

## Transarterial Embolization of Intermediate Hepatocellular Carcinoma in Elderly Patients: Which Technique Should Be First-line?

In the last few decades, the treatment of hepatocellular carcinoma (HCC) has significantly improved with established efficacy of many interventional radiologic therapies. As per current international guidelines, the choice of optimal therapy is based on clinical, biological, and radiological factors such as performance status, tumor characteristics, liver functions, and comorbidities. However, age is not quoted in any treatment strategies.<sup>[1]</sup> The management of HCC in elderly patients is significantly more complicated than that of younger patients due to the comorbidities and fear of potential toxicity that may be related to any given therapy, which may result in poor adherence to guidelines recommendations. Thus, elderly patients did not receive optimal therapy.<sup>[2]</sup> This article discusses several questions that surround treatment of elderly patients with HCC:

- What does palliative treatment really mean to the physician and the patient?
- How does the overall patient's condition impact treatment decisions to ensure that the selected therapy has a safe and speedy recovery?
- How does the technical complexity, clinical effectiveness, and cost-effectiveness impact treatment decisions in elderly patients with the availability of all treatments options?
- How does quality-of-life (QoL) impact treatment decisions in elderly patients with limited survival time?
- How should these priorities be weighed when choosing the treatment?

Hepatobiliary cancers have been associated with a poor prognosis and diminished health-related QoL, with pain, jaundice, anorexia, and depression as common symptoms.<sup>[3]</sup>

Majority of patients with HCC are treated with palliative intent due to the late-stage presentation, comorbidities, and limited donor availability. Many locoregional therapies are available as palliative therapies to treat those patients with differences regarding patient and disease characterizations, indications, side effects, and cost but may have similar survival rate. That is clear when comparing two transarterial embolotherapies; transarterial chemoembolization (TACE) to radioembolization with Y-90 (RE). Both TACE and RE have been shown to improve overall survival in HCC patients with equivalent survival rate.<sup>[4-9]</sup> Although no randomized prospective trials comparing TACE to RE, it has been reported that RE may have better profile in terms of adverse events, clinical toxicities, response rate, and time-to-progression compared with TACE.<sup>[10,11]</sup> Moreover, RE performed better than TACE in downstaging to transplantation, time-to-progression<sup>[12]</sup> and in safe use

for advanced patient population such as vascular invasion without the risk of ischemic hepatitis.<sup>[13]</sup>

Postembolization syndrome is the most common adverse effect of TACE. It manifests by pain, nausea, vomiting, and fever and it usually managed during the hospitalization (1–3 days). Other complications may include biliary duct injury, liver abscesses in patients after biliary interventions, duodenal, or gastric ulcers from the inadvertent deposition of the chemotherapeutic agents, vascular injuries such as spasm/dissection from repeated chemotherapy injection in the arterial system, tumor rupture, and hepatic failure.<sup>[14-16]</sup> Adverse effects of RE are distinctly different from those related to TACE. Fatigue and nausea are the dominant adverse effects. Others adverse include duodenal or gastric ulcer from nontarget deposition of microspheres, fibrosis/scarring of the liver parenchyma, cholecystitis, and radioembolization-induced liver disease.<sup>[17,18]</sup>

In general, TACE is associated with higher rates of clinical toxicities including abdominal pain, nausea, and hospitalization compare to RE.<sup>[10,19]</sup>

In elderly patients (>70 years), RE appeared to be well tolerated and effective with no more toxicity compared to younger patients with unresectable HCC.<sup>[20,21]</sup> Elderly patients should be considered for RE if they otherwise meet the inclusion criteria applicable to younger patients and age alone should not be a discriminating factor for the management of HCC patients.

### Quality of Life

Although in oncology outcomes are generally measured in terms of toxicities and survival, it has been reported that up to 95% of patients with advanced cancer state that their QoL was at least as important as the length of life.<sup>[22]</sup> For HCC with reduced life expectancy and unavailable curative treatment, the goal of treatment is to relieve the symptoms and maintain the patients' functional status. Therefore, health-related QoL has emerged as both clinically significant and biologically meaningful in HCC patients outcome analysis. It is as relevant as the disease progression and response to treatment.<sup>[23]</sup> A recent prospective study has compared health-related QoL in HCC patients receiving TACE or 90Y RE using Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep), a validated tool for hepatobiliary malignancies.<sup>[24,25]</sup>

It used an embolotherapy-specific score (ESS) that reflects the summation of embolization specific toxicities most commonly experienced by patients after TACE or RE. The

score was created from the FACT-Hep items, capturing QoL parameters most relevant to embolization procedures including the following items: pain, bothered by treatment side effects, able to work, diarrhea, and good appetite. The study concluded that patients who received RE had significant increase in several features of QoL, whereas patients who received TACE had decrease in QoL scores. The increase was greatest in the ESS representing that RE is better in maintaining health-related QoL when compared with TACE.

## Cost

The cost of interventional radiology (IR) procedures in the treatment of HCC is a factor that may impact treatment decision. A cost analysis from the payer perspective was performed to determine whether there is a cost advantage for one of the commonly performed IR procedures in the treatment of HCC using decision-tree analysis and taking into consideration repeat procedure rate.<sup>[14]</sup> The study uses Monte Carlo Simulation for randomizing the distribution of the value for each variable in the models. The variables included allowable reimbursements of each procedure type, the probability of the need for repeat procedures, and the underlying mortality rate (which was determined by the age and sex of any potential subject). The direct cost comparison between TACE and TARE showed that although TACE is less costly on a per procedure basis, it is typically repeated far more frequently than TARE which makes it potentially more costly and the Monte Carlo simulation showed a preference for RE in more than one-third of all scenarios. Sensitivity analyses showed that the most important variables assessed were the need for repeat procedures.

## Palliative Therapy

The World Health Organization defined palliative care as “an approach that improves the QoL of patients and their families facing the problem associated with life-threatening illness, through the prevention, and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.”<sup>[26]</sup> The goal of palliative treatment then is to prevent and relieve suffering and to improve the QoL for people facing serious, complex illness. To be successful, palliative care requires attention to all aspects of a patient’s suffering.

The choice of IR procedure in treating patients with HCC should be evidence based to ensure optimal outcome. However, the therapeutic decisions have to be personalized and based on the individual circumstances taking into consideration the patient’s overall condition and the QoL before proceeding with any intervention. Although there are needs for randomized prospective trials comparing TACE and RE that incorporate QoL and econometrics in addition to other oncologic variables such as time-to-progression

and combination with systemic therapy, the aforementioned seminal studies in this manuscript should be taken into consideration and QoL should be considered as important as overall survival and the goal of all palliative measures should include QoL as endpoints in HCC patients with reduced life expectancy. As patients grow increasingly knowledgeable about available treatment options, their concerns about QoL emerge as leading factors in decision-making. The Belmont Principles of medical ethics require both respect for patient’s autonomy and beneficence, that is, acting in the best interest of the patient.<sup>[27]</sup> It is reasonable and ethical to provide the patients with detailed information on the available therapies weighing benefits versus risks. Since TACE and TARE are medically equivalent in benefit and risk in intermediate-advanced HCC, it is appropriate to let the patients decide which form of embolotherapy to have at the first-line rather than to take decision on their behalf.

In summary, when considering an intervention for patients with intermediate HCC, a decision should not be based on the sole cost of the procedure but should take into account more comprehensive view about risk-benefit assessment, input on QoL, and patient preference. The role of multidisciplinary teams and institutional experience cannot be overemphasized.

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