V (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* **246**: 693-701

Pestieau SR, Sugarbaker PH (2000) Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. *Dis Colon Rectum* **43**: 1341-1346

Pilati P, Mocellin S, Rossi CR, Foletto M, Campana L, Nitti D, Lise M (2003) Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from colon adenocarcinoma. *Ann Surg Oncol* **10**: 508-513

Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, Belghiti J, Piedbois P, Guimbaud R, Nordlinger B, Bugat R, Lazorthes F, Bedenne L (2006) Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* **24**: 4976-4982

Quirke P, Cuvelier C, Ensari A, Glimelius B, Laurberg S, Ortiz H, Piard F, Punt CJ, Glenthoj A, Pennickx F, Seymour M, Valentini V, Williams G, Nagtegaal ID (2010) Evidence-based medicine: the time has come to set standards for staging. *J Pathol* **221**: 357-360

Quirke P, Durdey P, Dixon MF, Williams NS (1986) Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* **2**: 996-999

Quirke P, Morris E (2007) Reporting colorectal cancer. *Histopathology* **50**: 103-112

Quirke P, Risio M, Lambert R, von KL, Vieth M (2011) Quality assurance in pathology in colorectal cancer screening and diagnosis-European recommendations. *Virchows Arch* **458**: 1-19

Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, Sebag-Montefiore D (2009) Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* **373**: 821-828

Regimbeau JM, Yzet T, Brazier F, Jean F, Dumont F, Manaouil D, Delcenserie R, Dupas JL, Verhaeghe P (2004) [Self expanding metallic stent in the management of malignant colonic obstruction]. *Ann Chir* **129**: 203-210

Rivera B, Gonzalez S, Sanchez-Tome E, Blanco I, Mercadillo F, Leton R, Benitez J, Robledo M, Capella G, Urioste M (2011) Clinical and genetic characterization of classical forms of familial adenomatous polyposis: a Spanish population study. *Ann Oncol* **22**: 903-909

Rodel C, Martus P, Papadoupolos T, Fuzesi L, Klimpfinger M, Fietkau R, Liersch T, Hohenberger W, Raab R, Sauer R, Wittekind C (2005) Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* **23**: 8688-8696

Rodriguez-Bigas MA, Petrelli NJ (2002) Management of hereditary colon cancer syndromes. In *Colorectal Cancer: Multimodality Management.*, Saltz LB (ed) pp 99-114. Humana Press: Tutoa, NJ

Rodriguez-Bigas MA, Vasen HF, Pekka-Mecklin J, Myrhoj T, Rozen P, Bertario L, Jarvinen HJ, Jass JR, Kunitomo K, Nomizu T, Driscoll DL (1997) Rectal cancer risk in hereditary nonpolyposis colorectal cancer after abdominal colectomy. International Collaborative Group on HNPCC. *Ann Surg* **225**: 202-207

Rosin D, Zmora O, Hoffman A, Khaikin M, Bar ZB, Munz Y, Shabtai M, Ayalon A (2007) Low incidence of adhesion-related bowel obstruction after laparoscopic colorectal surgery. *J Laparoendosc Adv Surg Tech A* **17**: 604-607

Rougier P, Van CE, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* **352**: 1407-1412

Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, Francois Y, Vignal J, Gilly FN (2000) Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* **88**: 358-363

Saltz LB, Clarke S, az-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F, Cassidy J (2008) Bevacizumab in

combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* **26**: 2013-2019

Samee A, Selvasekar CR (2011) Current trends in staging rectal cancer. *World J Gastroenterol* **17**: 828-834

Sanjuan X, Salas A, Lloreta J, Manchon WP (2010) Colorectal Cancer OncoGuia: surgical pathology report guidelines. *Clin Transl Oncol* **12**: 211-213

Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, French AJ, Kabat B, Foster NR, Torri V, Ribic C, Grothey A, Moore M, Zaniboni A, Seitz JF, Sinicrope F, Gallinger S (2010) Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* **28**: 3219-3226

Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* **351**: 1731-1740

Schwenk W, Neudecker J, Raue W, Haase O, Muller JM (2006) "Fast-track" rehabilitation after rectal cancer resection. *Int J Colorectal Dis* **21**: 547-553

SCOTIA Study Group (1995) Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation. The SCOTIA Study Group. Subtotal Colectomy versus On-table Irrigation and Anastomosis. *Br J Surg* **82**: 1622-1627

Seah DW, Ibrahim S, Tay KH (2005) Hartmann procedure: is it still relevant today? *ANZ J Surg* **75**: 436-440

Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de MC, Myint AS, Bessell E, Griffiths G, Thompson LC, Parmar M (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* **373**: 811-820

Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ (2007) Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* **370**: 143-152

Shen P, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA, Levine EA (2004) Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol* **11**: 178-186

Shen P, Levine EA, Hall J, Case D, Russell G, Fleming R, McQuellon R, Geisinger KR, Loggie BW (2003) Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. *Arch Surg* **138**: 26-33

Shepherd NA, Baxter KJ, Love SB (1995) Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. *J Clin Pathol* **48**: 849-855

Shia J, Guillem JG, Moore HG, Tickoo SK, Qin J, Ruo L, Suriawinata A, Paty PB, Minsky BD, Weiser MR, Temple LK, Wong WD, Klimstra DS (2004) Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome. *Am J Surg Pathol* **28**: 215-223

Shihab OC, Brown G, Daniels IR, Heald RJ, Quirke P, Moran BJ (2010) Patients with low rectal cancer treated by abdominoperineal excision have worse tumors and higher involved margin rates compared with patients treated by anterior resection. *Dis Colon Rectum* **53**: 53-56

Shihab OC, Moran BJ, Heald RJ, Quirke P, Brown G (2009) MRI staging of low rectal cancer. *Eur Radiol* **19**: 643-650

Shirouzu K, Ogata Y (2009) Histopathologic tumor spread in very low rectal cancer treated with abdominoperineal resection. *Dis Colon Rectum* **52**: 1887-1894

Sinicrope FA, Foster NR, Thibodeau SN, Marsoni S, Monges G, Labianca R, Yothers G, Allegra C, Moore MJ, Gallinger S, Sargent DJ (2011) DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. *J Natl Cancer Inst* **103**: 863-875

Slim K, Vicaut E, Launay-Savary MV, Contant C, Chipponi J (2009) Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg* **249**: 203-209

Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G (2008) Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg* **95**: 229-236

Soop M, Nelson H (2008) Is laparoscopic resection appropriate for colorectal adenocarcinoma? *Adv Surg* **42**: 205-217

Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, Kakolyris S, Tsousis S, Kouroussis C, Vamvakas L, Kalykaki A, Samonis G, Mavroudis D, Georgoulias V (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* **94**: 798-805

Souglakos J, Philips J, Wang R, Marwah S, Silver M, Tzardi M, Silver J, Ogino S, Hooshmand S, Kwak E, Freed E, Meyerhardt JA, Saridaki Z, Georgoulias V, Finkelstein D, Fuchs CS, Kulke MH, Shivdasani RA (2009) Prognostic and predictive value of common mutations for treatment response and survival in patients with metastatic colorectal cancer. *Br J Cancer* **101**: 465-472

Squillaci E, Manenti G, Mancino S, Ciccio C, Calabria F, Danieli R, Schillaci O, Simonetti G (2008) Staging of colon cancer: whole-body MRI vs. whole-body PET-CT--initial clinical experience. *Abdom Imaging* **33**: 676-688

Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G, Steves MA, Sugarbaker PH (1999) Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* **6**: 790-796

Steup WH, Moriya Y, van d, V (2002) Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. *Eur J Cancer* **38**: 911-918

Stocchi L, Nelson H, Sargent DJ, O'Connell MJ, Tepper JE, Krook JE, Beart R, Jr. (2001) Impact of surgical and pathologic variables in rectal cancer: a United States community and cooperative group report. *J Clin Oncol* **19**: 3895-3902

Sugarbaker PH (1995) Peritonectomy procedures. *Ann Surg* **221**: 29-42

Sugarbaker PH, Jablonski KA (1995) Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* **221**: 124-132

Sugarbaker PH, Schellinx ME, Chang D, Koslowe P, von MM (1996) Peritoneal carcinomatosis from adenocarcinoma of the colon. *World J Surg* **20**: 585-591

Sun DS, Zhang JD, Li L, Dai Y, Yu JM, Shao ZY (2011) Accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy for locally recurrent and irresectable rectal cancer. *Br J Radiol*

Suppiah A, Hunter IA, Cowley J, Garimella V, Cast J, Hartley JE, Monson JR (2009) Magnetic resonance imaging accuracy in assessing tumour down-staging following chemoradiation in rectal cancer. *Colorectal Dis* **11**: 249-253

Suppiah A, Maslekar S, Alabi A, Hartley JE, Monson JR (2008) Transanal endoscopic microsurgery in early rectal cancer: time for a trial? *Colorectal Dis* **10**: 314-327

Syn WK, Patel M, Ahmed MM (2005) Metallic stents in large bowel obstruction: experience in a District General Hospital. *Colorectal Dis* **7**: 22-26

Tan E, Gouvas N, Nicholls RJ, Ziprin P, Xynos E, Tekkis PP (2009a) Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. *Surg Oncol* **18**: 15-24

Tan WS, Tang CL, Shi L, Eu KW (2009b) Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. *Br J Surg* **96**: 462-472

Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, Sebag-Montefiore DJ, Tekkis P, Brown G (2011) Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. *Ann Surg* **253**: 711-719

Taylor FG, Swift RI, Blomqvist L, Brown G (2008) A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. *AJR Am J Roentgenol* **191**: 1827-1835

Tejpar S, Saridaki Z, Delorenzi M, Bosman F, Roth AD (2011) Microsatellite instability, prognosis and drug sensitivity of stage II and III colorectal cancer: more complexity to the puzzle. *J Natl Cancer Inst* **103**: 841-844

Tekkis PP, Senagore AJ, Delaney CP, Fazio VW (2005) Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections. *Ann Surg* **242**: 83-91

Tilney HS, Tekkis PP (2008) Extending the horizons of restorative rectal surgery: intersphincteric resection for low rectal cancer. *Colorectal Dis* **10**: 3-15

Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de GA (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* **22**: 229-237

Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Andre T, Tabah-Fisch I, de GA (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol* **24**: 394-400

Toyota S, Ohta H, Anazawa S (1995) Rationale for extent of lymph node dissection for right colon cancer. *Dis Colon Rectum* **38**: 705-711

Valentini V, Glimelius B, Minsky BD, Van CE, Bartelink H, Beets-Tan RG, Gerard JP, Kosmidis P, Pahlman L, Picciocchi A, Quirke P, Tepper J, Tonato M, van d, V, Cellini N, Latini P (2005) The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas which support the need for an European Consensus. *Radiother Oncol* **76**: 241-250

Van Cutsem E., Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* **360**: 1408-1417

Van Cutsem E., Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P, Ciardiello F (2011) Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* **29**: 2011-2019

Van Cutsem E., Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* **25**: 1658-1664

Van Tilborg AA, Meijerink MR, Sietses C, Van Waesberghe JH, Mackintosh MO, Meijer S, Van KC, Van Den TP (2011) Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. *Br J Radiol* **84**: 556-565

Vandecaveye V, De KF, Nuyts S, Deraedt K, Dirix P, Hamaekers P, Vander P, V, Delaere P, Hermans R (2007) Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. *Int J Radiat Oncol Biol Phys* **67**: 960-971

Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Jarvinen H, Mecklin JP, Moller P, Myrhoi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* **57**: 704-713

Vasen HF, Moslein G, Alonso A, Bernstein I, Bertario L, Blanco I, Burn J, Capella G, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Mecklin JP, Moller P, Nagengast F, Parc Y, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Wijnen J (2007) Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet* **44**: 353-362

Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy AM (2005) Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* **6**: 477-484

Verwaal VJ, Bruin S, Boot H, van SG, van TH (2008) 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* **15**: 2426-2432

Verwaal VJ, van RS, de BE, van Sloothen GW, van TH, Boot H, Zoetmulder FA (2003) Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* **21**: 3737-3743

Villar JM, Martinez AP, Villegas MT, Muffak K, Mansilla A, Garrote D, Ferron JA (2005) Surgical options for malignant left-sided colonic obstruction. *Surg Today* **35**: 275-281

Vogl TJ, Pegios W, Mack MG, Hunerbein M, Hintze R, Adler A, Lobbeck H, Hammerstingl R, Wust P, Schlag P, Felix R (1997) Accuracy of staging rectal tumors with contrast-enhanced transrectal MR imaging. *AJR Am J Roentgenol* **168**: 1427-1434

Vogl TJ, Zangos S, Eichler K, Yakoub D, Nabil M (2007) Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update. *Eur Radiol* **17**: 1025-1034

Wanebo HJ, Belliveau J, Begossi G, Levy A (2003) Isolated chemotherapeutic perfusion of the pelvis for advanced rectal cancer. *Colorectal Dis* **5**: 508-514

Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G (2002) Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* **287**: 321-328

West NP, Anderin C, Smith KJ, Holm T, Quirke P (2010a) Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. *Br J Surg* **97**: 588-599

West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P (2010b) Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol* **28**: 272-278

Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, van Berge Henegouwen MI, Fuhring JW, Dejong CH, van Dam RM, Cuesta MA, Noordhuis A, de JD, van ZE, Engel AF, Goei TH, de S, I, van Tets WF, van Wagensveld BA, Swart A, van den Elsen MJ, Gerhards MF, de Wit LT, Siepel MA, van Geloven AA, Juttmann JW, Clevers W, Bemelman WA (2006) Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). *BMC Surg* **6**: 16

Witkamp AJ, de BE, Kaag MM, Boot H, Beijnen JH, van Slooten GW, van CF, Zoetmulder FA (2001) Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. *Eur J Cancer* **37**: 979-984

Wong SL, Ji H, Hollenbeck BK, Morris AM, Baser O, Birkmeyer JD (2007) Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA* **298**: 2149-2154

Yamada K, Ogata S, Saiki Y, Fukunaga M, Tsuji Y, Takano M (2009) Long-term results of intersphincteric resection for low rectal cancer. *Dis Colon Rectum* **52**: 1065-1071

Yamamoto S, Fujita S, Ishiguro S, Akasu T, Moriya Y (2008) Wound infection after a laparoscopic resection for colorectal cancer. *Surg Today* **38**: 618-622

Yan TD, Black D, Savady R, Sugarbaker PH (2006) Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* **24**: 4011-4019

Yan TD, Morris DL (2008) Cytoreductive surgery and perioperative intraperitoneal chemotherapy for isolated colorectal peritoneal carcinomatosis: experimental therapy or standard of care? *Ann Surg* **248**: 829-835