Ann Colorectal Res. 2018 December; 6(4):e83855. doi: 10.5812/acr.83855.

Published online 2018 October 9. **Brief Report**

Liver Transplantation for Non-Resectable Colorectal Liver Metastases

Ashwin Rammohan [1, *]

[1]Institute of Liver Disease & Transplantation, Dr.Rela Institute & Medical Centre, Chennai, India

[*]*Corresponding author*: Dr. Rela Institute & Medical Centre, Chennai, India. E-mail: ashwinrammohan@gmail.com

Received 2018 September 02; **Accepted** 2018 October 01.

Abstract

Improved results following liver transplantation (LT) over the past 20 years have led clinicians to push boundaries and expand its indications. LT in non-resectable colorectal liver metastases (NCRLM) is being revisited with an aim to radically improve survival. By utilizing new tools for preoperative patient selection, modern operative techniques for LT and an aggressive attitude against metastases, long-term survival, and even cure could be expected. This paper reviews the current status of liver transplantation for NCRLM with an eye on the future.

Keywords: Non-Resectable Colorectal Liver Metastases, Liver Transplantation, Review

1. Background

Colorectal cancer (CRC) is the third most common cancer worldwide and over half of these patients develop liver metastases during the course of their disease, resulting in two-thirds of CRC-related deaths (1, 2). Hepatectomy remains the only potentially curative treatment available for resectable colorectal liver metastases (CRLM) (3, 4). This modality is however, plagued with disease recurrence rates of over 70% during the first three years (5, 6). These patients and those who present initially with non-resectable CRLM (NCRLM) are either treated with palliative chemotherapy or forms of regional ablative therapy with an overall survival of 10 - 38 months (3-7).

In the past, liver transplantation (LT) has been performed for NCRLM with unacceptably high recurrence and poor outcomes, leading to restrictions in allotting organs for this indication (8-10). Over the last decade however, treatment of CRLM has markedly improved with advances in radiologic imaging and more accurate staging, as well as improved systemic chemotherapy, leading to a cautiously renewed interest in LT for NCRLM (10). There still remains a lot to be defined before LT can enter the NCRLM treatment armamentarium; especially keeping in mind the universal shortage of deceased donors. Thus, rigorous patient selection, as well as a critical review of the outcomes of LT for CRLM is needed to continually reassess whether this therapy is warranted. The aim of this paper is to provide the current and evolving evidence on the status of LT for NCRLM.

2. Results of LT for NCRLM

Scandinavian countries, especially Norway, are fortunate to have surplus of deceased donor organs, with median waiting time for a liver transplant being less than a month. This led a team from Oslo University Hospital to perform a pilot study on the role of LT for CRLM (11). Their study, named the SECA trial, had an inclusion criteria of patients with post R0 primary colorectal resection with at least six weeks of one or more chemotherapy agents being administered for metastatic disease, along with the presence of NCRLM with no extrahepatic disease in patients with ECOG performance status 0 - 1. Pre-transplantation, all patients underwent a staging laparotomy to rule out extrahepatic disease. Of the 21 patients who underwent deceased-donor LT (DDLT), recurrence was noted in 19 (90%) patients and 6 (29%) patients died of disseminated CRC after a median of 26 (6 - 41) months. The median follow-up time was 27 (8 - 60) months and the 1-, 3-, and 5-year overall survival (OS) was 95%, 68%, and 60%, respectively (11). Seven patients had CRC recurrence in the transplanted liver. No preoperative or adjuvant chemotherapy was administrated in this study and the post-transplant immunosuppressive protocol included mTOR inhibitors. Despite this trial having a few shortfalls, it marked a change in thought process, breaking the conventional reluctance towards LT for NCRLM due to poor results.

Another study by the same group, compared the SECA trial cohort with a subpopulation from those of a multicentre randomized three-arm trial (NORDIC VII trial), which assessed outcomes following various chemotherapeutic

regimens in patients with advanced CRC (12, 13). The 47 patients with liver-only metastases who did not undergo liver resection in the NORDIC VII trial (and therefore were treated with chemotherapy only) were compared with the 21 patients who underwent LT in the SECA trial. The five-year survival of the SECA trial cohort was 56%. This was significantly longer than that of the NORDIC VII cohort (19%), highlighting the survival advantage provided by LT in these patients (12, 13). Given that there are no randomized controlled trials comparing LT with standard chemotherapy, this likely is the best available evidence comparing LT with standard of care chemotherapy.

Twelve patients from a European consortium underwent LT for NCRLM at a median of 41 months following primary tumour resection, of which 11 patients received chemotherapy before LT. LT was part of the planned treatment strategy in six of the patients. The median follow-up was 26 months and the 1-, 3-, and 5-year OS was 83%, 62%, and 50%, respectively (14). Four of the patients were alive without cancer recurrence after 48 months. Despite its shortcomings (e.g., lack of standardization and small sample size), this is the first report to show that long-term cure can be achieved with LT (14). Improving results over the past two decades could in part be due to a stringent selection criterion along with the development of effective chemotherapy regimens and dramatic improvements in the perioperative care of LT recipients (15). However, the recurrence rates in these studies remained high, and adversely patient survival.

3. The Future & Ethical Considerations

With sporadic studies showing encouraging results, there are now several ongoing trials to further address the potential of LT for NCRLM (16). The SECA-II trial is an open label, randomized controlled trial to assess the OS between patients undergoing LT or liver resection. Recruitment is ongoing and the study is likely to conclude in 2027. Another trial from the Oslo University group is the resection and partial liver segment 2/3 transplantation with delayed total hepatectomy (RAPID) trial (17). The principle is to perform a left lateral segmentectomy followed by an orthotopic transplantation of a left lateral segment graft. Total hepatectomy of the remaining diseased liver is delayed until the transplanted graft has reached sufficient volume (18). The RAPID trial will assess safety and benefit of this procedure in transplanted patients undergoing a completion hepatectomy within four weeks. Stipulated completion time of the study is 2028 (18). The French TRANSMET trial is recruiting patients with CRLM to a randomized open label trial to receive standard of care chemotherapy or LT plus chemotherapy (19). The results are planned to be published in 2027.

The ethical dilemma always remains of randomizing patients to receive chemotherapy alone when smaller studies have shown better survival with LT. Another conundrum is that of offering deceased donor organs to CRLM-LT recipients, especially when hardcore evidence in its favour is yet lacking. Given the eternal shortage of deceased donor organs, live donor LT (LDLT) may help ease this situation. Even with LDLT, the principle of double equipoise (balancing donor safety with recipient outcomes) need to be addressed conclusively before LT for CRLM can become part of its evidence-based treatment algorithm (20).

4. Conclusion

Dramatic improvements in patient survival after LT, along with effective chemotherapeutic agents, adequate risk stratification, and patient selection criteria have led to better survival in patients with CRLM undergoing LT than was seen two decades ago. Further large structured studies along with ethical debates on this topic are needed before LT can become the standard of care for NCRLM.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;**127**(12):2893–917. doi: 10.1002/ijc.25516. [PubMed: 21351269].
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;**62**(1):10–29. doi: 10.3322/caac.20138. [PubMed: 22237781].
3. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: Expert consensus statement. *Ann Surg Oncol*. 2006;**13**(10):1271–80. doi: 10.1245/s10434-006-9045-5. [PubMed: 16955381].
4. de Haas RJ, Wicherts DA, Andreani P, Pascal G, Saliba F, Ichai P, et al. Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic resection. *Ann Surg*. 2011;**253**(6):1069–79. doi: 10.1097/SLA.0b013e318217e898. [PubMed: 21451388].
5. Saiura A, Yamamoto J, Koga R, Takahashi Y, Takahashi M, Inoue Y, et al. Favorable outcome after repeat resection for colorectal liver metastases. *Ann Surg Oncol*. 2014;**21**(13):4293–9. doi: 10.1245/s10434-014-3863-7. [PubMed: 24962942].
6. House MG, Ito H, Gonen M, Fong Y, Allen PJ, DeMatteo RP, et al. Survival after hepatic resection for metastatic colorectal cancer: Trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg*. 2010;**210**(5):744–52. 752-5. doi: 10.1016/j.jamcollsurg.2009.12.040. [PubMed: 20421043].
7. 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. doi: 10.2147/CLEP.S34285. [PubMed: 23152705]. [PubMed Central: PMC3496330].
8. Muhlbacher F, Huk I, Steininger R, Gnant M, Gotzinger P, Wamser P, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc*. 1991;**23**(1 Pt 2):1567–8. [PubMed: 1989293].

9. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery*. 1991;**110**(4):726–34. discussion 734-5. [PubMed: 1656538].
10. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. *Transpl Int*. 2008;**21**(12):1107–17. doi: 10.1111/j.1432-2277.2008.00735.x. [PubMed: 18713148].
11. Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg*. 2013;**257**(5):800–6. doi: 10.1097/SLA.0b013e3182823957. [PubMed: 23360920].
12. Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? *Ann Surg*. 2015;**261**(5):956–60. doi: 10.1097/SLA.0000000000000786. [PubMed: 24950280].
13. Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII study. *J Clin Oncol*. 2012;**30**(15):1755–62. doi: 10.1200/JCO.2011.38.0915. [PubMed: 22473155].
14. Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, et al. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. *Liver Transpl*. 2017;**23**(8):1073–6. doi: 10.1002/lt.24791. [PubMed: 28544246].
15. Chua TC, Liauw W, Chu F, Morris DL. Viewing metastatic colorectal cancer as a curable chronic disease. *Am J Clin Oncol*. 2012;**35**(1):77–80. doi: 10.1097/COC.0b013e3181fe4444. [PubMed: 22257778].
16. Bethesda (MD): National Library of Medicine (US) . *A randomized controlled clinical trial to evaluate the benefit and efficacy of liver transplantation as treatment for selected patients with liver metastases from colorectal carcinoma*. 2011, [cited 2018 Sep 02]. Available from: https://clinicaltrials.gov/ct2/show/NCT01479608.
17. Bethesda (MD): National Library of Medicine (US) . *A Phase I/II clinical trial to evaluate the benefit and efficacy of liver resection and partial liver segment 2/3 transplantation with delayed total hepatectomy as treatment for selected patients with liver metastases from colorectal carcinoma*. 2014, [cited 2018 Sep 02]. Available from: https://clinicaltrials.gov/ct2/show/NCT02215889.
18. Line PD, Hagness M, Berstad AE, Foss A, Dueland S. A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: The RAPID concept. *Ann Surg*. 2015;**262**(1):e5–9. doi: 10.1097/SLA.0000000000001165. [PubMed: 25692361].
19. Bethesda (MD): National Library of Medicine (US) . *Liver Transplantation in Patients With Unresectable Colorectal Liver Metastases Treated by Chemotherapy (TRANSMET)*. 2015, [cited 2018 Sep 02]. Available from: https://clinicaltrials.gov/ct2/show/NCT02597348.
20. Pomfret EA, Lodge JP, Villamil FG, Siegler M. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. *Liver Transpl*. 2011;**17 Suppl 2**:S128–32. doi: 10.1002/lt.22356. [PubMed: 21656657].