2021 in Review: Key Papers in Interventional Oncology

An overview of the most significant interventional oncology articles published in the recent literature and summaries on their impact on the field.

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Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study

Jennings JJ, Prologo JD, Garnon J, et al. Radiol Imaging Cancer. 2021;3:e200101. doi: 10.1148/rycan.2021200101

SUMMARY/TAKEAWAY POINTS

This article reports results of a multicenter, single-arm, prospective study of cryoablation for patients with painful bone metastases. The study included 66 patients across 11 sites in the United States and France. Eligible patients were those with metastatic bone lesions and unresolved pain despite standard-of-care treatments including radiation therapy and analgesics. A minimum "worst pain" score of 4 out of 10 on the Brief Pain Inventory (BPI) scale was required. Patients with primary bone malignancies and those with lesions adjacent to critical structures, such as the spinal cord, nerves, or blood vessels, were excluded. Treatments were performed to single sites of disease, and pain assessments specific to that site of disease were obtained, with a maximum follow-up of 6 months. Technical success was defined as the ability to treat the lesion with palliative intent. If patients received additional local therapy to the target lesion after the cryoablation procedure, they were taken off the protocol; concomitant analgesics and systemic anticancer therapies were allowed on the protocol. The most common malignancy in the study cohort was lung cancer (29%), followed by breast cancer (14%). The most common sites of bony metastasis treated were pelvic lesions (32%) and rib lesions (24%). Mean tumor size was 5.7 cm (maximum size, 17 cm). Most tumors were predominantly lytic (73%), and only 9% were predominantly blastic. Cryoablation was found to be effective at reducing pain at all time points after week 8, and the effect was sustained through week 24. The mean improvement in BPI score was approximately 2.5 points, and most patients (92%) achieved some degree of pain palliation. The median time to maximal pain relief was 39 days, although most patients exhibited maximal palliation sooner than that (34% at week 1, 25% at week 4). The improvement in pain was matched by a decrease in pain medication requirements as well. Adverse events were identified in 22% of patients, although the serious adverse event rate was much lower (4.6%).

WHY THIS ARTICLE IS IMPORTANT

This study advances our knowledge of treatment options for patients with bone metastases in several ways. Although there were several pivotal prospective clinical trials in this space in the early 2000s (several of which were also conducted by authors of this study), almost all of these utilized radiofrequency ablations. Thus, while cryoablation of bone metastases has increased in popularity over the past decade, the availability of clinical data commensurate to that of radiofrequency ablation has been lacking. Technically, this study did not meet its predefined success criterion, which was an improvement in BPI by at least 2 points in both bounds of the confidence interval at 8 weeks. Nonetheless, two important conclusions can be drawn from the data in this trial. First, cryoablation is safe and effective for the palliation of painful bone metastases. Although previous large studies have suggested this in a retrospective manner, this study substantially adds to

the literature by its prospective and multi-institutional design. Second, cryoablation provides durable pain relief; sustained improvements in BPI scores were noted out to 24 weeks, albeit in only the 56% of patients who remained on the protocol to that point. Radiation is the mainstay for painful bone metastases, and so it is interesting to see that 42% of patients were radiation-naive to the target lesion, and thus cryoablation served as the first-line locoregional therapy. It is also important to note that given the median tumor size of almost 6 cm, these were not "cherry-picked" patients with small lesions; this study highlights cryoablation's role, particularly with palliative intent, for larger tumors. Part of this capability is predicated on the capacity of the conventional cryoablation systems for numerous probes, with one patient on this study treated with 10 cryoablation needles. The management of patients with painful bone metastases is a substantial challenge, and this study helps strengthen the role of cryoablation in the contemporary armamentarium of tools to help these patients.

Personalised Versus Standard Dosimetry Approach of Selective Internal Radiation Therapy in Patients With Locally Advanced Hepatocellular Carcinoma (DOSISPHERE-01): A Randomised, Multicentre, Open-Label Phase 2 Trial

Garin E, Tselikas L, Guiu B, et al. Lancet Gastroenterol Hepatol. 2021;6:17-29. doi: 10.1016/S2468-1253(20)30290-9

SUMMARY/TAKEAWAY POINTS

This study reports a randomized, four-center, open-label phase 2 study of personalized versus standard dosimetry radioembolization with glass microspheres for advanced hepatocellular carcinoma (HCC) in France. Eligibility criteria included unresectable locally advanced HCC, at least one measurable lesion ≥ 7 cm, and a hepatic reserve of at least 30% after radioembolization. Patients were randomly assigned (1:1) to receive either standard dosimetry (120 ± 20 Gy) targeted to the perfused lobe or personalized dosimetry (≥ 205 Gy targeted to the index lesion). The primary endpoint was objective response rate (ORR) in the index lesion at 3 months. Secondary endpoints were dose-response evaluation, safety, and time-to-event measures of progression-free survival (PFS) and overall survival (OS). Sixty patients were enrolled, and 28 patients were treated in each group. The median prescribed activity was 3.6 GBq (interquartile range [IQR], 2.4-4.8 GBq) in the personalized dosimetry group compared with 2.6 GBq (IQR, 2.2-3.0 GBq) in the standard dosimetry group (P = .0049). In the modified intention-to-treat population, 20 (71%; 95% CI, 51%-87%) of 28 patients in the personalized dosimetry group and ten (36%; 95% CI, 19-56) of 28 patients in the standard dosimetry group had an objective response (P = .0074). Adverse events were similar between the two groups. Compared with standard dosimetry, personalized dosimetry significantly improved the ORR in patients with locally advanced HCC. Median OS was 26.6 months (95% CI, 11.7—not reached) in the personalized dosimetry group compared with 10.7 months (95% CI, 6.0-16.8 months) in the standard dosimetry group (P = .0096). The results of this study suggest that personalized dosimetry is likely to improve outcomes in clinical practice and should be used in future trials of selective internal radiation therapy (SIRT).

WHY THIS ARTICLE IS IMPORTANT

Radioembolization dosimetry has evolved significantly over time, and this paper lends much-needed data and credence to the belief that more accurately calculating and optimizing tumor-absorbed dose improves outcomes. This is the first randomized study to compare partition dosimetry and standard dosimetry (medical internal radiation dosimetry for glass microspheres) in patients with HCC. In patients with locally advanced HCC, the ORR was significantly higher in the personalized dosimetry group with no increase in the toxicity profile. A meaningful improvement in OS was also observed in the partition dosimetry group. All randomized phase 3 studies of SIRT for advanced HCC published to date have reported negative results, and one of the arguments for these findings has been the design of these trials that relied on outdated dosimetry. Although there are inherent limitations to partition dosimetry and some of the tumor-absorbed dose thresholds used, this study provides a strong rationale for clinical care and future radioembolization studies to utilize multicompartment dosimetry to improve patient outcomes.

Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study

Salem R, Johnson GE, Kim E, et al. Hepatology. Published online March 19, 2021. doi: 10.1002/hep.31819

SUMMARY/TAKEAWAY POINTS

This paper reports results of a three-center, single-arm, retrospective study assessing yttrium-90 (Y-90) glass microspheres for the treatment of unresectable HCC. Eligibility criteria included solitary HCC ≤ 8 cm, no vascular invasion or extrahepatic metastases, Child-Pugh A cirrhosis, Eastern Cooperative Oncology Group performance status < 1, and treatment with lobar or selective hepatic radioembolization. Primary endpoints were ORR and duration of response (DoR) based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) in the treated area. Secondary endpoints included time to progression (TTP), PFS, and OS.

A total of 162 patients were included, and the median tumor size was 2.7 cm (range, 1-8 cm). Of note, the perfused volume was measured retrospectively using either the treatment cone-beam CT or post–Y-90 single-proton emission CT. The absorbed dose to the perfused volume was then calculated based on the infused Y-90 activity and the perfused volume. The median absorbed dose to the treated liver volume was 410.1 Gy. Median follow-up was 29.9 months, and ORR was 88.3% (95% CI, 82.4%-92.4%), with 62.2% (95% CI, 54.1%-69.8%) exhibiting a DoR ≥ 6 months. PFS by localized mRECIST was 93.9% at 2 years. At 3 years, OS was 86.6% for all patients and 92.8% for neoadjuvant patients with resected or transplanted liver. The authors concluded that clinically meaningful response rates and prolonged DoR were observed in the treatment of unresectable, solitary HCC ≤ 8 cm with radioembolization.

WHY THIS ARTICLE IS IMPORTANT

The FDA agreed with key positive parameters of the LEGACY protocol (ORR and DoR), and this served as the basis for premarket approval for TheraSphere Y-90 glass microspheres (Boston Scientific Corporation) with the indi-

cation for local tumor control of unresectable, solitary HCC < 8 cm. This has caused a major shift in the current clinical practice of radioembolization, as the use of TheraSphere microspheres previously required local institutional review board oversight given initial FDA approval with humanitarian device exemption in 1999. This has made TheraSphere microspheres easier to use and more accessible, improving access for patients and treating physicians. However, there are limitations in extrapolating these data to radioembolization use in all patients with HCC. Most patients in this study received selective infusions (95.7%, 155/162), 1.9% (3/162) received lobar segmental infusions, and 2.5% (4/162) received mixed treatments. Moreover, the study lacked a control arm, and most patients were Barcelona Clinic Liver Cancer (BCLC) stage A (60.5%, 98 of 162) with a median tumor size of 2.7 cm. BCLC stage A patients typically receive thermal ablation or surgical resection rather than radioembolization as the standard of care. Regardless, the data continue to establish radiation segmentectomy as a viable curative-intent treatment option for HCC.

Percutaneous Liquid Ablation Agent for Tumor Treatment and Drug Delivery

Albadawi H, Zhang Z, Altun I, et al. Sci Transl Med. 2021;13:eabe3889. doi: 10.1126/scitranslmed.abe3889

SUMMARY/TAKEAWAY POINTS

This preclinical study reports on a new liquid ablation technology termed LATTE (locally active agent for tumor treatment and eradication) and its efficacy in animal models of liver tumors as well as explanted human tumor tissue. The authors frame the clinical need for such technology by reviewing the predicate liquid ablation therapies, most notably percutaneous ethanol (EtOH) injection. They also highlight the renaissance of intratumoral delivery of anticancer therapies, particularly immunotherapies, and the recognition that local retention of intratumorally injected drugs when delivered in conventional aqueous solution is a major challenge. To address this need, the authors hypothesized that ionic solutions would result in not only improved local tumor control but also efficient drug delivery and retention. Tumor cell death by ionic liquids is driven by shifts in osmotic gradients; furthermore, hydrophobic anions can improve the diffusion of the liquid across microenvironmental barriers that may hinder other therapies. After evaluating various formulations of LATTE in normal rat livers, the authors percutaneously injected LATTE versus EtOH and saline in an orthotopic rat model of HCC. At 2 weeks posttreatment, there was near-complete control of tumor growth in the LATTE-treated tumors, with significantly improved outcomes compared to saline or EtOH. Histologic analysis of these tumors found increased tumor cell apoptosis and macrophage and T-cell infiltration with LATTE. The authors then tested whether LATTE could improve on local delivery of anticancer therapies. LATTE mixed with doxorubicin was injected percutaneously into rabbit liver tumors. Uniform retention of doxorubicin was seen in the explanted tumors, compared to barely detectable doxorubicin when injected in saline alone. Finally, to demonstrate clinical feasibility, the authors injected LATTE mixed with the fluorescent imaging agent indocyanine green into freshly resected tumor tissues. Imaging at 24 hours postinjection revealed increased apoptosis within these tumors.

WHY THIS ARTICLE IS IMPORTANT

Percutaneous delivery of liquid ablation agents and anticancer therapies has a long history in interventional radiology but until recently had fallen out of favor due to the availability of thermal (and nonthermal) ablation modalities and the impracticality of treating every site of disease in patients with widespread malignancy. This paradigm has shifted in the past decade due to the rebirth of cancer immunotherapies and the recognition that local interventions can have systemic anticancer ramifications. However, although the procedural aspects of percutaneous drug delivery are typically straightforward, ensuring the injected therapy localizes within the desired tissue is anything but. It is highly likely that the challenge of drug retention, rather than drug efficacy, is a major driver of treatment failure. Thus, novel technologies such as LATTE have a tremendous potential to revolutionize not only the field of locoregional therapies but also cancer immunotherapy. Although the authors primarily focused on HCC, it is readily apparent how this technology can be extended to liver metastases or indeed essentially any malignant lesion amenable to percutaneous access. In addition, while the authors focused on LATTE's delivery of cytotoxic drugs, it is intriguing to speculate how LATTE would improve the delivery and efficacy of immunotherapy drugs. ■

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