Minimally invasive liver resection—more evidence of oncologic advantage

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Liver resection for colorectal cancer liver metastases (CRCLM) improves survival in patients with metachronous and synchronous metastases, and adjuvant systemic chemotherapy (AC) is often utilized (1,2). Furthermore, the timing of AC seems to be important, with studies reporting a survival benefit to initiation within 8 weeks of resection (3,4).

Utilization of minimally invasive laparoscopic liver resection (LLR) is increasing in CRCLM, with robust evidence that LLR is safe and offers clinical advantages over open liver resection (OLR) (5-9). To further elucidate the oncologic advantages of LLR, Kawai *et al.* report results of a retrospective, propensity-matched analysis of LLR *vs.* OLR in patients with CRCLM (10). They examine time to AC as the primary endpoint. Over a 2-year period, they report on 30 LLR and 87 OLR, with a propensity-matched comparison of 22 LLR and 44 OLR. The two groups were propensity-matched according to baseline and comorbidity variables, preoperative receipt of chemotherapy, pathologic tumor factors, and extent of resection. On overall analysis, the LLR cohort was older, and had a greater proportion of solitary metastasis. There was no difference in postoperative complications or length of stay (LOS). LLR, however, had a shorter time to AC initiation (45 *vs.* 53 days), and a higher proportion of those initiating AC within 8 weeks (100% *vs.* 70%) compared to OLR. Propensity-matched analysis reinforced these findings with continued 12-day delay to AC initiation in OLR, and a 34% rate of failure to initiate AC within 8 weeks.

The findings by Kawai *et al.* are consistent with other reports on the oncologic benefits of LLR over OLR with regards to time to AC initiation. Our group has previously reported that LLR was associated with a shorter time to AC (42 *vs.* 63 days), and higher recurrence-free survival compared to OLR (11). In addition, we found that LLR was associated with less blood loss, shorter LOS (4 *vs.* 5 days), and less 30-day overall, complications (26% *vs.* 28%). After adjusting for blood loss, LOS, and complications, LLR remained an independent contributor to earlier AC initiation with a two-fold higher likelihood as compared to OLR. This same topic was analyzed by Mbah *et al.* in a series of major liver resections alone for CRCLM (12). They compared 44 LLR to 76 OLR matched by extent of resection, and found that time to AC was significantly shorter after LLR (24 *vs.* 39 days). In addition, they also identified less blood loss, shorter LOS (5 *vs.* 9 days), and less complications (14% *vs.* 36%) with LLR as compared to OLR. This echoes the large body of literature whereby OLR has been reported to have increased incidence of postoperative complications and LOS as compared to LLR (13-17). In the present study by Kawai *et al.*, however, there was no statistically significant difference in complications or LOS between LLR and OLR. Interpreted in the context of a longer than expected LOS of 8 days in both groups, it does raise concerns for postoperative complications or other confounders not captured in the analysis.

Taken together, these studies indicate that LLR for CRCLM is associated with earlier time to initiation of AC. The specific mechanism of this benefit remains unclear. Although LLR is usually associated with fewer complications

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than OLR, decreased postoperative complications and shorter LOS do not seem to explain the entire benefit. In the series by Tohme *et al.*, LLR remained an independent predictor of earlier AC initiation after adjusting for postoperative complications and LOS (11), and Kawai *et al.* also identified a shorter time to AC after LLR that cannot be attributed to a difference in complications, blood loss, extent of resection, pathologic tumor factors or LOS.

There is emerging evidence that minimally invasive approaches may be associated with different levels of circulating cytokines as compared to open surgery, affecting overall recovery as well as oncologic outcomes (18). Yamashita *et al.* recently reported lower postoperative serum C-reactive protein (CRP) levels following minimally invasive esophagectomy (19). Those patients with lower CRP levels demonstrated improved disease-free survival and improved overall survival. Furthermore, in the Oslo-CoMet randomized clinical trial of LLR *vs.* OLR of CRCLM, five inflammatory cytokines including CRP were present at significantly higher levels after OLR, reaffirming the association between operative approach and the inflammatory state postoperatively (18). Given the known association between surgical inflammation and cancer proliferation, modulation of the circulating inflammatory milieu could explain why LLR is associated with earlier initiation of AC and survival (20). Further mechanistic studies detailing the impact of minimally invasive surgery on the surrounding inflammatory milieu may thus serve to improve our understanding of the molecular basis for the improved oncologic outcomes. Other hypotheses worth considering for the independent effect of LLR on earlier AC initiation include improved patient perceptions and referring medical oncologist perceptions of health after minimally invasive surgery. Given that one of the main criterion to initiate AC is the subjective medical 'readiness' of a patient, smaller incisions and smaller scars psychologically may make patients and medical oncologists 'feel' that a patient is ready to initiate AC earlier than after OLR.

In conclusion, Kawai *et al.* contribute to the growing body of literature supporting LLR over OLR for improved cancer-related quality benchmarks and outcomes (21). Additional investigations are certainly warranted to provide more mechanistic explanations for this advantage.

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