# Chemotherapy-associated liver injury

# Valorisation

# Valorisation

To transfer academic research findings for the benefit of the society is one of the main tasks of Dutch universities by law.[1] Therefore, it is obligated to translate academic wisdom to societal benefit in ways that go beyond numerous academic findings. This is especially the case when research has been sponsored by foundations, non-profit organizations, taxpayers, or charities. This chapter is intended to describe how the research results presented in this thesis could be used in clinical practice and subsequently how a broadest community could benefit.

## Relevance

*Scientific relevance*

Annually, approximately half of globally 1.3 million patients with colorectal cancer develop colorectal liver metastases (CRLM),[2-4] of whom over 75% are not eligible for curative hepatic resection.[4,5] Neoadjuvant chemotherapy enhances resectability by approximately 15% in this group,[6,7] but has been associated with regimen-specific parenchymal liver injury, collectively referred to as chemotherapy-associated liver injury (CALI, i.e. sinusoidal dilatation, nodular regeneration, steatosis, and steatohepatitis).[8-11] Once occurred, CALI can persist for at least nine months even after cessation of chemotherapy.[12] The potential downstream side-effects of CALI on clinical outcome (i.e. postoperative morbidity, mortality, and long-term survival) after partial hepatectomy are an active area of research surrounded with controversy, and the molecular mechanisms underlying its development are still mostly unknown. Therefore, the central theme of the studies conducted in the present thesis was to unravel these questions.

*Economic relevance*

The current thesis has revealed that CALI is a risk factor for increased postoperative morbidity after partial hepatectomy for colorectal liver metastases. The presence of increased morbidity results in a prolonged length of hospital stay and may therefore eventually increase hospital cost. Moreover, in many cases, after discharge from the hospital, patients with postoperative morbidity remain to have the need of being followed by the first referral doctors (e.g. general practitioner) for a certain period. Therefore, it is reasonable to speculate that the increased cost as a consequence of extra health-care may eventually burden the government finance. Based on the findings from the current thesis, we were able to advise clinicians to adapt surgical management once CALI is diagnosed preoperatively or observed during liver surgery (e.g., ‘blue’ or

'yellow' liver). Therefore, the side-effects of CALI on postoperative morbidity and, as a consequence, the effects of CALI on the economic burden could be limited.

*Societal relevance*

Increased postoperative morbidity due to the presence of CALI has important potential negative influences on society. This is related to increased financial cost, but also to patients spending increased time on health-care related services, and, as a consequence, taking more sick leaves and spending less time on work. This negative influence may even radiate from the employer to the entire work-related network. Moreover, this thesis demonstrated that the presence of sinusoidal dilatation diminished tumour response to neoadjuvant chemotherapy. Of note, complete tumour response would allow patients to receive future curative surgical treatment and result in an increased tumour recurrence-free survival and overall survival. However, the diminished tumour response due to the occurrence of sinusoidal dilatation may alter the treatment strategy from curative to palliative. The latter, unfortunately, is related to a shorter lifespan. Additionally, being sick negatively affects quality of life, and the side effects of CALI are usually persistent for months.[12] Importantly, addition of bevacizumab to oxaliplatin-based chemotherapeutic regimens has been confirmed to be a beneficial approach to prevent sinusoidal dilatation, thereafter minimizing its negative effect on tumour response. Moreover, the development of oxaliplatin-induced sinusoidal dilatation, which we suggested to be related to the low expression of hepatic miR-21 and miR-150, may be prevented by treatment targeting these microRNAs in the future. With these evidence-based advices, patients would benefit from personalized treatment by prevented sinusoidal dilatation, increased tumour response, increased lifetime without tumour recurrence, and even increased lifespan. As a consequence, the negative influence of CALI on the society could be diminished.

## Target groups

CRLM treatment involves multidisciplinary clinicians (e.g. gastroenterologists, surgeons, oncologists, and radiologists). The entire studies performed in this thesis focused on the population of patients with this disease. Therefore, in addition to the academic community, the research results benefit the group of patients with primary colorectal cancer and those with or without liver metastases. Additionally, our findings may also benefit paediatric patients who undergo hematopoietic stem cell transplantation and develop busulfan-induced hepatic sinusoidal injury[13,14]; and those with breast cancer who develop tamoxifen-induced nonalcoholic steatohepatitis.[15]

## Innovation and Implementation

The studies conducted in this thesis are novel and elaborated important clinical concerns. For instance, a first meta-analysis which aimed to study the downstream effect of CALI on postoperative morbidity was described in Chapter 2. Based on the findings from the previous chapter, Chapter 3 presents a first individual participant data analysis conducted on this topic. This new approach enables consistent statistical modelling and unified definitions for surgical outcomes when handling data from multiple international cohorts. Moreover, the relationship between CALI and postoperative infectious complications as shown in Chapter 4 was previously unknown in literature. Additionally, the links between microRNA profiles, complement activation, and the presence of CALI depicted in Chapter 6 and Chapter 7 provided novel insight into the mechanisms underlying its pathological features.

Because addition of bevacizumab to oxaliplatin-based regimens prevents the occurrence of sinusoidal dilatation, which has been demonstrated to be a risk factor for increased postoperative morbidity and diminished tumour response to neoadjuvant chemotherapy, it is advised to add bevacizumab to oxaliplatin-based treatment. Once CALI is diagnosed, treatment for patients with CRLM should be discussed in multidisciplinary meetings and surgical management is advised to be adapted (e.g. apply radiofrequency ablation and two-stage hepatectomy) to prevent the occurrence of morbidity. The role of miR-21 and miR-150 in oxaliplatin-induced sinusoidal dilatation is interesting, however, in view of the small cohort size, further validation in a large cohort is encouraged and warranted.

# References


1. OCW, Brief valorisatie van onderzoek als taak van de universiteiten; van de bewindslieden Van der Hoeven en Rutte aan de voorzitters van de Colleges van Bestuur van 27 januari 2005 (OWB/AI/04-57055).
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136(5):E359-86.
3. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005; 23(9):2038-48.
4. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4:283-301.
5. Scheele J. Hepatectomy for liver metastases. *Br J Surg* 1993; 80(3):274-6.
6. Lam VW, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. *Ann Surg Oncol* 2012; 19(4):1292-301.
7. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; 240(4):644-57; discussion 657-8.
8. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; 15(3):460-6.
9. Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 2010; 56(4):430-9.
10. Vigano L, Ravarino N, Ferrero A, Motta M, Torchio B, Capussotti L. Prospective evaluation of accuracy of liver biopsy findings in the identification of chemotherapy-associated liver injuries. *Arch Surg* 2012; 147(12):1085-91.
11. Khan AZ, Morris-Stiff G, Makuuchi M. Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. *J Hepatobiliary Pancreat Surg* 2009; 16(2):137-44.
12. Vigano L, De Rosa G, Toso C, Andres A, Ferrero A, Roth A, et al. Reversibility of chemotherapy-related liver injury. *J Hepatol* 2017.
13. Huezo-Diaz Curtis P, Uppugunduri CR, Muthukumaran J, Rezgui MA, Peters C, Bader P, et al. Association of CTH variant with sinusoidal obstruction syndrome in children receiving intravenous busulfan and cyclophosphamide before hematopoietic stem cell transplantation. *Pharmacogenomics J* 2016.
14. Hwang DY, Kim SJ, Cheong JW, Kim Y, Jang JE, Lee JY, et al. High pre-transplant serum ferritin and busulfan-thiotepa conditioning regimen as risk factors for hepatic sinusoidal obstructive syndrome after autologous stem cell transplantation in patients with malignant lymphoma. *Leuk Lymphoma* 2016; 57(1):51-7.
15. Saphner T, Triest-Robertson S, Li H, Holzman P. The association of nonalcoholic steatohepatitis and tamoxifen in patients with breast cancer. *Cancer* 2009; 115(14):3189-95.