March 29, 2023
World Journal of Gastroenterology
Manuscript ID: 84134
Title: Real-time continuous image guidance for ERCP based on 3D/2D registration and respiratory compensation

Dear Dr. Ma:

We would like to thank you and the reviewers for reviewing our work and providing us with very helpful comments. In the revised manuscript and this letter, we have made our best effort to address all the points that the reviewers raised. The major changes in the new version of the manuscript are in red, so the reviewers and the editor can follow the modifications easier. Detailed revisions are as follows.

(84134-Answering Reviewers)

Reviewer #1:

The following revisions are made according to the comments of Reveiwer #1.

1) The language needs major polishing: the text cannot be accepted in the present form.

Thanks for the reviewer's comment. To make the revised manuscript meet the publication requirement (Grade A), we have improved the paper organization. And the content of this paper is refined and polished by the recommended professional English language editing company. Modifications have been done accordingly. The proof of the article's touch-up has also been uploaded.

2) I would focus the aim of this approach/technology to the potential help when performing ERCP for perihilar cholangiocarcinoma and the consequent need to cannulate specific biliary ducts, rather than the time exposure to X-ray. The authors don't even mention literature about X-ray exposure times or the actual exposure times of their patients.

Thanks for the reviewer's comment. Previous literature has demonstrated that preoperative 3D image assisted ERCP for right and left bile duct superselection in hilar cholangiocarcinoma（HCCA）also reduces contrast and operative time and improves

the success rate of the procedure. (PMID: 32118109; PMID: 25675173). Therefore, the focus of this study is to explore the feasibility and superiority of real-time continuous image-guided ERCP using a new algorithm based on previous work and to lay the foundation for further clinical applications. We have added more details about the usefulness of this technology when performing ERCP to cannulate specific biliary ducts for HCCA. Modification has been done in line 30-33, 70-76, 187-192, 196-205.

Here is an additional explanation：

The prognosis of hilar cholangiocarcinoma (HCCA) is extremely poor, and surgery is the only radical treatment modality. However, most patients are already in an unresectable condition or with cholangitis, high bilirubin and insufficient volume of the residual liver during diagnosis, and biliary drainage by ERCP is the best choice for HCCA. Data from a large sample in our center showed the effectiveness of ERCP-administered biliary stenting in patients with type III-IV HCCA was 52.6%. (reference: PMID: 34168496). Data from a large sample of other centers showed that ERCP with bile duct stenting was a procedure of average 45 minutes with an efficiency of 70% in patients with all types of HCCA. (reference: DOI:10.27433/d.cnki.gxyku.2022.000348). Previous literature has demonstrated that preoperative 3D image assisted ERCP for right and left bile duct superselection in HCCA also reduces contrast and operative time and improves the success rate of the procedure. (reference: PMID: 32118109; PMID: 25675173). In the procedure of biliary stent placement via ERCP in indeterminate biliary stricture (non-PSC), its X-ray exposure time is reduced to 8.1-35.1 min (reference: PMID: 32118109). However, preoperative 3D images cannot be projected onto intraoperative ERCP cholangiography images, which causes great inconvenience to the operator, and in addition, it is not possible to achieve real-time fusion of preoperative static 3D images and intraoperative dynamic images. Therefore, we believe that it would be a great innovation and breakthrough if we can combine the preoperative and intraoperative images of ERCP patients in real time based on the previous work and other surgical

image navigation. But one of the most critical steps is to solve the problem of real-time integration of preoperative static 3D images and intraoperative dynamic images, that is, to solve the problem of respiratory and body alignment. Therefore, we first applied our adapted set of algorithms to fuse preoperative 3D images with intraoperative images on the abdominal biliary body membrane to verify the auxiliary role of preoperative 3D images in ERCP, then collected preoperative 3D images and intraoperative dynamic cholangiography images of patients with HCCA for internal validation of algorithms and procedures, and finally found that the high fusion rate of preoperative intraoperative images makes it a good ERCP surgical aid. Future larger studies are required to definitively determine whether this new approach can increase the clinical yield and technical success, while at the same time reducing radiation exposure and contrast medium usage during ERCP.

3) The role and purpose of the biliary 3D-printed models, created for only 2 of the 20 patients, needs a major clarification, because it is not clear from the text.

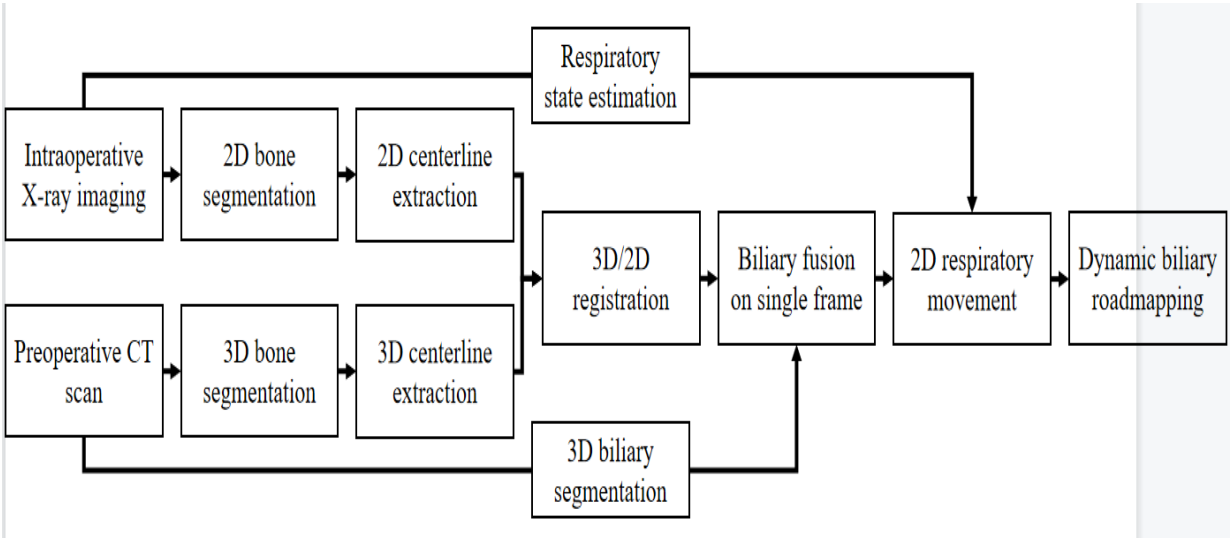
Thanks for the reviewer's comment. To make the role and purpose of the biliary 3D-printed models more clear, we have added description about 3D-printed biliary models. Modification has been done in line 38-39, 98-100, 107-109, 133-137.

Here is an additional explanation：

We first applied our adapted set of algorithms to fuse preoperative 3D images with intraoperative images on the abdominal biliary body membrane to verify the auxiliary role of preoperative 3D images in ERCP, then collected preoperative 3D images and intraoperative dynamic cholangiography images of patients with HCCA for internal validation of algorithms and procedures

In this paper, in order to verify the accuracy of our 3D/2D registration algorithm, We only selected two abdominal images of 20 patients with HCCA for biliary tract 3D printing models with different structures. Different from clinical experiments, model experiments can be repeated many times to simulate real intraoperative conditions to

adjust the algorithm parameters. The biliary ducts can be clearly observed in X-ray images without contrast agents during model experiments (Fig. 4). After the 3D/2D registration is completed, the biliary ducts segmented from CT can be projected onto X-ray image and we can judge the validity of the registration according to the edge blending effect. In addition, using the X-ray image sequence of moving phantoms can help us accelerate the debugging of the registration algorithm to meet the real-time requirements of X-ray image guidance during intervention. Therefore, after the model experiments are successfully complete, we further conduct the experiments in the remaining 18 patients.



The principle and flow of the whole experiment

Reviewer #2:

The following revisions are made according to the comments of Reveiwer #2.

1) Should discuss other implications for other minimally invasive procedures PMID: 36844926 and implications for the covid era PMID: 35762309. If the above are addressed and references included, paper could be of interest.

Thanks for the reviewer's comment. To demonstrate the more implications of this technology for other minimally invasive procedures, we have added more discussion

about the implications for the covid era and added the references (PMID: 36844926 and PMID: 35762309) in line 233-272.

Here is an additional explanation：

The coronavirus disease-2019 (COVID-19) had devastating impacts on healthcare system operations. The pandemic disrupted normal spine surgery proceedings, restricting and postponing elective procedures [21]. This disruption may result in the prolonged impairment of patients who are forced to postpone their procedures. Minimally invasive surgery and perioperative telemedicine are inevitable trends in spine surgery after COVID-19. Spine surgery is usually completed under the guidance of X-ray images, and physicians need to conceive the 3D structure of the patient's spine based on clinical experience. The spine is different from the soft liver and there is no respiratory interference; however, the similarity of the structure between the joints and the overall length makes surgery more difficult to perform by physicians only under the guidance of X-ray images. Meanwhile, the increase in the operation time has also caused more patients to wait longer for treatment. Under this condition, our method can extract the 3D spine structure from preoperative CT and complete 3D/2D registration through the bone structure line, achieving the fusion of 3D information with intraoperative X-ray images. This technology can help physicians better localize lesions and enhance visual perception of depth. 3D/2D fusion can also help physicians — especially those with insufficient clinical experience — to observe the patient's spine structure more intuitively and improve surgical efficiency. In summary, the number of spinal surgery increased following COVID-19 and it has continued to rise. Our technology may help the hospital to perform more operations and allow patients to receive timely and effective treatment.

COVID-19 is associated with an increased risk for ischemic and hemorrhagic strokes [22], which are often treated with vascular intervention — a procedure very similar to TACE — which is achieved by embolizing the vessels connected to the aneurysm. Unlike liver vessels, intracranial vessels are not affected by respiratory

motion and they can remain static when guided by the use of X-ray images. However, intracranial vessels are generally thin and have multiple branching structures, and thus the risk of intracranial surgery is high. Surgeons need to have more clinical experience to ensure the accuracy of the surgery, otherwise, they may injure other blood vessels or tissues and cause secondary damage to the patient. Our technology can extract related blood vessels connected to the lesion such as an aneurysm before the surgery and guide the surgeon during the surgery through high-precision registration and fusion. Given the risk of intracranial vascular interventions, we can display the vessels around the catheter and render them in different colors to remind the surgeon to be cautious not to injure the surrounding vessels, thus ensuring the safety of the procedure. We believe that our technology may have a potential clinical value in treating cerebrovascular diseases and could precisely treat ischemic and hemorrhagic strokes triggered by COVID-19.

The mentioned references are as follows:

[21] Lucke-Wold B, Cerillo J L, Becsey A N, et al. Minimally Invasive Procedures, Perioperative Telemedicine, and Decreased Hospital Stays Following Covid-19 Surgical Restrictions: Spinal Surgery[J]. Archives of medical case reports and case study, 2022, 6(5).

[22] Small C, Mehkri Y, Panther E, et al. Coronavirus Disease-2019 and Stroke: Pathophysiology and Management[J]. Canadian Journal of Neurological Sciences, 2022: 1-8.

We believe that we have addressed all the points raised by the reviewers. We sincerely hope that you would find the revised version satisfactory for publication in World Journal of Gastroenterology, and we look forward to your favorable reply.

Sincerely,

Daya Zhang & Shuo Yang