Top Papers in Interventional Oncology: Year in Review

Summarizing significant recent publications and their potential impacts on the field.

By Christopher D. Malone, MD, and Tyler Sandow, MD

EMERALD-1: A Phase 3, Randomized, Placebo-Controlled Study of Transarterial Chemoembolization Combined With Durvalumab With or Without Bevacizumab in Participants With Unresectable Hepatocellular Carcinoma Eligible for Embolization

Lencioni R, Kudo M, Erinjeri J, et al. J Clin Oncol. 2024;42(3 suppl). doi: 10.1200/JCO.2024.42.3_suppl.LBA432

SUMMARY

EMERALD-1 is a double-blind, global, multicenter, prospective, phase 3 study evaluating the efficacy of (1) a PD-L1 inhibitor (durvalumab) and a vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) plus transarterial chemoembolization (TACE) or (2) durvalumab alone plus TACE versus (3) TACE alone. The trial included patients with TACE-eligible unresectable hepatocellular carcinoma (uHCC), and the primary endpoint was progression-free survival (PFS). Patients had preserved liver function (Child-Pugh A-B7), and the majority were Barcelona Clinic Liver Cancer (BCLC) B/intermediate (57.3%) followed by stage A/early (25.8%) and stage C/advanced (16.1%).

Patients received between one to four sessions of TACE followed by randomization to durvalumab plus bevacizumab (D+B+TACE, n = 204), durvalumab (D+TACE, n = 207), or placebo (TACE, n = 205) every 3 weeks. This study met its primary endpoint, with significantly improved PFS in the D+B+TACE group compared to the TACE group (median PFS, 15 vs 8.2 months; hazard ratio [HR], 0.77; 95% CI, 0.61-0.98; *P* = .032). The D+B+TACE group also saw a longer median time to progression of 22 months versus 11.5 and 10 months for the D+TACE and TACE groups, respectively. Although treatment-related grade 3 or 4 adverse events were higher in the D+B+TACE group compared to the D+TACE and TACE groups (32.5% vs 15.1% and 13.5%), these were manageable and no new safety signals were identified.

WHY THIS STUDY MATTERS

This is the first global phase 3 trial demonstrating a significant improvement in PFS when adding an immunotherapy plus anti-VEGF systemic therapy regimen to TACE in patients with uHCC. This is impactful because it demonstrates that this systemic regimen can improve outcomes of TACE, the dominant and standard locoregional therapy across the world. Improvement with durvalumab and bevacizumab but not durvalumab alone may speak to the role of increased VEGF after ischemic embolization therapies such as TACE. These patients are still being followed to ascertain differences in overall survival (OS) between groups, and the data can be expected in the near future. It is likely that these results will have a large impact on standard of care in BCLC stage B (intermediate) patients in centers where TACE is the first locoregional therapy of choice.

In addition, these positive results give justification and anticipation for the ongoing EMERALD-3 trial, which will assess the impact on PFS of STRIDE (single tremelimumab, regular-interval durvalumab) immunotherapy with lenvatinib plus TACE versus STRIDE alone plus TACE versus TACE alone. Finally, the recently initiated EMERALD-Y90 trial (durvalumab plus bevacizumab with yttrium-90 [Y90] radioembolization) will evaluate whether these positive results can be extrapolated and applied to patients undergoing Y90 radioembolization and will have particular relevance in centers where this is the first-line transarterial locoregional therapy for uHCC.

Chemotherapy and Liver Transplantation Versus Chemotherapy Alone in Patients With Definitively Unresectable Colorectal Liver Metastases: A Prospective Multicentric Randomized Trial (TRANSMET)

Adam R, Piedvache C, Chiche L, et al. J Clin Oncol. 2024;42(16 suppl). doi: 10.1200/JCO.2024.42.16_suppl.3500

SUMMARY

TRANSMET is a prospective randomized study across multiple centers in Belgium, France, and Italy that is assessing the impact of liver transplant (LT) plus chemotherapy versus chemotherapy alone in unresectable, non-*BRAF*–mutated, colorectal liver metastases (uCLM) on 5-year OS. To qualify, patients must have demonstrated an objective response for a duration of at least 3 months after no more than three lines of chemotherapy. Patients were then randomized to chemotherapy plus LT (n = 47) or chemotherapy alone (n = 47). Across both groups, patients had a median number of 20 lesions, with a median maximum diameter of 51.5 mm. Objective response was achieved after a median number of 20 cycles of first-line (44%), second-line (40%), or third-line (16%) chemotherapy. Patients in the chemotherapy plus LT arm underwent transplantation at a median of 51 days after randomization. In the intention-to-treat analysis, the 5-year OS was significantly higher in the chemotherapy plus LT group versus chemotherapy alone (57% vs 13%; HR, 0.37; 95% CI, 0.20-0.58; $P = .0003$). This difference was even greater in the per-protocol analysis (73% vs 9%; HR, 0.16; 95% CI, 0.20-0.58). In the chemotherapy-only arm, 19% of patients underwent partial hepatectomy or LT, while 19% of patients in the chemotherapy plus LT arm did not undergo transplantation due to tumor progression. Most patients in the chemotherapy plus LT group did develop recurrence, but most were amenable to additional surgery or local ablation. Ultimately, 40% in this group remained disease free.

WHY THIS STUDY MATTERS

Very few patients with uCLM are ever eligible for curative-intent treatment options. The 5-year OS rate seen in the chemotherapy plus LT arm is seldom seen in patients with unresectable disease. Traditionally, LT is thought of in the context of HCC, but this study highlights the growing role and potential for curative outcomes of LT in other malignancies, including metastatic disease. The study will need to be validated, but these promising results will inevitably bring LT into the conversation for these patients, especially at high-volume transplant centers.

Interventional oncologists already play an integral role in the care of transplant patients, so there could be opportunities for increased involvement in this patient cohort—not only in the peritransplant setting but also regarding opportunities for locoregional bridging therapies before and after LT, especially in those with oligoprogressive disease. Further details on optimal patient selection for this treatment pathway are eagerly awaited.

Surgery Versus Thermal Ablation for Small-Size Colorectal Liver Metastases (COLLISION): An International, Multicenter, Phase III Randomized Controlled Trial

Meijerink MR, van der Lei S, Dijkstra M. J Clin Oncol. 2024;42(17 suppl). doi: 10.1200/JCO.2024.42.17_suppl.LBA3501

SUMMARY

COLLISION is a randomized, prospective, multicenter phase 3 study conducted across the Netherlands, Belgium, and Italy assessing whether thermal ablation is noninferior to surgical resection in patients with small (≤ 3 cm) resectable CLM. Patients with up to 10 lesions and no extrahepatic disease were stratified into subgroups of low, intermediate, and high disease burden and then randomized to undergo resection or thermal ablation. The primary outcome was OS. Of 299 patients, 147 were randomized to thermal ablation, 148 were randomized to surgical resection, and four were excluded after randomization for not having the disease assessed. After a median follow-up of 28.8 months, there was no difference in OS between groups. The study was

stopped at interim analysis after having achieved predefined stopping rules. The total number of adverse events and length of hospital stay were lower in the thermal ablation versus the surgical resection group. There were no differences in rates of local or distant PFS between groups.

WHY THIS STUDY MATTERS

This study strongly supports the role that thermal ablation plays as a curative-intent therapeutic option in patients with CLM. With a favorable safety profile, thermal ablation may be a preferred option over surgical resection for curative-intent treatment in many patients with this malignancy. Additional analysis of patient subgroups is eagerly awaited to further optimize patient selection between treatments. Interventional oncologists should welcome these results as validation of the curative-intent capabilities of thermal ablation in the liver.

Voxel-Based Tumor Dose Correlates to Complete Pathologic Necrosis After Transarterial Radioembolization for Hepatocellular Carcinoma

Pianka KT, Barahman M, Minocha J, et al. Eur J Nucl Med Mol Imaging. Published online June 24, 2024. doi: 10.1007/s00259-024-06813-8

SUMMARY

This single-center retrospective study explored the use of voxel-based dosimetry to predict pathologic response in HCC patients treated with transarterial radioembolization (TARE) with glass microspheres. In the study, 41 patients were bridged/downstaged to LT with TARE. Of those 41 patients, 26 demonstrated complete pathologic necrosis (CPN) at explant without the need for any additional treatment. The authors used dosimetry software to explore tumor-absorbed dose and dose-volume histograms. Voxel-based dose metrics such as D50, D70, and D95 were significantly associated with complete pathologic necrosis. Most importantly, D95 (the minimum dose to 95% of the tumor volume) > 719 Gy had the highest accuracy for predicting CPN.

WHY THIS STUDY MATTERS

Our understanding of radiation segmentectomy has evolved since it was first described in 2011. In 2014, a multicenter study found that target perfused territory dose > 190 Gy resulted in CPN for 67% compared to 25% for doses < 190 Gy.[1] In 2021, LEGACY established a new bar for threshold dose to the perfused territory at 400 Gy, with CPN noted in 100% of patients who underwent resection or transplant.[2,3] Montazeri et al further expounded on threshold dose by showcasing the importance of high sphere activity (≥ 570 Bq/sphere or 8 days postcalibration) and a dose ≥ 446 Gy.[4]

This study takes the understanding of radiation segmentectomy dosimetry even further by looking at actual tumor-absorbed dose and the variation in dose distribution within a tumor. Pianka et al indicate that radiation microsphere distribution within a tumor is very heterogeneous (as noted by the differences in D50, D70, and D95), validating the conclusions by Pasciak et al in 2016.[5] However, despite heterogeneous microsphere distribution in HCC, achieving a critical dose in the coldest areas of the tumor drives favorable CPN rates. This adds another piece to the puzzle in optimizing radiation segmentectomy results for HCC and provides a stepping stone for future studies optimizing D95.

Resection Postradioembolization in Patients With Single Large Hepatocellular Carcinoma

Tzedakis S, Sebai A, Jeddou H, et al. Ann Surg. 2023;278:756-762. doi: 10.1097/SLA.0000000000006061

SUMMARY

In this single-center retrospective study, the efficacy of Y90 TARE in converting large, initially unresectable HCC into resectable tumors is evaluated. Patents underwent up-front surgery or TARE, and TARE patients either were converted to resection (TARE-surgery) or were not (TARE-only).

Of the 216 consecutive patients evaluated over a 5-year period, 144 (67%) underwent up-front surgery. Compared to up-front surgery, the TARE cohort

was notable for having higher rates of vascular invasion (54% vs 4%) and higher alpha-fetoprotein. In the 72 patients who underwent TARE, an objective response was noted in 60 patients (83%), and 20 (28%) were later converted to resection. Nonresection was due to ineffectiveness of TARE in downsizing the tumor in 12 patients and due to insufficient future liver remnant or Eastern Cooperative Oncology Group score > 1 in the remaining 40 cases. TARE-surgery patients received a higher mean Y90 dose compared to the TARE-only patients (211 Gy vs 128 Gy; $P < .001$). Notably, surgical outcomes were similar between the up-front surgery and TARE-surgery cohorts. Additionally, OS was similar at 1, 3, and 5 years in the two surgery groups, and both also compared favorably against the TARE-only cohort. Although TARE-surgery patients had more aggressive features that prevented up-front resection, propensity score matching demonstrated significantly better OS for the TARE-surgery patients compared to the up-front surgery patients.

WHY THIS STUDY MATTERS

Although TARE is routinely discussed in the setting of standalone therapy or bridge to transplant, TARE's role in downsizing to resection often gets overlooked. This study highlights the role of TARE in very large, unresectable tumors with aggressive features in achieving definitive therapy comparable to standalone resection, if not better. Several "Easter eggs" are also buried in this study, if one knows where to look. First, there was a notable difference in perfused liver dose for TARE-surgery patients compared to TARE-only patients (211 Gy vs 128 Gy). This is related to enrollment in DOSISPHERE-01. Although personalized dosimetry was used to target > 205 Gy to the tumor and < 120 Gy to the normal perfused liver, patients randomized to the standard dosimetry arm of DOSISPHERE-01 only received a target dose of 120 Gy to the perfused liver. Second, a very high objective response rate to TARE was noted in this study, especially for very large tumors. Complete response was not reported for this study, but larger tumors with or without vascular invasion are prone to higher rates of residual and recurrence.

An important note about this study and DOSISPHERE-01 is that all patients only underwent radioembolization treatment of the targeted lesion(s) *one time*. Therefore, it makes sense to see a difference in OS between the TARE-surgery and up-front surgery patients compared to the TARE-only patients, as they likely never achieved definitive tumor response. Similar findings are also noted in the updated long-term analysis of DOSISPHERE-01.[6]

The key message of this study is clear: (1) Radioembolization allowed previously unresectable cases to achieve surgical resection; (2) higher doses to the perfused liver were associated with downsizing to resection; (3) definitive treatment resulted in better OS for patients with larger tumors; and (4) TARE-surgery patients had better OS compared to up-front surgery patients after appropriate propensity score matching. ■

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