French Editorial Commentary from the ACHBPT

Implications of the surgical approach for complex liver resection in the era of enhanced recovery programs: a critical appraisal of the "Orange Segments" randomized controlled trial

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Laparoscopic liver resections (LLR) of posterosuperior segments (PS) (7, 8, and 4a) are technically challenging. Adequate surgical exposure during parenchymal transection and bleeding control from the deep liver cut surface can be difficult to achieve. Both the IWATE (1) and IMM (2) LLR scoring systems classify PS segment resections as either advanced/expert level (IWATE) or group 3 (IMM), reflecting a high level of technical difficulty. Studies comparing laparoscopy to open surgery for this indication are mainly retrospective and the level of evidence supporting the superiority of laparoscopy remains low. The PS segment subgroup analysis of the OSLO-COMET randomized trial concluded that laparoscopy yielded a shorter hospital stay with no significant differences between open and LLR groups in complications and mortality rates (3).

"ORANGE Segments" (4) is the first multicenter randomized controlled superiority trial comparing the laparoscopic approach to open surgery for liver resections of the PS segments. The primary endpoint was time to functional recovery (TTFR) with a targeted difference of 2 days in favor of laparoscopy.

TTFR is a composite endpoint, already used by the ORANGE Trials Collaborative for the ORANGE II (5) and ORANGE II Plus (6) randomized trials (*Table 1*). All following criteria must be fulfilled to consider the patient functionally recovered: (I) adequate pain control with oral medication; (II) autonomous mobilization with a Mobility Score ≥8 (or at least equal to the preoperative value); (III) solid food intake for at least 24 h; (IV) independent of intravenous fluid administration; and (V) normal or normalizing liver function tests.

Patients with a body mass index (BMI) between 18 and 35 kg/m^2 and candidates to a parenchymal-sparing liver resection involving segments 4a, 7, and 8 or segments 6/7, were eligible to be enrolled in the trial. Patients were randomized to either groups in a 1:1 ratio with a stratification by center and lesion size (<3 or ≥3 cm). Close proximity of lesions to vascular and/or biliary structures was an exclusion criterion.

Seventeen European liver hepato-pancreato-biliary (HPB) centers from 5 countries participated to the trial. During the study period (November 2017 to November 2021), 125 patients were randomized to LLR and 126 patients to open liver resection (OLR).

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Table 1 Comparison of major randomized controlled trials evaluating laparoscopy *vs.* open surgery for liver resection

	ORANGE II [2017]	OSLO-COMET [2017]	ORANGE II Plus [2024]	ORANGE Segments [2025]
Design	RCT, patient-blinded, multicenter, superiority trial	RCT, open-label, single-center, superiority trial	RCT, patient-blinded, multicenter, superiority trial	RCT, patient-blinded, multicenter, superiority trial
Type of hepatectomy	Left lateral sectionectomy	Parenchyma-sparing liver resection for liver metastases from colorectal cancer	Hemihepatectomy	Liver parenchymal preserving resection of lesions in the posterosuperior segments
Primary endpoint	Time to functional recovery	Post-operative complication within 30 days	Time to functional recovery	Time to functional recovery
Results	No conclusion	Lower 30-day complication rate in the laparoscopy group	Reduction in time to functional recovery (1 day)	Reduction in time to functional recovery (1 day)
Commentary	Stopped prematurely owing to slow recruitment	Reduction in time to hospital stay, in flavor of laparoscopic approach	Reduction in time to hospital stay, improvement in QoL, shorter time to initiation of systemic therapy in flavor of laparoscopic approach	

QoL, quality of life; RCT, randomized controlled trial.

In the intention-to-treat analysis, laparoscopy reduced TTFR, with a median of 3 [interquartile range (IQR), 3–5] *vs.* 4 (IQR, 3–5) days in the OLR group, with an unadjusted difference of –19.2% [96% confidence interval (CI): –28.8% to –8.4%; P<0.001]. The trial was deemed negative since the alternative hypothesis was not achieved. Alongside, hospital stay was significantly shorter in the laparoscopic group [4 (IQR, 3–5) *vs.* 5 (IQR, 4–7) days; P<0.001]. Among the secondary endpoints, operative time was longer in the laparoscopic group, with a median of 240 (IQR, 186.3–300) *vs.* 200 (IQR, 155–270) minutes in the open group (unadjusted difference 20.5%, 99% CI: 8.1–34.3%; P<0.001). Ninety-day mortality was 2.5% in the laparoscopic group and 0.8% in the open group (P=0.336). There were no significant differences between the two approaches in overall morbidity, severe morbidity (Clavien-Dindo classification), liver-specific complications, or 90-day readmission rates.

Most of the enrolled patients underwent liver resection for a malignant disease (225/246), mainly colorectal liver metastases and hepatocellular carcinoma. The R0 resection rates were comparable between the two groups, with 87.7% for the LLR group and 85.8% for the OLR group (P=0.539). Similarly, time to initiate adjuvant chemotherapy, recurrence rates, and survival outcomes, both overall and recurrence-free, showed no significant differences between the groups. In subgroup analysis for the primary endpoint, the benefit of laparoscopy was more significant among women, patients who did not receive preoperative chemotherapy and ASA 2 patients. Among other secondary endpoints, quality of life assessments showed non-significant better EQ5D scores up to 6 months post-surgery and superior QLQ-C30 scores at discharge in the LLR group. Similar improved body image and cosmetic scores were noted up to 12 months after LR without reaching statistical significance. Health resource costs were comparable (€11,249 for LLR; €11,848 for OLR; mean difference €598; P=0.408).

The "ORANGE segments" randomized trial aimed to address the question of whether laparoscopy is superior to OLR for the resection of PS segments. The study was "negative" for its primary endpoint showing only a 1-day reduction in TFFR.

This randomized controlled trial (RCT) underscores the importance of choosing a clinically relevant primary outcome: TFFR meets perfectly this benchmark. Indeed, it addresses one of the main benefits of minimally invasive surgery compared to OLR. It is also more consistent than the length of hospital stay, which is more frequently used in clinical studies, but may vary significantly with institutional policies and center-specific protocols.

"ORANGE Segments" is a methodologically robust trial, with an appropriate sample size calculation and two comparable groups with no significant differences especially regarding resection type and surgical indications.

The analysis of the primary endpoint was adjusted for relevant features (center, lesion size, age, sex, and benign/malignant disease). Multiple outcomes testing for secondary endpoints were also accounted for to avoid type I error rate inflation. Sijberden *et al.* (4) have also selected a broad panel of secondary endpoints, covering 90-day mortality, postoperative complications, incisional hernias, quality of life, and in patients treated for malignant tumors, oncological resection quality and survival outcomes.

However, few key comments warrant further discussion:

(I) First, the authors have thoroughly defined and standardized each component of TTFR: Solid food intake and cessation of IV fluids are objective criteria. Likewise, the assessment of autonomous mobilization was based on the ERAS Mobility Score, which includes 10 simple, objective, and easily measurable items. Nevertheless, the biological feature ("normal or normalizing liver function tests, bilirubin and coagulation") can be considered debatable. While "normal liver function tests" is a concrete observation, "normalizing" may vary based on individual perspective. For example, normalizing total bilirubin (TB) was defined as follow:

Time to improvement of total bilirubin (days) = Date (TB POD_x – TB POD_{x-1}) <0

Which means that a decrease in bilirubin level over two successive daily measurements (alongside transaminases and prothrombin time) indicates a positive outcome. Nevertheless, the duration of this time window may be insufficient, and there is a possibility of subsequent deterioration in liver function tests. Consequently, patients may be misclassified as having functional recovered despite abnormal or deteriorating liver function tests. Such misclassification may overestimate the rate of full Functional Recovery and wrongly shorten TFFR. A sustained decrease in bilirubin level (during at least 48 h) may provide more accurate definition and avoid potential misclassification bias.

(II) Second, the primary endpoint was a 2-day reduction of TFFR after LLR. The clinical meaningfulness of this endpoint may be debatable. Several previous retrospective studies comparing mini-invasive and open LR have reported 2- to 5-day reduction in hospital stay with LLR (7-10). The authors did not provide a clear explanation of the rationale behind this 2 days-threshold and its clinical implication.

(III) Third, 17 "expert" hepatobiliary centers across Europe enrolled patients in "Orange Segments". However, the investigators did not clearly define the "expertise" conditions. Indeed, the literature describing the essential requirements for an "expert" HPB center is scarce and absolute requirements are not uniformly accepted, but several criteria are currently used to define an expert center (11): availability of a structured unit dedicated to HPB diseases, specialized multidisciplinary team with an ongoing research program. Operative volume, technical difficulty of the performed procedures and failure-to-rescue rates are also closely linked to the quality of care and should be considered as valuable criteria for the selection of expert centers (11). All participating centers are well-recognized HPB surgery departments but disparities in surgical caseloads or laparoscopic expertise may contribute to a center effect that could potentially bias the outcomes.

Furthermore, in all participating centers, patients were managed according to the enhanced recovery after surgery (ERAS) implemented protocols. TTFR reduction likely resulted not only from mini-invasive surgery but also from adherence to all other ERAS guidelines, with minimally invasive surgery being one of the 20 ERAS recommendations (12). Compliance rates to enhanced recovery programs (above 70%) were associated with significantly fewer postoperative complications, mainly non-specific morbidity, and a higher likelihood of achieving the textbook outcome after liver resection (13,14). More importantly, it appears that high adherence rates collectively influence postoperative outcomes more significantly than each individual component alone (13,14). Unfortunately, the present study did not provide comprehensive data on ERAS adherence rates across centers and/or between laparoscopy and open groups. A substantial disparity in compliance with ERAS guidelines could represent a significant source of bias. Without ERAS compliance data (stratified by group and center), it is statistically debatable to attribute the observed benefits solely to the surgical approach.

Also, all included patients had a BMI between 18 and 35 kg/m^2, with a median BMI of 26.3 (IQR, 23.5–28.7) kg/m^2 in the laparoscopy group and

26.7 (IQR, 24.2–29.1) kg/m^2 in the open group. Only 18 (14.7%) and 22 (17.7%) patients had a BMI between 30 and 35 kg/m^2. This low inclusion rate of obese patients may have contributed to a reduced conversion rate (13%) but could restrict the applicability of these results to this population. Considering the increasing obesity rates among surgical patients, the results of this trial may not be generalizable to such complex patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

(IV) Last, it is important to highlight the higher 90-day mortality rate in the LLR group (4.2%; 5 patients) compared to the OR group (0.8%; 1 patient), even though it was not statistically significant. This should be viewed in light of the trial's context: technically challenging but minor resections performed in expert HPB centers. The increased mortality must be weighed against the 1-day reduction in TTFR with laparoscopy.

In conclusion, the "ORANGE Segments" randomized trial failed to demonstrate the superiority of laparoscopy over open surgery in reducing TTFR by two days following liver resections of the PS. However, it clearly highlighted the value of ERAS protocols in reducing recovery time after complex liver resections by mitigating the physiological stress response to surgery. Future RCTs should consider further refinements, such as standardized metrics for defining HPB mini-invasive expert centers and a clear analysis of ERAS adherence metrics. This will better identify the clinical and statistical value of surgical approaches on postoperative outcomes following LR.

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Footnote

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