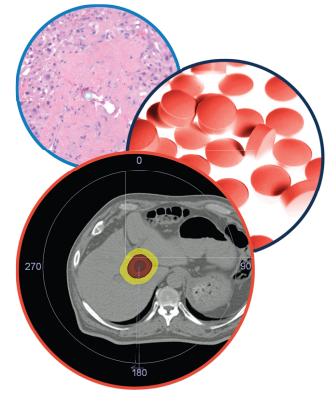
Editorial

For reprint orders, please contact: reprints@futuremedicine.com



Hepatic Oncology

Towards precision medicine in colorectal cancer liver metastases

Juan Manuel O'Connor*,[1] & Fernando Sanchez Loria[1]

[1]GI Clinical Oncology & GI Surgical Oncology, Instituto Alexander Fleming, Av Cramer 1180, Buenos Aires, C1426ANZ, Argentina

*Author for correspondence: juanmanuel.oconnor@gmail.com

"Liver is the most common site of metastasis from colorectal cancers (50–60% of the cases). Close to a third of patients have liver metastases either at the time of diagnosis (synchronous in 1/3 of cases) or during the disease course (metachronous in 2/3 of cases)."

First draft submitted: 2 April 2020; Accepted for publication: 4 June 2020; Published online: 29 July 2020

Keywords: colorectal cancer • Liver metastases • KRAS • precision medicine

Colorectal cancer (CRC) is a prevalent disease globally; it is the third leading cause in cancer incidence and the second cause of cancer-related death worldwide [1]. According to the data published by GLOBOCAN 2018 CRC incidence rates in developed countries are approximately threefold higher than in transitioning countries; however, CRC related mortality rates do not differ significantly due to the fact that average case fatality is higher in lower human developments index settings.

Liver is the most common site of metastasis from colorectal cancers (50–60% of the cases). Close to a third of patients have liver metastases either at the time of diagnosis (synchronous in 1/3 of cases) or during the disease course (metachronous in 2/3 of cases) [2].

The approach to the treatment of liver metastases from CRC includes surgical resection, in various modalities, some examples are one-stage hepatectomy, two-stage hepatectomy (TSH) with portal vein ligation or embolization, TSH with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [3] or ultrasound guided one stage hepatectomy associated with or without ablating methods such as radiofrequency ablation or microwave ablation [4] and systemic treatment, with different chemotherapy protocols in combination with biological agents, such as antiangiogenic therapy or I-EGFR (panitumumab or cetuximab). The strategic alliance between the surgical oncologist and the medical oncologist has been defined through the International Consensus Meeting (Expert Group on OncoSurgery management of Liver Metastases) published in 2012 [5]. One of the most important issues is to define the resectability criteria, which have varied over time as well as the timing of chemotherapy, either neoadjuvant, perioperative or postresection of metastases, with a pseudoadjuvant criteria. The most important issue in almost all cases is multidisciplinary work to guarantee the best therapeutic results and survival benefits for the individual patient. Specialized hospitals with multidisciplinary tumor boards including radiologists, pathologists, oncologists and liver surgeons show better resectability and survival rates than general hospitals or nonspecialized centers. Five year survival has increased from less than 8%, with palliative chemotherapy, to 25–40% using multimodal management including chemotherapy and surgical procedures [6].

On the other hand, resectability criteria have been defined on the basis of technical and oncologic data, the latter according to the presence or lack of extrahepatic disease and progression of disease after systemic treatment, both variables are associated with poor prognosis [7].

There is growing interest in directly assessing tumor biology by molecular profiling and integrating biomarkers into prognostication systems [8]. The *KRAS* gene has been extensively studied, as there was found to be a high concordance of KRAS status between primary CRC and colorectal liver metastases, this biomarker can be evaluated upon biopsy or resected specimens from the primary tumor [9].

The most recent publications of new and more effective chemotherapies and novel surgical techniques developed in recent years have increased the number of resectable patients with colorectal liver metastases [10]. The caveat of

Future Medicine

multiple bilobar metastases surgery is the fact that a large proportion of normal parenchyma must be resected to achieve R0 resection, causing an augmented risk of liver failure after surgery, considering that the only limit today for liver resection is the proportion of future liver remnant.

Several strategies were developed to avoid this risk. The first was TSH, described in 2000 [11]. This is now a standard surgical approach achieving excellent oncologic results [12]. The main problem with this strategy is tumor progression between surgical procedures that excludes patients from the second stage surgery [13].

In order to avoid this progression, ALPPS was described [14]. ALPPS is a variation of TSH that in a short interval of time induces an astonishing increase in future liver remnant. Results published regarding ALPPS are controversial, it clearly reduces drop-outs because of the short inter-stage period, but increased morbidity and mortality are reported. Posthepatectomy liver failure and bile leak account for the majority of ALPPS morbidity (35–40%) and mortality (9–12%) causes. Posthepatectomy liver failure accounts for 75% of ALPPS mortality [15,16]. Despite short follow up studies, whether the theoretical advantages of ALPPS can be extrapolated to survival benefits remains uncertain and warrants further studies.

Finally, we can mention enhanced/ultrasound guided one stage hepatectomy, a technique that allows the surgeon to perform multiple wedge resections, including deep seated metastases in only one operating time with or without associating ablative techniques generating a liver-sparing approach [17]. It requires a huge imaging and surgical expertise to reach good surgical and oncological results.

There is clear evidence showing that, the higher the objective response rate, the greater the likelihood of liver metastases resection [18]. Current chemotherapy schemes with a combination of triplets with drugs such as FOLFOXIRI with or without biological agents have shown objective response rates greater than 80%, with greater potential to achieve surgical resection of metastases [19,20].

In the current literature, there is agreement for the association between KRAS and BRAF mutations and poor long-term outcome after hepatectomy [21]. On the other hand, location of the primary tumor emerges as a prognostic factor in patients with advanced CRC, albeit with a less clear role in liver metastases resection [22].

What do we know about KRAS and liver metastases resection? According to the current literature a worse prognosis is observed in patients with KRAS mutations or BRAF mutations, with a higher chance of intrahepatic and extrahepatic recurrence [23]. In our multicenter study performed in Argentina we observed the same poor prognosis associated with KRAS mutation status. Our survival analysis showed that KRAS mutation was an independent predictor of death or recurrence, expressed as recurrence free survival, which was 22% at 5 years for mt-KRAS and 33% at 5 years for wt-KRAS (p = 0.0053; hazard ratio [HR]: 1.42) [24].

Margonis *et al.* found that anatomic resection may be better than nonanatomic resection for KRAS-mutated CLM to obtain a larger clear margin [25]. While mt-KRAS itself does not contraindicate metastases resection in resectable patients, it is advisable to consider this variable in borderline cases or with other poor prognostic factors, because the augmented death or recurrence prediction rate demonstrated in our study.

In the clinical setting, it is important to seek a new insight into molecular biomarkers, beyond KRAS. However, it is likely that in the future, genomic analysis, through liquid biopsy and real-time monitoring, will determine which particular patient is amenable to resective surgery, establish timing of surgery versus other modalities, as well as how to technically approach the metastases. It will also be enable us to define the role of systemic treatment or to determine the appropriate timing of chemotherapy. Only then we will be able to get closer to an old axiom expressed by a great surgeon who explained: "Biology is King, selection is Queen and technical maneuvers are the Prince and Princess" Blake Cady, Presidential Address to the Society of Surgical Oncology, 1988.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA J. Clin.* 68(6), 394–424 (2018).
2. van Cutsen E, Cervantes A, Nordlinger B *et al.* Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis treatment follow-up. *Ann. Oncol.* 25(3), iii1–9 (2014).
3. Chow FC, Chok KS. Colorectal liver metastases: an update on multidisciplinary approach. *World J. Hepatol.* 11(2), 150–172 (2019).
4. Masuda T, Margonis GA, Andreatos N *et al.* Combined hepatic resection and radio-frequency ablation for patients with colorectal cancer liver metastasis: a viable option for patients with a large number of tumors. *Anticancer Res.* 38(11), 6353–6360 (2018).
5. Adam R, de Gramont A, Figueras J *et al.* The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 17(10), 1225–1239 (2012).
6. Chow FC, Chok KS. Colorectal liver metastases: an update on multidisciplinary approach. *World J. Hepatol.* 11(2), 150–172 (2019).
7. Adams RB, Aloia TA, Loyer E. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB (Oxford)* 15(2), 91–103 (2013).
8. Balachandran VP, Arora A, Gönen M *et al.* A validated prognostic multigene expression assay for overall survival in resected colorectal cancer liver metastases. *Clin. Cancer Res.* 22(10), 2575–2582 (2016).
9. Han CB, Li F, Ma JT, Zou HW. Concordant KRAS mutations in primary and metastatic colorectal cancer tissue specimens: a meta-analysis and systematic review. *Cancer Invest.* 30(10), 741–747 (2012).
10. Wicherts DA, Miller R, de Haas RJ Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann. Surg.* 248(6), 994–1008 (2008).
11. Adam R, Laurent A, Azoulay D. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann. Surg.* 232(6), 777–85 (2000).
12. Brouquet A, Abdalla EK, Kopetz S. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J. Clin. Oncol.* 29(8), 1083–90 (2011).
13. Imai K, Benitez CC, Allard MA *et al.* Failure to achieve a 2-stage hepatectomy for colorectal liver metastases: how to prevent it? *Ann. Surg.* 262(5), 772–8 (2015).
14. Schnitzbauer AA, Lang SA, Goessmann H *et al.* Right portal vein ligation combined with *in situ* splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann. Surg.* 255(3), 405–14 (2012).
15. Moris D, Ronneklei-Kelly S, Kostakis ID *et al.* Operative results and oncologic outcomes of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH) in patients with unresectable colorectal liver metastases: a systematic review and meta-analysis. *World J. Surg.* 42(3), 806–815 (2018).
16. Au KP, Chan ACY. Current status of associating liver partition with portal vein ligation for staged hepatectomy: comparison with two-stage hepatectomy and strategies for better outcomes. *World J. Gastroenterol.* 25(43), 6373–6385 (2019).
17. Torzilli G, Cimino MM. Extending the limits of resection for colorectal liver metastases enhanced one stage surgery. *J. Gastrointest. Surg.* 21(1), 187–189 (2017).
18. Folprecht G, Grothey A, Alberts S *et al.* Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann. Oncol.* 16(8), 1311–1319 (2005).
19. Loupakis F, Cremolini C, Masi G *et al.* Initial therapy with folfoxiri and bevacizumab for metastatic colorectal cancer. *N. Engl. J. Med.* 371, 1609–1618 (2014).
20. Modest D, Martens UM, Riera-Knorrenschild J *et al.* Folfoxiri plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer: the randomized, open-label, Phase II VOLFI study (AIO KRK0109). *J. Clin. Oncol.* 37(35), 3401–3411 (2019).
21. Karagkounis G, Torbenson MS, Daniel HD *et al.* Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. *Cancer* 119(23), 4137–4144 (2013).
22. Petrelli F MD, Tomasello G, Borgonovo K *et al.* Prognostic survival associated with left-sided vs right-sided colon cancer a systematic review and meta-analysis. *JAMA Oncol.* 3(2), 211–219 (2016).
23. Okuno M, Goumard C, Kopetz S *et al.* RAS mutation is associated with unsalvageable recurrence following hepatectomy for colorectal cancer liver metastases. *Ann. Surg. Oncol.* 25(8), 2457–66 (2018).
24. O'Connor J, Sanchez Loria F, Ardiles V *et al.* Prognostic impact of K-RAS mutational status and primary tumor location in patients undergoing resection for colorectal cancer liver metastases: an update. *Future Oncol.* 15(27), 3149–57 (2019).
25. Margonis GA, Buettner S, Andreatos N *et al.* Anatomical resections improve disease-free survival in patients with KRAS-mutated colorectal liver metastases. *Ann. Surg.* 266(4), 641–649 (2017).