66329-Answering Reviewers

Reviewer #1: Linda Calistri et al reported the image findings of chemotherapy related liver injury. They reviewed the pathogenesis and image presentations of CT/MRI clearly. This is an informative report and some valuable CT/MRI pictures are presented.
We thank the reviewer.

There are only 2 suggestions:
1a. Some chemotherapy-associated liver injury (CALI) could happen rapidly and be detected within days or weeks, but some cases of CALI develop slowly (months or years later). Some drug related liver damages are through immune reaction (hypersensitive) and could happen rapidly. Could authors give some image examples of acute onset of CALI?
According to our oncological follow-up protocols, CT/MRI scans are not executed before 3 months after beginning of therapy. For this reason, our study does not include acute forms of CALI. However, we can affirm that possible acute forms of CALI do not present different radiological features in term of pattern/distribution.
1b. And give a time table of CALI, such as diseases types in 0-1 months, 1-3 months, 3-6 months and 6-12 months following certain chemotherapy.
These two questions proposed by the reviewer are certainly very interesting, and deal with the problem of time evolution. As you can see, we have done a conspicuous bibliographic research and mostly article reporting the association between drug and related effects were found, but very few evidences about temporal evolution and possible involution. The most common acute forms of DILI/CALI involve idiosyncratic hepatotoxicity (isoniazid, nitrofurantoin, and diclofenac) and these topics are covered at pages 6-9. Moreover, many antineoplastic agents can cause acute hepatic necrosis due to direct hepatoxicity, as well as SOS (myeloablative agents, alkylating agents and monoclonal antibody-cytotoxic conjugates such as gemtuzumab and ozogamicin) or NRH (azathioprine, mercaptopurine and thioguanine). Lastly, we can remind an indirect immune-mediated liver injury due to various immunomodulatory agents, tumor necrosis factor antagonists, and, most important, antineoplastic checkpoint inhibitors.
We can state that the arterial reaction after a portal blockage is very precocious and an arterial phase CT can demonstrate it after a few hours. Persisting the portal blockage, the parenchymal involution (regression) can be seen in a variable time from some weeks to few months. After about 1-2 years imaging can demonstrate the parenchymal hypotrophy and then related atrophy (see "Transient hepatic attenuation differences (THAD) not connected to focal lesions", Colagrande S et al, Radiol Med 2002; "Meaning and etiopathogenesis of sectorial transient hepatic attenuation differences (THAD)", Colagrande et al, Radiol Med 2003). However, the timing of the arterial reaction is quite reproducible, while that of parenchymal regression (steatosis-like), hypotrophy and atrophy is related to many variables and so we cannot find a confident and reproducible time table as kindly requested by the reviewer. As a consequence, in the images we have

proposed, the reader can find the interval of occurrence of the phenomena, but this interval, as far as we know, is not confidently reproducible.

2. Most cases in this report were followed for the responses of liver metastases following the chemotherapies. The image finding of non-tumor part may be detected incidentally. Are these image findings of yellow liver or blue liver, such as peliosis, correlated with the chemotherapy efficiency (survival time) or just a reversible finding, such as steatosis?
The steatosis-like damage (parenchymal regression, e.g. parenchymal depletion) can be reversible if the noxa ceases and portal flow is restored. Also in this context, timing of possible reversibility is not confidently reproducible.
The evolution of peliosis is variable and unpredictable. Peliosis occasionally worsens in terms of extension, but at times, especially in young patients, regression is also possible once the etiologic agent causing secondary peliosis is identified and treated. Also regression of primary-idiopathic forms is reported [ref. 140]. Reviewer asks to us, why peliosis sometimes worsens and some other times vanishes. It is hard to answer!
The noxa (usually oxaliplatin) induces depolymerization of F-actin in sinusoidal endothelial cells with activation of matrix metallopeptidase, then of cytokines with sinusoidal endothelial damage and swelling. So, in the early phase, vascular alterations are predominant, including sinusoidal dilatation and congestion, perisinusoidal hemorrhage and peliosis. Till this stage in our opinion (just a logic hypothesis) the damage can regress. Otherwise, if red blood cells enter the space of Disse through the peliotic lacunae and collagen fibers are deposited so forming perisinusoidal fibrosis, the environment changes and in addition to clogging of necrotic sinusoidal endothelial cells a fibrotic sinusoidal narrowing is demonstrable. This stage is, in our opinion, not reversible.

3. Could author add the duration of time following chemotherapy in Figure 13-15?
We revised the figure legends.
Figure 13: as indicated, this is a chemotherapy naïve patient, i.e., she did not start any chemotherapy, as she died a few days after diagnosis.
Figure 14: the features of pseudocirrhosis appeared 12 months after starting therapy
Figure 15: chemotherapy was started 1 year after surgery; liver pseudocirrhotic changes appeared 6 months after starting chemotherapy.

Reviewer #2: in my opinion, this paper has better revealed the different imaging manifestations caused by chemotherapy-induced liver injury, and has a certain guiding effect on clinical targeted treatment.
We thank the reviewer

Editorial office's comments:

1. Format: The title page is not consistent with the formatting rules of the journal.

The formatting of the title page has been revised.

2. There are 15 figures, including many and very interesting radiological images that gives a significant value to this paper. The authors should clarify if these are coming from their own clinical experiences (patients) and all required permissions to publish them have been obtained at the local institutions.
We confirm that all the figures are original, coming from our personal experience. We provided a correct anonymization and we removed any detail that could allow to recognize patients. In addition, our local institution released a certification of the required permission.

3. Self-cited references: There are 12 self-citations (by Colagrande et al.). The authors should revise this consistent number of self-citations, if not all of them are strictly necessary. For instance, ref. 23-26 are self-citations related to a short paragraph. I would suggest linking in the text the specific contribution of each self-citation to specific concepts/information.
We revised the self-cited reference, and removed 4 of then. We clarify that all of then were relevant but not strictly necessary, and therefore removable.

4. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.
The forms are correctly compiled and attached.