R1 Resection of LIver Metastas in Colorectal Cancer

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Achieving an R0 hepatic resection, optimally with more than 1 mm of clear margin, should always be the goal. In the era of the aggressive multimodality treatment of liver metastatic colorectal cancer, an R1 resection might be the cost of increasing the pool of patients finally eligible for resection. The majority of literature reports have highlighted the detrimental effect of R1 resections on local recurrence and overall survival. There are indeed studies that degraded the prognostic handicap as a consequence of an R1 resection in selected patients and highlighted the presence of RAS mutations, the response to chemotherapy, and, in general, factors that reflect the biology of the disease as important, if not the determinant, prognostic factors. In these patients, the aggressive disease biology seems to outperform the resection margin status as a prognostic factor, and the recorded differences between R1 and R0 resections are equalized.

colorectal cancer liver metastases | resection margins | R0 resection | R1 resection

1. Introduction

Metastatic colorectal cancer is associated with a rather dismal 5-year overall survival of 14% [1]. Liver is the most commonly affected organ. Improved 5-year survival rates, even up to 58% after successful hepatic resections, for metastases confined to the liver, have been reported [2]. Therefore, surgery, in the form of hepatic resection with clear resection margins, can assign these stage IV colorectal cancer patients with resectable colorectal cancer liver metastases (CRLM) into a prognostic group with an associated overall survival pretty much similar to stage III colorectal cancer [3]. The technical definition of resectability has, notably, evolved over time with an obvious trend towards the expansion of the indications for surgery. In general, the disease is considered resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant or a remnant liver to body weight ratio >0.5 [4]. However, there are patients eligible for hepatectomy according to the technical criteria that the disease relapses shortly after the operation and ultimately do not experience benefits, in terms of survival, out of this approach. Indeed, as much as half of the patients submitted to hepatectomy for CRLM will develop widespread systemic disease within 3 years of resection [5].

The proper patient selection relies upon the identification of the risk factors behind the devastating event of early recurrence following hepatic resection for CRLM. In 1999, Fong et al. published a classic, in the field of liver surgery, analysis of 1001 patients submitted to hepatectomy for CRLM aiming to define the risk factors for recurrence after hepatic resection on the background of metastatic colorectal cancer [6]. The authors identified

seven factors as independent predictors of poor long-term outcome: (1) Positive margin, (2) Extrahepatic disease, (3) Node-positive primary tumor, (4) Disease-free interval, from the diagnosis of the primary tumor to the development of the metastases, less than 12 months, (5) Number of hepatic tumors > 1, (6) Largest hepatic tumor larger than 5 cm in diameter, and (7) Carcinoembryonic antigen (CEA) levels > 200 ng/mL [6]. It becomes obvious that apart from the technical aspects of resectability, oncological criteria should be taken into account, as well, when deciding the treatment plan in patients with CRLM [7]. In practice, parameters such as the number of lesions, the possible presence of extrahepatic disease, and, in general, the criteria highlighted by Fong et al. [6], in their classic report, can predict a higher likelihood of longer disease-free survival [7]. Surgery is probably not the best option, at least upfront, when these risk factors are present.

2. Risk Factors for R1 Resection

An important aspect before assessing the prognostic correspondence of an R1 hepatic resection for CRLM is to identify patients at risk for such a resection. Welsh et al. developed a predictive index for quantifying the likelihood of an R1 hepatic resection for CRLM by studying a cohort of 929 patients. The authors reported an R1 resection incidence of 8.8%, while they identified five risk factors as independent predictors of an R1 resection: (1) Non-anatomical resection, (2) >3 hepatic metastases involving >50% of the liver parenchyma, (3) Bilobar disease, (4) Repeat hepatic resection, and (5) Abnormal preoperative liver function tests [8].

RAS mutations, which have been linked to more invasive and migratory tumor biology and a poor response to modern chemotherapeutic agents, have been implemented, as well. Brudvik et al. studied 663 patients with CRLM, of whom 229 had mutant RAS. The positive margin rate, defined as tumor cells < 1 mm from the resection margin, was 11.4% in the mutant RAS group and 5.4% in the wild-type RAS group ($p = 0.007$). The only factors associated with a positive margin were RAS mutation status ($p = 0.005$) and carcinoembryonic antigen levels of more than 4.5 ng/mL ($p = 0.026$). Furthermore, the authors analyzed the patients presenting with metachronous liver metastases and reported that those with mutant RAS had narrower clear resection margins during hepatectomy (median 4 mm vs. 7 mm—$p = 0.031$) [9].

The role of preoperative chemotherapy on resection margin status has been also investigated. Solaini et al. conducted a retrospective analysis, but with a propensity score matched analysis, and reported that preoperative chemotherapy was significantly associated with the rate of positive resection margin (25.5% vs. 8.5%) [10]. Aligned in the same direction, a multicenter study by Benedetti et al. analyzed a cohort of 3387 patients who underwent open or laparoscopic liver resection for CRLM in nine European high-volume referral centers. According to the results, the risk factors for R1 resection were: (1) The type of resection (non-anatomic or anatomic), (2) The number of nodules, and (3) The size of the tumor. In regard to the laparoscopic group specifically, blood loss proved to be a risk factor, whereas the Pringle maneuver had a protective effect against an R1 resection. The predictive size of a tumor for R1 resection was >45 mm for the open surgery and > 30 mm for the laparoscopic approach; the presence of more than two metastases increased the risk in both groups, while blood loss of more than 350 cc increased the risk in the laparoscopic approach [11].

It becomes clear that an R1 hepatic resection should not be considered solely synonymous to a poor surgical technique because the oncological characteristics of the metastatic disease could occasionally compromise the goal for an R0 resection. The presence of parameters that predict aggressive disease biology such as the increased number of lesions, the presence of bilobar disease, the mutant RAS status, and the poor response to chemotherapy could increase the likelihood for an R1 resection even when extensive hepatic resections, aiming to guarantee clear resection margins, are undertaken.

3. Definition and Prognostic Implications of R1 Resection

In general, curative surgery prerequisites the complete resection of the tumor with clear pathological resection margins, i.e., an R0 resection. Aligned with this dogma of surgical oncology, multiple studies in the early 2000s analyzing the results of hepatic resection on the background of CRLM have demonstrated that when a microscopically positive resection margin, i.e., an R1 resection, is the case, then a worse overall survival should be anticipated. More specifically, 5-year survival rates following a microscopically negative R0 resection and an R1 resection have been reported to range from 37% to 64%, and less than 20%, respectively [2][12][13][14]. However, de Haas et al., in their 2008 study with 436 patients treated with combined modality therapy utilizing chemotherapy and surgical resection, directly questioned these results. The authors reported that R1 resection had comparable long-term survival outcomes to R0 resection, i.e., 5-year overall survival rates were similar, i.e., 61% vs. 57%, between patients who had undergone an R0 or an R1 resection, respectively [15]. The study was greeted with skepticism by the surgical community and criticized for its methodology. However, it created the necessary creative doubt in regard to the actual impact of the resection margin status on overall survival. The logical assumption was that additional factors, besides the resection margin status, acting either synergically or independently could decisively influence the prognosis of patients with CRLM.

Traditionally, an R1 resection is considered a resection where, although there is no macroscopic tumor involvement on the resection margin, the pathology report highlights the microscopic resection margin as infiltrated by tumor cells. However, in 2015, the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group suggested that a minimal surgical clearance margin of 1 mm can be considered adequately safe when performing hepatic resection for CRLM [16]. This statement decisively influenced the definition of R1 resection as a resection with at least 1 mm of clear resection margin. However, in the literature, a microscopically positive margin (R1) has been commonly equated with either an involved margin (margin width = 0 mm) or a margin width of less than 1 mm. Unavoidably, the absence of a universally adopted definition acted as the starting point for problems with the interpretation of the results out of different studies. In practice, the proposal of the >1 mm clear margin definition of R0 resection appears justified as long as a notable difference in prognosis can be documented in the cohorts of patients created when the two definitions are separately applied.

Wang et al. aimed to test the validity of the definition of R1 resection focusing especially on patients with a margin width of 0–1 mm, a group of patients that have been inconsistently classified in either the R0 or R1 categories. The authors studied 633 patients who underwent a resection of CRLM and reported that a margin width of ≥1 mm was associated with improved survival vs. a sub-mm margin (65 vs. 36 months—$p = 0.03$) or an involved margin (65 vs.

33 months—$p < 0.001$) [17]. Using the same methodology, another study with 2368 patients submitted to a liver resection for CRLM at the Memorial Sloan Kettering Cancer Center compared survival according to the resection margin width. According to the results, the median overall survival of the R1 (0 mm), 0.1 to 0.9 mm, 1 to 9 mm, and 10 mm or more groups were 32, 40, 53, and 56 months, respectively. Compared with R1 resection (0 mm), all margin widths, including sub-mm margins, correlated with prolonged overall survival ($p < 0.05$). The authors concluded that wide margins should be the goal whenever possible, but resection should not be precluded if narrow margins are anticipated, as submillimeter margin clearance is also associated with improved survival [18].

The existing reports on the subject are mainly retrospective in nature with significant limitations. Propensity score matching is a statistical technique that has been widely used in order to reduce confounding biases such as selection bias in observational studies. A study by Sakai et al. represents an example on how propensity scores can alter the results of an observational study. The authors evaluated the influence of R1 resection on recurrence patterns and prognosis in 232 patients submitted to hepatic resection for CRLM. According to the results, patients with R1 resection had significantly poorer recurrence-free survival and overall survival compared to patients with R0 resection. However, after propensity score matching, there were no significant differences in recurrence-free survival and overall survival associated with the margin status. The authors concluded that among the group of patients with similar characteristics, as created by the propensity score matching, R1 resection does not seem to affect long-term outcomes and the R1 resection status should be regarded as an indicator of aggressive tumor biology [19].

In general, achieving an R0 resection with at least 1 mm of clear resection margin should always be the goal of a hepatic resection for CRLM because this seems to be consistently the safest way to achieve optimal long-term results. However, several technical and disease-related factors could lead to a suboptimal, i.e., less than 1 mm, resection margin. This R1 resection patient group exhibits notable heterogeneity in regard to prognosis. More specifically, among R1 resections, there are patients with a prognosis pretty much similar to R0 resections, while there are also patients with significantly worse prognosis compared to R0 resections. Within this context, adapting the definition of an R0 resection as a resection with at least 1 mm of clear resection margin appears justified. In regard to R1 resections, the actual challenge is to accurately define the oncological, technical, and clinical parameters that could neutralize the possible prognostic handicap associated with this certain resection margin status.

References

1. Provenzale, D.; Gupta, S.; Ahnen, D.J.; Markowitz, A.J.; Chung, D.C.; Mayer, R.J.; Regenbogen, S.E.; Blanco, A.M.; Bray, T.; Cooper, G.; et al. NCCN guidelines insights: Colorectal cancer screening, version 1.2018. J. Natl. Compr. Cancer Netw. 2018, 16, 939–949.
2. Pawlik, T.M.; Scoggins, C.R.; Zorzi, D.; Abdalla, E.K.; Andres, A.; Eng, C.; Curley, S.A.; Loyer, E.M.; Muratore, A.; Mentha, G.; et al. Effect of surgical margin status on survival and site of

recurrence after hepatic resection for colorectal metastases. Ann. Surg. 2005, 241, 715–722; Discussion 722–724.

3. Li, C.; Pei, Q.; Zhu, H.; Tan, F.; Zhou, Z.; Zhou, Y.; Li, Y.; Pei, H. Survival nomograms for stage III colorectal cancer. Medicine 2018, 97, e13239, PMCID:PMC6310595.
4. Clavien, P.A.; Petrowsky, H.; DeOliveira, M.L.; Graf, R. Strategies for safer liver surgery and partial liver transplantation. N. Engl. J. Med. 2007, 356, 1545–1559.
5. Kanas, G.P.; Taylor, A.; Primrose, J.N.; Langeberg, W.J.; Kelsh, M.A.; Mowat, F.S.; Alexander, D.D.; Choti, M.A.; Poston, G. Survival after liver resection in metastatic colorectal cancer: Review and meta-analysis of prognostic factors. Clin. Epidemiol. 2012, 4, 283–301, PMCID:PMC3496330.
6. Fong, Y.; Fortner, J.; Sun, R.L.; Brennan, M.F.; Blumgart, L.H. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann. Surg. 1999, 230, 309–318; Discussion 318–321, PMCID:PMC1420876.
7. Adam, R.; De Gramont, A.; Figueras, J.; Guthrie, A.; Kokudo, N.; Kunstlinger, F.; Loyer, E.; Poston, G.; Rougier, P.; Rubbia-Brandt, L.; et al. Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: A multidisciplinary international consensus. Oncologist 2012, 17, 1225–1239, PMCID:PMC3481888.
8. Welsh, F.K.; Tekkis, P.P.; O'Rourke, T.; John, T.G.; Rees, M. Quantification of risk of a positive (R1) resection margin following hepatic resection for metastatic colorectal cancer: An aid to clinical decision-making. Surg. Oncol. 2008, 17, 3–13.
9. Brudvik, K.W.; Mise, Y.; Chung, M.H.; Chun, Y.S.; Kopetz, S.E.; Passot, G.; Conrad, C.; Maru, D.M.; Aloia, T.A.; Vauthey, J.N. RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases. Ann. Surg. Oncol. 2016, 23, 2635–2643, PMCID:PMC5527830.
10. Solaini, L.; Gardini, A.; Passardi, A.; Mirarchi, M.T.; D'Acapito, F.; La Barba, G.; Cucchi, M.; Casadei Gardini, A.; Frassineti, G.L.; Cucchetti, A.; et al. Preoperative Chemotherapy and Resection Margin Status in Colorectal Liver Metastasis Patients: A Propensity Score-Matched Analysis. Am. Surg. 2019, 85, 488–493.
11. Benedetti Cacciaguerra, A.; Görgec, B.; Cipriani, F.; Aghayan, D.; Borelli, G.; Aljaiuossi, A.; Dagher, I.; Gayet, B.; Fuks, D.; Rotellar, F.; et al. Risk Factors of Positive Resection Margin in Laparoscopic and Open Liver Surgery for Colorectal Liver Metastases: A New Perspective in the Perioperative Assessment: A European Multicenter Study. Ann. Surg. 2022, 275, e213–e221.
12. Choti, M.A.; Sitzmann, J.V.; Tiburi, M.F.; Sumetchotimetha, W.; Rangsin, R.; Schulick, R.D.; Lillemoe, K.D.; Yeo, C.J.; Cameron, J.L. Trends in longterm survival following liver resection for

hepatic colorectal metastases. Ann. Surg. 2002, 235, 759–766.

13. Cady, B.; Jenkins, R.L.; Steele Jr, G.D.; Lewis, W.D.; Stone, M.D.; McDermott, W.V.; Jessup, J.M.; Bothe, A.; Lalor, P.; Lovett, E.J.; et al. Surgical margin in hepatic resection for colorectal metastasis: A critical and improvable determinant of outcome. Ann. Surg. 1998, 227, 566–571.
14. Steele, G., Jr.; Bleday, R.; Mayer, R.J.; Lindblad, A.; Petrelli, N.; Weaver, D. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. J. Clin. Oncol. 1991, 9, 1105–1112.
15. De Haas, R.J.; Wicherts, D.A.; Flores, E.; Azoulay, D.; Castaing, D.; Adam, R. R1 resection by necessity for colorectal liver metastases: Is it still a contraindication to surgery? Ann. Surg. 2008, 248, 626–637.
16. Adam, R.; de Gramont, A.; Figueras, J.; Kokudo, N.; Kunstlinger, F.; Loyer, E.; Poston, G.; Rougier, P.; Rubbia-Brandt, L.; Sobrero, A.; et al. Managing synchronous liver metastases from colorectal cancer: A multidisciplinary international consensus. Cancer Treat. Rev. 2015, 41, 729–741.
17. Wang, J.; Margonis, G.A.; Amini, N.; Andreatos, N.; Yuan, C.; Damaskos, C.; Antoniou, E.; Garmpis, N.; Buettner, S.; Barbon, C.; et al. The Prognostic Value of Varying Definitions of Positive Resection Margin in Patients with Colorectal Cancer Liver Metastases. J. Gastrointest. Surg. 2018, 22, 1350–1357.
18. Sadot, E.; Groot Koerkamp, B.; Leal, J.N.; Shia, J.; Gonen, M.; Allen, P.J.; DeMatteo, R.P.; Kingham, T.P.; Kemeny, N.; Blumgart, L.H.; et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: Surgical technique or biologic surrogate? Ann. Surg. 2015, 262, 476–485; Discussion 483–485, PMCID:PMC4533113.
19. Sakai, N.; Furukawa, K.; Takayashiki, T.; Kuboki, S.; Takano, S.; Ohtsuka, M. Recurrence patterns and their effects on clinical outcomes after R1 resection of colorectal liver metastases: A propensity score-matched analysis. Langenbecks Arch. Surg. 2021, 406, 2739–2747.