JHEP|Reports

Editorial musings

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This is the second issue of *JHEP Reports*, EASL's new online journal. There are 3 reviews on the topic of hepatocellular carcinoma (HCC) and 4 original articles. Although this will not always be the case a few comments on these articles are in order given their contents.

Drs. Bang and Dawson[1] have summarized the current state of radiotherapy for HCC. Radiotherapy is not standard of care in most countries, although radioembolization is popular in many places. Nonetheless, radioembolization has yet to be proven to be an effective form of therapy in head to-head studies. Yet HCC is a radiosensitive tumour,[2] with impressive tumour shrinkage achievable. This raises the question of why radiotherapy is not yet standard of care. Tumor shrinkage should translate into effective therapy. Radiation-induced injury to the liver and adjacent organs has always been a limiting factor, but the major barrier is the lack of randomized controlled trials *vs.* standard forms of therapy with survival as an outcome. Some studies have used endpoints that although encouraging, are not definitive, such as progression-free survival. The message from this review, although not explicitly stated, is that randomized studies are necessary. If radiotherapy is as effective as preliminary studies suggest, randomized trials of this therapy are urgent, particularly given the recent failure of the 2 most promising immunological agents, pembrolizumab and nivolumab.[3,4]

The second HCC paper deals with a comparison between the guidelines presented by the 3 continental liver disease societies, EASL, APASL and AASLD.[5] What is obvious is that in broad strokes all 3 society guidelines are similar. All advocate for HCC surveillance in those at risk. All clearly separate potentially curative *vs.* palliative therapies. Indications for transarterial chemoembolization and systemic therapy are common to all guidelines. None recommend adjuvant therapy. The AASLD guidelines[6] were targeted at some specific questions, rather than being a fully comprehensive guideline like the 2 previous AASLD guidelines.[7,8] Despite the similarities there were differences, for example in HCC surveillance methodology, specifically the use of alpha-fetoprotein (AFP). To some extent, the Asian and US guidelines reflect common practice in those regions, whereas the European guidelines adhere more closely to evidence. The evidence that adding biomarkers to ultrasound for surveillance is beneficial is not convincing. It is clear that adding biomarkers improves sensitivity, most often with the accompanying loss of specificity. However, what has never been demonstrated is that the added sensitivity translates to better survival. It is not clear that a lesion that is AFP positive but ultrasound negative necessarily means that the potential for cure is greater than if the lesion had been documented on a subsequent ultrasound in the absence of AFP testing. AFP positivity is generally associated with an aggressive phenotype of tumour and early detection may therefore not change the outcome.

Guidelines are supposed to be evidence based. Yet the 3 continental liver disease societies, although broadly similar do have some significant differences. An observer of the opinions of thought leaders and authors in the different regions might have predicted these differences. AFP is widely used in Asia for HCC surveillance, despite that lack of evidence of efficacy in decreasing mortality (the gold standard for surveillance). North American recommendations initially included AFP as optional,[7] then excluded it altogether.[8] However, the most recent guidelines once again recommended AFP.[6] Not coincidentally this latest change followed a change in authorship of the guidelines, because in the 2005 and 2011 guidelines the surveillance section was written by myself, and everyone knows I believe that the evidence for using AFP was not adequate. I did not accept an invitation to join the writing team for the most recent AASLD guidelines, which included influential members who were proponents for the use of AFP. Another example where strong opinions held by influential members of the writing teams led to recommendations that are not supported by evidence involves the use of radiotherapy. In Asia where there are prominent advocates for radioembolization and external beam radiotherapy both procedures are recommended.[9]

There are other examples where the opinion of prominent thought leaders has led to recommendations that may not have been supported by evidence. The question is whether in this situation it is better to include expert opinion or not to make a recommendation. It is not the intention of this editorial to dissect this issue, but simply to point out that guideline recommendations are, like so much else in clinical medicine and clinical research, subject to bias (my comments not excluded).

The third review concerning HCC looks at how infection with hepatitis D might affect hepatitis B carcinogenesis. The review describes important pathways in carcinogenesis that may be altered by either hepatitis B or hepatitis D proteins, but the genetic and epigenetic changes that are found in HCC arising in liver infected with hepatitis D are completely unknown. It is unknown whether the apparent increase in HCC risk in HBV and HDV coinfected individuals can be attributed to genetic changes or changes in signaling pathways that are different to those in HBV monoinfection, or whether the increased incidence is related to more aggressive liver disease accompanied by

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increased necrosis and regeneration, leading to a greater chance of oncogenic mutations.

The 4 original articles are all on different topics. Piecha *et al.*[10] show that patients who receive a TIPS early, while paracentesis is relatively infrequent, survive better than those in whom the TIPS is inserted when paracentesis becomes more frequent. The sceptics view is that although the baseline characteristics of the early TIPS group are similar to those of the late TIPS group it is likely that the 2 groups are not really similar. The mere fact that one group requires more frequent paracentesis suggest that group has more advanced disease and that this alone may be responsible for the observed improvement in outcomes. Of course, control of ascites may also reduce the risk of hepatorenal syndrome and bacterial peritonitis, also leading to better outcomes.

Zuure *et al.*[11] describe how in a city such as Amsterdam, with a diverse immigrant population, the prevalence of hepatitis B varies by country, and even between different population groups within countries. The heading of the article suggests that this should result in different screening strategies for the different populations, but the article does not elaborate on this. Perhaps the most striking examples of how different populations within a country have different hepatitis B rates come from Africa, particularly Southern Africa, where the hepatitis B rates in the Black African population are much higher than in the white population.[12,13] This data is very old, but no doubt still holds true today given the epidemiology of the disease in that part of the world.

Chapman *et al.*[14] describe a retrospective study in which patients with advanced liver disease were treated with terlipressin for the usual clinical indications. Terlipressin was started in hospital, and patients continued to take terlipressin intravenously at home or in hospital until transplant or other indication to stop (2 recovered with antiviral therapy and 3 continued awaiting transplant). They noted that several different markers of liver health improved. These included nutritional intake, grip strength, decreased frequency of paracentesis and, of course, renal function. This is a small retrospective study, but the findings are noteworthy. It might be difficult to confirm these findings in a prospective comparative study because one cannot withhold terlipressin from the control group. Perhaps this could be confirmed initially in a less severely ill group of patients on paracentesis. If confirmed this would represent a major therapeutic improvement.

Finally, Elshaarawy *et al.*[15] evaluated the significance of spleen stiffness as a measure of portal hypertension and therefore liver disease severity compared to liver stiffness. They also compared these parameters between alcohol-related liver disease and hepatitis C-induced cirrhosis. There is a hypothesis that because the brunt of the fibrosis is different between alcohol-related liver disease (zone 3 fibrosis) and viral hepatitis (zone 1) there may be a differential effect on portal hypertension. They show, using spleen stiffness and spleen length, that portal hypertension is generally more severe in patients with hepatitis C than alcohol-related liver disease. Patients with hepatitis C are more likely to die of consequences of portal hypertension, whereas patients with alcohol-related liver disease are more likely to die of liver failure. This is interesting data, which should find a place in the evaluation of patients with end-stage liver disease, but at present the role that these measurements might play is not clear.

These musings on the articles in this issue must come with a caveat that you might have noticed from some of my comments, namely that I am a sceptic and require a lot of convincing that published information is first, valid, and second, useful. That is the role of an associate editor of a medical journal, so If you want your article published – convince me!

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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