



Special Section: Synchronous Colorectal Cancer & Liver Metastases; Edited by Dr. Ajith Siriwardena

Evidence-based management of the patient with synchronous colorectal cancer and liver metastases

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Editorial

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States of America with up to one third of these patients demonstrating hepatic metastases at presentation [1]. Although there is a large body of work on patients with stage IV colorectal cancer, specific evidence to guide management of those individuals with metastases either confined to the liver or predominantly in the liver is limited [2–4]. The METASYNC randomized trial compared synchronous to staged resection, but it is noteworthy that it took a decade to recruit 105 patients [5]. The CoSMIC study used a prospective inception cohort approach to study outcomes in 125 patients with synchronous colorectal cancer and liver metastases but was observational in nature [6].

Thus, in current practice, decision-making for the patient with synchronous colorectal cancer and liver metastases typically falls to a multidisciplinary tumour board to make individualized care plans taking into consideration patient fitness, patients' preferences, mode of presentation, distribution and extent of disease.

In this setting, how can clinicians find a care plan for treatment which is evidence-based, uses modern terminology and is acceptable to their patients?

First, the use of standardized terminology is critically important. In this regard, current insights into the molecular biology of colorectal cancer indicate that metastasis to the liver may occur early in the disease course [7]. The genetic heterogeneity of liver metastases results in differential transcriptomic signalling leading in turn to variation in expression between metastases. In addition, there is evidence of a

differential “host” response within the liver [7]. These phenomena manifest clinically in differential “declaration” of liver metastases, thus although it is possible that all metastases are “synchronous” only some of these will be detected by conventional cross-sectional imaging including liver-contrast specific magnetic resonance scan (MR) and ¹⁸F-fluoro-deoxyglucose positron emission tomography (FDG-PET) at the time of clinical presentation.

Incorporating this knowledge into existent terminology, the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) together with the European Society of Surgical Oncology (ESSO) worked with the European Society of Coloproctology (ESCP), the European Society of Gastrointestinal Radiology (ESGAR) and the Cardiovascular and Interventional Radiology Society of Europe (CIRSE) over a two-year period to produce a multidisciplinary, multi-societal consensus on the terminology for patients with synchronous colorectal cancer and liver metastases [8,9]. This builds on pre-existent terminology [10] to produce a practical and clinically relevant terminology. Patients who present with liver metastases at the time of diagnosis of their colorectal cancer are termed synchronous. In this setting, treatment in those patients who are fit for active therapy should include a combination of systemic chemotherapy and interventions directed at the primary tumour and metastases.

Patients who present in the first year after diagnosis of the primary but in whom the metastases were not detectable on cross-sectional imaging at presentation are termed to have early metachronous disease. This distinction from those with liver metastases at presentation is practical as patients in the early metachronous category will typically have had therapy directed at the primary tumour by the time of

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presentation with liver metastases. The final category is those patients who present with liver metastases more than twelve months beyond the diagnosis of their primary and these are termed to have late metachronous disease. Those with late metachronous disease are thought to represent a more favourable subgroup with a more indolent cancer biology. In these patients, treatment can focus on the metastatic burden (provided that the primary tumour has been resected).

Although any terminology needs to have sufficient flexibility to be modified with the incorporation of new evidence and will only be accepted if widely used, the buy-in and consensus agreement from multiple professional societies holds promise for a useable system.

Continuing then to look at the management of the individual patient with synchronous colorectal cancer and liver metastases this special edition will feature a series of articles highlighting specific aspects of management. First and following on from standardized terminology, the series will examine variations in international and national guidelines on management of synchronous colorectal cancer and liver metastases. Guidelines form the backbone of management and variation in their advice can constitute an important source of heterogeneity in care.

Second, the series will examine the important issue of practical treatment-sequencing in patients with synchronous colorectal cancer and liver metastases including the evidence guiding systemic chemotherapy as first treatment, the timelines between neoadjuvant chemotherapy and surgery and considerations for the three treatment pathways: synchronous liver and bowel surgery, the liver-first approach and the bowel-first approach. In terms of treatment sequencing, the mode of presentation is important. For those patients who present as an emergency with obstruction, perforation or bleeding, attention should be directed at treatment of the symptomatic primary and management of liver metastases is of secondary concern. In patients with extrahepatic metastatic disease in addition to liver metastases, indicating a significant systemic cancer burden, systemic chemotherapy should be the mainstay of treatment. In terms of management, a practical distinction is made between those patients with a colonic primary tumour and those with a rectal tumour as the latter are more likely to require radiotherapy. In patients with liver-limited, resectable hepatic metastases and a resectable primary tumour, the three management options of synchronous resection of both sites of disease, the bowel-first approach or the liver-first approach come into play. The question of practical treatment-sequencing in these settings will be reviewed.

Third, this series will examine the evidence and use of the total minimally invasive approach to synchronous colorectal cancer and liver metastases and the fourth article in this series will examine the role of the cancer biology of colorectal cancer in the management of the patient with a synchronous presentation including the influence of sidedness and mutation status.

These articles will build to a comprehensive overview of important aspects of the management of synchronous colorectal cancer and liver metastases. Although none can substitute for high level evidence from randomized trials, they can serve to guide physicians and their patients in selecting optimal treatments in situations where there are diverse treatment options with broad evidence windows.

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Ajith K. Siriwardena: Conceptualization, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There are no conflicts of interest to declare.

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