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New Tools for HCC Management

The best indication for particle therapy in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC), one of the most common malignant tumors with high mortality, poses a great challenge to both patients and physicians. The majority of the patients suffers from co-existing chronic liver disease and compromised liver function, which stands as a hurdle in applying effective therapies not only systemic but also local therapies. Radiotherapy is also severely limited in its indication depending on functional status of liver as described in current therapeutic guideline for HCC established by Korean National Cancer Center-Korean Liver Cancer Association.

In cancer radiotherapy, photon-based therapy has long been used and still most popular. Adopting modern technologies involving intensity modulation as well as image-guided radiotherapy, delivery of high dose radiation precisely on the target tumor is achievable in daily practice. However, conformal coverage of the tumor with high dose cloud inevitably results in huge area of low dose radiation on surrounding tissues, mostly liver and gastrointestinal tracts. Actually, clinical significance of low dose radiation has long been ignored as long as it remains under the threshold level that can cause obvious toxicity. However, a certain volume of low dose radiation may cause further deterioration of liver function in HCC patients suffering from associated chronic liver disease, which supports limiting the indication of radiotherapy to those with good liver function as shown in current guideline. Another important issue is that even low dose radiation can induce severe lymphopenia. Considering popular use of immuno-oncologic therapy in current practice, significant level of lymphopenia needs to be avoided.

Charged particle therapy (CPT) involving proton beam therapy (PBT) and carbon ion radiotherapy (CIRT) has emerged as a promising modality in cancer radiotherapy. It shows unique physical characteristics, Bragg peak, which is deposition of very high dose at the certain depth with little to no post-peak exit dose. It is an ideal tool that can spare normal tissues surrounding the tumor, hence overcome therapeutic indication beyond the current limit with regard to liver function. Under the same reason, CPT is also ideal to avoid lymphopenia by reducing low dose radiation volume to adjacent lymphoid organs. While PBT and CIRT shares the same physical characteristics, biological potency between the two modalities is significantly different in terms of relative biological effectiveness (RBE); RBE of PBT seems similar to photon therapy at around 1.1 however, RBE of CIRT is known around 3.0, which means CIRT provides 3-fold or higher therapeutic potency in cancer cell killing. Radioresistant tumors may be benefited by higher RBE involving tumors suffering from hypoxia or tumor showing refractoriness to multiple therapies.

To summarize, CPT may have rather a broad indication similarly to photon radiotherapy regardless PBT or CIRT. Its unique physical characteristics may significantly reduce normal tissue toxicity so that widen the therapeutic indication further than current criteria as well as avoiding lymphopenia. In particular, CIRT may have additional benefit for resistant or refractory HCCs based on its higher potency. Retrospective and prospective studies have demonstrated encouragingly high rates of local control and overall survival and low rates of hepatotoxicity with PBT and CIRT. The efficacy of PBT has been documented through a randomized trial over other standard liver-directed therapy and future randomized trials are needed to assess the value of CIRT over PBT.

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