

Management of colorectal cancer metastases to the liver, lung or peritoneum suitable for curative intent: summary of NICE guidance

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The management of metastatic colorectal cancer has undergone a strategic evolution with improvements in imaging, biomarker-based selection for systemic anticancer therapy (SACT), and innovations in surgical and local ablative techniques. Since the concept of oligometastatic disease was introduced¹, the benefit of adding metastases-directed local therapy to standard-of-care systemic treatment has been unclear. Decision-making in these situations is often complex and dynamic, involving clinicians from a variety of specialties.

The most common sites of metastases from colorectal cancer are the liver, lung and peritoneum. As part of the National Institute for Health and Care Excellence (NICE) guideline update for colorectal cancer² the Guideline Committee reviewed the evidence to support treatment decisions for patients with metastases to these sites. The evidence reviews and the methods used are available on the NICE website². Here, the key evidence behind the NICE guidance is highlighted.

Metastases in the liver amenable to treatment with curative intent

The most common site of colorectal metastases is the liver, occurring in

25–30 per cent of patients³. Surgical resection is considered standard treatment. Uncertainty persists around the benefits of systemic treatment in addition to liver resection, treatment other than surgical resection, and, for synchronous presentation, whether a simultaneous or staged resection of the primary tumour and liver metastases should be employed.

An improvement in disease-free survival was observed among people who had chemotherapy and surgery compared with those who underwent surgery alone (hazard ratio (HR) 0.79, 95 per cent c.i. 0.66 to 0.95)^{4,5}. The RCTs differed in terms of chemotherapy regimen (oxaliplatin/5-fluorouracil (5-FU) and 5-FU/leucovorin) and timing of chemotherapy (before and/or after resection), making pooling of the results questionable. Grade 3/4 chemotherapy-related toxicity occurred in around 25 per cent⁶.

Local ablative techniques are an alternative to surgical resection with potentially less morbidity and mortality. The LAVA (liver resection surgery *versus* thermal ablation for colorectal liver metastases) randomized trial⁷ compared these two approaches, but was discontinued owing to poor recruitment. Only retrospective studies of local ablation with or without liver resection *versus* liver resection

alone were available. For most patients undergoing ablation, resection was not possible because of poor performance status. The committee had concerns about comparability of groups and selection bias influencing outcomes.

Evidence review showed no clinically important differences in survival, morbidity or mortality between simultaneous resection of the primary tumour and liver metastases or staged resection⁸. Health economic analysis was undertaken but did not allow any clear recommendations.

Metastases in the lung amenable to local treatment

The lung is the second most common site of colorectal metastases. Although pulmonary metastasectomy is a commonly used treatment, other less invasive approaches including stereotactic body radiation therapy (SBRT) and percutaneous ablation are used.

Comparative evidence for the most effective treatment is scarce, retrospective and of low quality. Poorer lung progression-free survival at 2.5 years was observed in those receiving SBRT compared with surgery (HR 2.78, 1.67 to 4.63), but there was no difference in overall survival (HR 1.28, 0.58 to 2.83)⁹.

Treatment-related mortality was similar in both groups. In another study¹⁰, a decrease in 5-year overall survival was observed among those who received chemotherapy or best supportive care rather than surgery (HR 2.18, 1.01 to 4.73)¹⁰.

The committee acknowledged the PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer) trial, an RCT of the effectiveness of pulmonary metastasectomy in patients treated previously for colorectal cancer, which was due to report, and has now been published¹¹. Outcomes include 5-year overall survival, relapse-free survival, lung function and quality of life. The small sample size precludes a conclusive answer regarding any of these outcomes.

Metastases isolated in the peritoneum

The second most common cause of death from colorectal cancer is peritoneal metastases. Efforts to achieve long-term survival have seen the combined use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Two RCTs^{12,13} of CRS and HIPEC have been carried out. The first trial¹² showed an increase in 2-year overall survival in patients who received CRS and HIPEC and SACT compared with those who had conventional surgery and SACT (HR 0.55, 0.32 to 0.95). No difference in 5-year overall survival was observed in the second more recent trial (PRODIGE 7)¹³, which compared CRS and HIPEC using oxaliplatin with CRS alone (HR 1.00, 0.73 to 1.37). Overall survival rates for all patients were higher than expected (median survival 42 months) indicating that high-quality surgery is of value. No difference in 30-day treatment-related mortality was seen in either RCT, although PRODIGE 7 did show a greater rate of grade 3/4

morbidity with the use of high-dose oxaliplatin HIPEC, mostly due to haemorrhagic complications.

An observational study¹⁴ reported increased overall survival at 50 months with SACT compared with best supportive care (HR 0.35, 0.22 to 0.56) and, despite the low quality of the evidence, the committee agreed that SACT appears to benefit patients with colorectal peritoneal metastases.

Recommendations

Many of the studies that informed the latest NICE guideline suffer from methodological limitations affecting the risk of bias and imprecision of the effect estimates. When uncertainty exists around survival benefit, quality-of-life data are key to decision-making, but this analysis was absent. The Guideline Committee was therefore unable to make strong recommendations for treatments in this setting.

Unsurprisingly, local multidisciplinary teams (MDTs) may lack the expertise necessary to make appropriate decisions. Access to specialists influences MDT decisions¹⁵ and initiatives such as IMPACT (Improving the Management for Patients with Advanced Colorectal Tumours) encourage MDTs around the country to establish networks with the knowledge to effectively manage patients with oligometastatic colorectal cancer.

Based on the evidence and the Guideline Committee's expertise, the following recommendations were made.

Liver metastases

- Consider resection, either simultaneous or sequential, after discussion by a MDT with expertise in resection of disease at all involved sites.
- Consider perioperative SACT if liver resection is a suitable treatment.

- Consider chemotherapy with local ablative techniques for people with colorectal liver metastases that are unsuitable for liver resection after discussion by a specialist MDT.

Lung metastases

- Consider metastasectomy, ablation or SBRT for people with lung metastases that are suitable for local treatment, after discussion by a MDT that includes a thoracic surgeon and a specialist in non-surgical ablation.
- Consider biopsy for people with a single lung lesion to exclude primary lung cancer.

Peritoneal metastases limited to the peritoneum

- Offer SACT and
- within a MDT, discuss referral to a nationally commissioned specialist centre to consider CRS and HIPEC.

Collaborators

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