Greater Manchester &
Cheshire Cancer Network

Colorectal Clinical Subgroup:

Non-Surgical Oncology Guidelines

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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. 5-Fluorouracil (5FU) given as a weekly intravenous bolus dose (QUASAR regimen) or as oral capecitabine.
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 between the treating oncologist and 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[2] 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

Additionally data from the recent PETACC-3 trial showed that 22% of stage 2 and 12% of stage 3 cancers are mismatch repair (MMR) deficient.[3] MMR deficient tumours appear to have improved prognosis compared to MMR proficient tumours but may not benefit from adjuvant 5FU chemotherapy. After discussion with the treating Oncologist immunohistochemical assessment of MMR status of a stage 2 or 3 colorectal tumour may be considered if the results would influence decisions regarding adjuvant treatment.

[2] Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. QUASAR Collaborative Group, Lancet 2007; 370: 2020-29.

[3] Roth AD, Tejpar S, Yan P, et al., Stage-specific prognostic value of molecular markers in colon cancer: Results of the translational study on the PETACC 3-EORTC 40993-SAKK 60-00 trial. J Clin Oncol, 2009. 27(15S): p. Abstract 4002.

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.[4] All patients with locally advanced or metastatic colorectal cancer should be discussed at an MDT with an oncologist. 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.

Recruitment to on-going clinical trials will be considered where possible.

[4] Irinotecan, Oxaliplatin and Raltitrexed for advanced colorectal cancer. NICE Technology Appraisal: TA93.

Management of liver only metastases

Inoperable liver only metastases - NICE guidance 2009[5]

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 an MDT with a hepatic surgeon and oncologist in attendance.

Responses to Cetuximab appear to be limited to patients whose tumours do not have mutations in the *KRAS* gene. Patients fulfilling the above criteria should all have their *KRAS* mutation status assessed as part of their initial work-up. This is a rapidly evolving area and it is likely that additional molecular predictors of response will be identified and recommended for assessment over the next few years.

Operable liver only metastases

Separate surgical guidelines on the assessment and management of potentially operable liver metastases have been produced by the CSG. All patients considered to have operable liver metastases and be fit for liver surgery should be discussed at an MDT with a liver surgeon and oncologist to plan management.

Adjuvant post-liver resection chemotherapy – 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. This strategy is now widely used in clinical practice and on-going clinical trials particularly for patients in 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 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 in these patients.

[5] Cetuximab for the first line treatment of metastatic colorectal cancer. NICE Technology Appraisal: TA176. August 2009.

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. T_4 disease
2. Circumferential Resection Margin (CRM) is threatened
    a. defined by tumour within 2mm of CRM on staging MRI
    b. due either to direct tumour spread or suspicious lymph nodes or vascular invasion
3. T_3 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) 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. T_2 or T_3 disease
2. CRM is not threatened either directly by tumour, or by vascular invasion or suspicious lymph nodes (> 2mm from CRM)

T_2 upper third tumours derive a small absolute benefit from short-course radiotherapy and these cases should all be discussed with an Oncologist but in some cases treatment may not be necessary.

Standard short course radiotherapy in the North West is 20 cGy given in 4 fractions although an alternative regimen of 25cGy 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 2mm of the CRM

Palliative radiotherapy

Management of rectal primary

In patients with established metastatic disease radiotherapy (30cGy in 8 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.