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Adjuvant chemotherapy

Dukes’ C/ TNM stage 3
All patients fit enough to tolerate adjuvant chemotherapy should discuss the treatment options including their benefits and side-effects with an oncologist.

Treatment options are:

1. Capecitabine oral chemotherapy. In selected cases IV 5-Fluorouracil (5FU) can be used e.g. GFR <30mls/min or high output stoma.
2. Combination chemotherapy with Oxaliplatin and infusional 5FU.

This practice is supported by NICE guidance.¹ The final treatment decision will be determined after a discussion at the MDT and subsequently between the treating oncologist and the patient. Patient-specific factors including pathological findings e.g. number of involved lymph nodes, apical node positivity, patient co-morbidity and patient preference will all be considered. Combination chemotherapy confers a greater benefit in higher-risk disease but is not indicated for all patients.

Additional considerations include:

1. Adjuvant chemotherapy should be commenced within a maximum 12 week window post-surgery for primary bowel cancer.
2. There is no evidence to support the use of other drugs such as raltitrexed and irinotecan in the adjuvant setting and they should not be used.
3. Evidence for the use of adjuvant chemotherapy following long-course radiotherapy is lacking. Decisions regarding adjuvant treatment need to be made after careful discussion with the patient.

¹ Capecitabine and oxaliplatin in the adjuvant treatment of stage 3 (Dukes’ C) colon cancer. NICE guidance: TA100. April 2006.
Dukes' B/ TNM stage 2
Data from the QUASAR trial and a meta-analysis suggest that adjuvant chemotherapy provides a small improvement in survival of 2-4% in absolute terms compared with observation. Given the excellent prognosis of many patients treated with surgery alone and the small benefit of adjuvant chemotherapy only patients with “high-risk” features should be selected and the risks and benefits of treatment discussed on an individual case basis.

Pathological high-risk features include:

- pT4 tumour
- low lymph node yield (<10 nodes)
- presence of lymphovascular or perineural invasion
- high grade/ poorly differentiated tumours
- obstructing or perforated tumours

Tumours demonstrating loss of mismatch repair (MMR) proteins (MMR deficient) by IHC assessment appear to have an improved prognosis compared to MMR proficient cancers. Assessment of MMR protein expression can be considered for stage 2 cancers where it’s considered the results would influence decisions regarding adjuvant treatment. More detail regarding this can be found in the separate guidance re MMR testing (http://www.cmft.nhs.uk/mismatchrepair).

Standard chemotherapy for Stage 2 cancer would be single agent capecitabine.

Locally advanced colon cancer
There is no evidence to support the use of neo-adjuvant chemotherapy for operable colon cancer.

Patients with operable colon cancer should be considered for clinical trials investigating the use of neo-adjuvant therapy e.g. FOxTROT. Patients with inoperable locally advanced colon cancer should be considered for chemotherapy on a case by case basis.

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Management of advanced disease

Palliative chemotherapy
There is extensive evidence from randomized trials to support the use of 5FU, Irinotecan and Oxaliplatin as palliative chemotherapy in advanced colorectal cancer patients who are fit for chemotherapy. NICE has approved the use of Irinotecan and Oxaliplatin in metastatic colorectal cancer patients. All patients with locally advanced or metastatic colorectal cancer should be discussed at an MDT with an oncologist. Mitomycin has also demonstrated activity in metastatic colorectal cancer and can be considered as a treatment option in selected cases. Decisions regarding the precise treatment a patient receives will be taken by the treating oncologist following assessment of the patient and discussion of the risks and benefits of treatment.

High cost drugs
A number of drugs have demonstrated benefits in phase 3 clinical trials which are not currently funded by the NHS. Whether these drugs are funded, by whom, and in which disease setting is subject to change and is therefore difficult to capture within guidelines. High cost drugs for which there is evidence from Phase 3 trials of benefit in colorectal cancer include:

- EGFR mAb – Cetuximab and Panitumumab
- VEGF targeted treatment – Bevacizumab, Aflibercept and Regorafenib

Funding of these drugs is currently considered via the NHS England Cancer Drugs Fund (CDF). The CDF reviews the list of drugs funded and reference should be made to the latest version of CDF criteria (http://www.england.nhs.uk/ourwork/pe/cdf/cdf-drug-sum/). It is currently planned that the CDF will be replaced from April 2016 and funding arrangements beyond that point are currently uncertain.

As of December 2015 the only drugs funded by the CDF are first-line EGFR mAb’s. Therefore all patients fit for systemic chemotherapy should have their RAS mutation status checked at baseline to establish whether EGFR mAb treatment (e.g. Cetuximab or Panitumumab) may be an option (see separate Colorectal Pathway Guidance - http://manchestercancer.org/wp-content/uploads/2014/09/RAS-mutation-testing-policy-June-14.pdf).

Selective Internal Radiation Therapy (SIRT)
In patients whose have liver only or liver predominant metastatic disease SIRT can be considered as a third line treatment following standard first and second line chemotherapy. Patients considered for this should be discussed at the Christie SIRT MDT.

Recruitment to clinical trials should be considered where possible.

1 Irinotecan, Oxaliplatin and Raltitrexed for advanced colorectal cancer. NICE Technology Appraisal: TA93.
Management of liver only metastases

Inoperable liver only metastases - NICE guidance TA176

NICE has recommended the addition of the EGFR targeted monoclonal antibody Cetuximab to standard combination chemotherapy (with either Oxaliplatin/ 5FU or Irinotecan/ 5FU) when the following criteria are all fulfilled:

- Surgery to the primary tumour has been performed with curative intent.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo potentially curative resection of metastases.

All patients who fulfill these criteria should be discussed at the regional HPB liver metastases MDT.

Responses to Cetuximab are limited to patients whose tumours do not have mutations in the KRAS and NRAS genes. Patients fulfilling the above criteria should all have their RAS mutation status assessed as part of their initial work-up.

For patients whose tumours have RAS mutations standard chemotherapy with Oxaliplatin or Irinotecan and 5FU should be considered. In selected patients 3 drug combination regimens of 5FU, Oxaliplatin and Irinotecan may be considered.

Operable liver only metastases

Guidelines for the assessment and management of potentially operable liver metastases have been produced by the HPB pathway board and should be referred to in the assessment of patients. All patients considered to have operable disease and be fit for liver surgery should be discussed at the regional liver metastases MDT to plan management.

Adjuvant chemotherapy post-liver resection – the evidence for post-operative adjuvant chemotherapy is uncertain and individual cases should be discussed with an oncologist.

Peri-operative chemotherapy -. This was used in the EORTC 40983 trial that showed a small improvement in disease-free survival of borderline statistical significance. No statistically significant difference in overall survival was seen although this was a secondary endpoint of the study. The strategy of peri-operative chemotherapy is now widely used in clinical practice for patients who are not optimally resectable (synchronous presentation of primary and metastases, liver metastases >5cm, >4 liver metastases, elevated tumour marker, LN positive primary, or technical surgical

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considerations). Combination chemotherapy with Oxaliplatin/ 5FU chemotherapy will be considered in most patients unless there is a relative or absolute contraindication (allergy, previous oxaliplatin chemotherapy, established peripheral neuropathy). Irinotecan/ 5FU chemotherapy may be considered as an alternative.

The use of Cetuximab in KRAS wild-type patients with operable liver disease was assessed in the NewEPOC trial and Cetuximab was not found to improve outcomes. Cetuximab should not therefore be used in patients with operable liver metastases.
Rectal cancer

Pre-operative Radiotherapy
Unless there is a contraindication all rectal cancers should be staged by a pre-operative MRI pelvis and discussed at an MDT meeting with a clinical oncologist or a medical oncologist following the clinical oncology guidelines.

Long course radiotherapy or chemo-radiotherapy
Long course treatment should be considered in tumours where pre-operative MRI or CT suggests:

1. T4 disease
2. Circumferential Resection Margin (CRM) is threatened
   a. defined by tumour within 1mm of CRM on staging MRI
   b. due either to direct tumour spread or suspicious lymph nodes or vascular invasion
3. T3 lower third rectal cancers have an increased risk of CRM threatened/ positive tumours and long course treatment may be considered.

Standard long course chemo-radiotherapy involves 5 weeks of radiotherapy (total dose of 45Gy) combined with Capecitabine chemotherapy. Radiotherapy alone is less effective than chemo-radiotherapy but is a less toxic and better tolerated treatment. Radiotherapy alone may therefore be offered to patients who are not fit for chemo-radiotherapy (45Gy in 20 fractions).

The benefit of adjuvant chemotherapy following long-course radiotherapy is uncertain. These cases, particularly patients with ypN1-2 disease (Dukes’ C) or those who had significant nodal metastases on initial pre-radiotherapy MR imaging should be discussed with an oncologist.

Short course radiotherapy
Short course radiotherapy should be considered in any patient considered for resection of a rectal cancer (curative or palliative intent) where pre-operative MRI or CT scan suggests:

1. Upper rectum: T3 tumours*
2. Mid rectum: T3 tumours*
3. Lower rectum: T3 tumours* and some T2 tumours* that could be considered to benefit from a SCRT by the MDT.

*CRM is not threatened either directly by tumour, or by vascular invasion or suspicious lymph nodes (> 1mm from CRM)

T2 mid and upper third tumours derive a small absolute benefit from short-course radiotherapy and the benefits of treatment are uncertain. Its standard practice for these cases to be discussed with an Oncologist but in some cases treatment may not be necessary.
Standard short course radiotherapy in the North West is 20Gy given in 4 fractions although an alternative regimen of 25Gy in 5 fractions is used nationally.

**Post-operative radiotherapy**

Pre-operative radiotherapy, either as a short- or long-course treatment is preferred, but in cases where surgery was performed as an emergency/urgency then post-operative chemoradiotherapy may be considered. All cases should be discussed at an MDT meeting in the presence of an oncologist.

Post-operative radiotherapy should be considered if any of the following are present;

1. Positive resection margin
2. T4 tumour
3. Positive nodes within 1mm of the CRM

**Brachytherapy**

Contact radiotherapy (brachytherapy) is available at Clatterbridge Centre for Oncology. It is not standard, and potentially inferior care, but provides a useful adjunct in a minority of selected cases, usually in combination with external beam radiotherapy. Each case should be discussed individually at the local MDT with a clinical oncologist but cases where referral might be considered include:

- T1-T3 low rectal cancer, where APR is indicated but patient is refusing to have a stoma.
- Rectal cancer in patients unfit for general anaesthesia
Palliative radiotherapy

Management of rectal primary
In patients with established metastatic disease radiotherapy (30Gy in 10 fractions or 25Gy in 5 fractions) may be considered for local control of symptomatic rectal primaries – particularly for pain and bleeding. Long course radiotherapy or chemo-radiotherapy may also be considered in some patients.

Management of symptomatic distant metastases
In patients with symptomatic distant metastases to bone, brain, lymph nodes or lungs palliative radiotherapy may be considered in individual cases. The exact details of treatment will be decided based upon clinical oncology review.