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Review Article

Treatment sequence of synchronously (liver) metastasized colon cancer

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ABSTRACT

No standards for staging, systemic therapy or the timing of an operation are defined for patients newly diagnosed with synchronous metastases and a primary in the colon. An expert group of radiologists, medical, radiation and surgical oncologists therefore came together to discuss staging and treatment sequence for these patients and came up with a recommendation based on current evidence of potential therapeutic options. The discussion was organized to debate recommendations centred on 5 topics and therefore the position paper is built upon these titles and their subtitles.

1. Definition of synchronous disease

There is uncertainty about the exact timing of synchronously metastasized colon cancer (mCC). The group agreed, as far as the prognosis is concerned, that the definition of synchronous does not only include patients diagnosed at the time of the primary tumour, but also those diagnosed within 3 months after initial finding [1]. However, for the purpose of treatment decisions patients with metastases discovered during the diagnostic workup for the primary tumour should be considered separately from those with the metastases discovered during or shortly after surgery.

Evidence Level 2: Grade of recommendation: B.

2. Definition of an obstructing primary tumour

The diagnosis of an obstructing colonic cancer is primarily a clinical one. A complete obstruction presents with the clinical picture of an ileus and necessitates an acute surgical procedure or an operative intervention. A partial obstruction presents with different degrees of difficulty in passing stool, nausea and vomiting and abdominal distention. A CT scan with faecal impaction and colonic dilatation proximal of the tumour can be a radiological

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sign of partial obstruction. Patients in whom the tumour cannot be passed by the colonoscope but who have little or no obstructive symptoms should not be considered as obstructed.

For decision making it is important to take into account the effectiveness of modern systemic therapy that often markedly improves the change of bowel habit and mild obstructive symptoms even after one cycle of systemic therapy.

Evidence Level 3: Grade of recommendation: C.

3. Staging

The assessment of a patient with newly diagnosed metastatic colon cancer should address comorbidity, previous surgery, ECOG status, physical examination, standard lab tests (e.g. haemoglobin, LDH, bilirubin), tumour markers (CEA, CA 19-9) and molecular markers (Ras, Braf). Radiological staging should include a 3-phase CT of the liver with inclusion of chest and abdomen, showing the number of involved organs and an estimate of the number of metastases. If a curative option for liver metastases exists, a contrast-enhanced MRI with use of liver specific contrast agents like dinatrium gadoxetate and a DWI (diffusion weighted imaging) sequence should be added to clearly delineate the extend of liver disease [2]. PET scan or PET/CT was not recommended as standard of care but could have added value in some specific situations; e.g. differential diagnosis of a suspicious lesion on CT. It should be kept in mind that inflammation can lead to false positive PET findings [3].

When the lesions in the liver and/or lung are clinically and radiologically typical for metastases, a histological confirmation is not required, as long as there is a good quality biopsy of the primary tumour.

Evidence Level 2: Grade of recommendation: B.

4. Assessment of resectability

4.1. The multidisciplinary team meeting (MDT)

Resectability of metastases and the primary tumour should be discussed within a MDT meeting with participation of a GI-radiologist, a surgical oncologist with expertise in both liver and colon resections, a medical GI oncologist and a pathologist. A radiation oncologist and an interventional radiologist are required if non-surgical local treatment of the metastases is considered. It is important that one of the participating physicians should know the patient and act as the case manager [4].

It is acknowledged that different centres and MDTs can have their different definitions of resectability, based on local expertise. Ideally centres should have outcome data available. Technical resectability does not necessarily define the best oncological therapy and the decision about the type and sequence of treatment options should therefore be discussed in the MDT setting and with the treating physician [5].

4.2. Definition of technical resectability

The potential of resecting all metastases is nowadays defined by an adequate function of the remaining organ and e.g. for the liver should represent a well-defined volume with adequate inflow, outflow and drainage. For the liver 30% of the total volume is usually enough to retain adequate liver function after the resection; it is however well recognized that it is not just volume that needs to be considered, but also function. Hepatic steatosis and especially hepatic damage (steatohepatitis, sinusoidal obstructive syndrome) observed after prolonged chemotherapy (3 months plus) can lead to a decreased function of the future remnant, requiring a remaining volume of 40% in these cases [6].

For optimal MDT decisions it is recommended to classify the initial metastatic disease in a three-tier system as (1) resectable, (2) potentially resectable after downsizing therapy, or (3) most likely never resectable [7]. This definition will help to define therapeutic strategy, sequence of therapies and their composition [8].

Although the number, size and location of metastases, and number of involved organs are all important factors to determine resectability, there are no longer absolute criteria for unresectabilty. It is the ability to resect all metastatic lesions that constitutes resectability or potential resectability.

If the decision is made that the patients' treatment should start with systemic therapy, it is important to define the objective: only targeting subclinical micrometastatic disease, or also obtaining maximal shrinkage of clinical disease. At the MDT meeting it should be decided on the timing and type of restaging (CT, MRI, US) and renewed discussion; often the restaging is planned after two months of treatment [9].

When at the MDT meeting a definitive conclusion on resectability cannot be reached, or the patient wishes to have a second opinion he/she should be referred to a specialized tertiary centre.

It was also agreed that scoring systems (e.g. Fong score [10]) can help defining the scope of the patient but do not necessarily be taken into account for the treatment sequence and the ability to resect all visible tumours as long as responding patients are depicted by initial treatment.

Evidence Level 3: Grade of recommendation: C.

5. Treatment algorithm

5.1. Influence of ECOG and age

The group agreed that the initial presentation, the age and the willingness of the patient to fight against the cancer are important factors to guide the decision of the MDT meeting and that the case manager should be the advocate of the patient [11]. When necessary, especially in young patients and patients with familial antecedents or multiple primaries an oncogenetic consultation should be done but should not delay treatment start.

5.2. The MDT meeting

It is nowadays essential that every newly diagnosed metastatic colon cancer patient is discussed within a multidisciplinary team meeting **prior** treatment start and that the MDT constitutes of a variety of specialists as discussed above. It is important to have the case manager of the patient and its clinical knowledge of the patients' symptoms and needs incorporated in the final treatment sequence decision [12].

5.3. Treatment of the primary

Significant changes have occurred over the past decade regarding the treatment of the primary colonic cancer. Previously the surgical paradigm was first to resect the primary tumour to prevent colonic obstruction, and to address the metastatic disease after the resection. With the effectiveness of the available systemic drugs and the recognition that these drugs are decreasing the size of the primary, in most MDTs it is now decided to start with systemic therapy in the majority of patients. Prospective trials evaluating the incidence of colonic obstruction or bleeding in initially unresectable metastatic patients during systemic therapy have demonstrated that with an effective therapy it is not required to resect the primary prior to systemic treatment [13]. However, a number of retrospective analyses of patients treated palliatively

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