Editorial

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Role of Yttrium-90 Radioembolization for Colorectal Hepatic Metastasis

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Take-home points

- A recent international multicenter randomized phase III trial (the EPOCH trial) showed that though the addition of transarterial radioembolization (TARE) to the conventional second-line chemotherapy for colorectal hepatic metastasis significantly prolonged the progression-free survival (PFS) and hepatic PFS (hPFS), it did not change the overall survival (OS) of patients unresponsive to the first-line chemotherapy.
- Although the EPOCH trial successfully demonstrated that an improved PFS and hPFS can be achieved with the addition of TARE, it does not equate that the caring physicians would recommend TARE for the patients.
- Multiple factors most likely make most caring physicians reluctant about recommending TARE for patients with progressive disease.

TARE using Yttrium-90 is commonly performed in patients with hepatocellular carcinoma (HCC), and its advantage over chemoembolization includes minimal post-embolization syndrome and longer PFS [1,2]. Recently, the results of an international multicenter randomized phase III trial on TARE in patients with colorectal liver metastasis (the EPOCH trial) were published [3]. Patients with metastatic colorectal carcinoma to the liver who had progressed on first-line chemotherapy were randomly assigned to the control and TARE groups [3]. Patients in the control group received second-line chemotherapy, and those in the TARE group received TARE followed by second-line chemotherapy. The two primary endpoints of the trial were PFS and hPFS, and the secondary endpoints included OS, objective response rate (ORR), and disease control rate.

There were some positive results as both PFS and hPFS were longer in the TARE group than in the control group. The median PFS of the TARE and the control group was 8.0 and 7.2 months, respectively ($p = 0.0013$). The median hPFS of the TARE and the control group was 9.1 and 7.2 months, respectively ($p < 0.001$). Although significant, the median PFS and hPFS of the TARE group were only longer by 1–2 months. In contrast, the difference in the median OS in the TARE (14.0 months) and the control group (14.4 months) based on the intention-to-treat analysis was not statistically significant ($p = 0.7229$). ORRs were 34.0% and 21.1% for the TARE and the control groups, respectively. A high ORR in the TARE group was expected because TARE is a liver-directed local therapy. The high ORR resulting in longer PFS and hPFS in this study is thus not surprising.

Based on these results, one question arises: why did longer PFS and hPFS not lead to a longer OS? There might be several reasons for this, including that colorectal liver metastasis is a systemic disease, that life expectancy depends on extrahepatic metastasis, and that TARE may worsen liver function and general condition.

There was a higher rate of grade 3 adverse events in the TARE group compared with the control group (68.4% vs.

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Korean Journal of Radiology
KJR

49.3%). Grade 3 fatigue was more common in the TARE group (8.6%) than in the control group (2.9%), and this significantly worsened the patient's quality of life. Four patients had TARE-specific complications (radiation pneumonitis, cholecystitis, and duodenal ulcer), and three died at 3–5 months after treatment related to TARE (radiation-induced liver disease, hepatic failure, and portal hypertension). Most oncologists would likely pay close attention to the high rate of grade 3 adverse events and TARE-specific complications and mortality.

Although the EPOCH trial successfully demonstrated that an improved PFS and hPFS can be achieved with the addition of TARE, it does not equate that the caring physicians would recommend TARE for patients with progressive disease after first-line chemotherapy anticipating a slightly longer PFS with the same OS, particularly with the risk of adverse events such as fatigue, radiation pneumonitis, cholecystitis, hepatic failure. If not critical, the cost of care is another factor that should be considered. Even though Korea (Republic of) is known for its low cost of medical care compared to some other countries, such as the United States, due to its National Health Insurance, the patients still have to pay approximately $7500 for TARE. In addition, the patients have to make at least two additional visits to the hospital for planning angiography/lung shunt scans and TARE procedures. All these factors would make most caring physicians reluctant to recommend TARE for patients with progressive disease.

The investigators of the EPOCH trial suggest that implementation of lobar (rather than bilobar) TARE, enhanced patient selection, and personalized dosimetry would improve the safety profile and outcomes. Though this sounds reasonable, the following issues need to be addressed beforehand. First, TARE has excellent tumor response in patients with HCC, because most HCCs are markedly hypervascular, and thus, radioactive microspheres are preferentially delivered into these carcinomas by lobar TARE. In contrast, colorectal liver metastases are typically hypovascular or minimally hypervascular. As the liver is a hypervascular organ, lobar TARE might not result in an objective response (partial response or complete response) for hypovascular or minimally hypervascular lesions. Selective TARE (segmental or subsegmental infusion of radioactive microspheres) may be a solution for hypovascular or minimally hypervascular lesions. However, selective TARE can be performed only for single or oligonodular lesions, making the indication of TARE markedly narrow. Second, single or oligonodular liver metastases can be treated with surgical resection. Thus, the indications for TARE may overlap with indications for surgical. Third, selective TARE requires multiple injections of radioactive microspheres into several segmental/subsegmental hepatic arteries. This requires the operator to order multiple vials of glass microspheres, which may be difficult to garner the manufacturer's support. Fourth, an effective radiation dose to the tumor and a safe radiation dose to the normal liver have not yet been established in patients with colorectal liver metastasis. Additionally, because of the relatively low vascularity of colorectal liver metastasis, the effective tumor dose and a safe liver dose are difficult to achieve simultaneously. Even though personalized dosimetry has been proven to have longer OS than the single-compartment dosimetry in the HCC population [4], there may be a long way to go until optimal dosimetry for colorectal liver metastasis is established.

In the author's institution, patients with colorectal liver metastasis are referred for TARE sporadically when all the following conditions are met: resistance to chemotherapy, single or oligonodular lesions, and unresectability due to anatomical or clinical reasons. These patients then undergo a simulation test comprising planning angiography and lung shunt scan/single photon emission computed tomography (SPECT). Radioactive microspheres are finally ordered after confirming that the tumors have higher arterial vascularity on angiography as well as a higher activity than the normal liver on SPECT, and that selective TARE is technically feasible.

In conclusion, TARE is a potent brand-new intra-arterial treatment modality for colorectal liver metastasis. However, given the current evidence, the patient indication is narrow.

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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