

# Chemotherapy-associated liver injury

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A large body of literature has been published demonstrating the benefits of partial hepatectomy for increasing long-term survival in patients with colorectal liver metastases (CRLM).<sup>1</sup> Surgery remains the mainstay of the CRLM treatment algorithm and provides the best prospect of cure.<sup>2,3</sup> To further increase the cure rate, surgeons have developed many advanced surgical procedures for tumours traditionally considered irresectable, particularly multiple tumours with bilobular distribution. These procedures include two-stage hepatectomy,<sup>4</sup> ultrasound-guided enhanced one-stage hepatectomy,<sup>5</sup> and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).<sup>6,7</sup> Apart from these advanced surgical techniques, neoadjuvant chemotherapy has been put forward as a treatment option that could reduce the tumour burden, thereby enabling surgical resection.<sup>1,8,9</sup>

Surgical safety, expressed as incidence of postoperative morbidity and mortality, is of great importance in the context of partial hepatectomy, and has been reported to be negatively influenced by neoadjuvant chemotherapy.<sup>10</sup> In particular, the presence of chemotherapy-associated liver injury (CALI) has been shown to impair liver regeneration, which is pivotal for recovery of liver function in patients after partial hepatectomy.<sup>11</sup> Moreover, CALI appears to be associated with reduced tumour responsiveness to neoadjuvant chemotherapy,<sup>12,13</sup> which has implications for long-term recurrence-free survival and overall survival. Understanding the relationship between the impact of CALI on postoperative short- and long-term outcome, and the mechanisms underlying CALI is of key importance for improving surgical outcomes of patients undergoing partial hepatectomy for CRLM.

The central aim of the current thesis was to investigate the influence of CALI on postoperative short- and long-term outcome after partial hepatectomy for CRLM. This was then translated into three main specific aims: **1)** to study the impact of CALI on short-term morbidity and mortality after partial hepatectomy for CRLM (**Chapter 2**, **Chapter 3**, and **Chapter 4**); **2)** to investigate the influence of CALI on long-term recurrence-free survival and overall survival after partial hepatectomy for CRLM (**Chapter 5**); and **3)** to provide better understanding of the mechanisms underlying CALI, the first step towards identification of potential biomarkers to predict CALI and of molecular targets to treat or prevent CALI (**Chapter 6** and **Chapter 7**).