Dakua and Nayak *Egyptian Liver Journal* (2022) 12:30
https://doi.org/10.1186/s43066-022-00191-2

Egyptian Liver Journal

REVIEW

Open Access

# A review on treatments of hepatocellular carcinoma—role of radio wave ablation and possible improvements

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## Abstract

**Background:** Currently, several treatment options are available for liver cancer depending on various factors such as location, size, shape, and liver function. Image fusion is required for the diagnosis, intervention, and follow-up of certain HCCs. Presently, mental fusion is the only way while diagnosing liver lesions by comparing the ultrasound (US) image with the computed tomography (CT) image. Nevertheless, mental fusion is bound to have errors. The objective of this paper is to study the present treatment options for hepatocellular carcinoma and review the present treatment options, list out their potential limitations, and present a possible alternative solution based on the findings to reduce errors and mistargeting.

**Methods:** This is a systematic review on the present treatment options for hepatocellular carcinoma, especially radio wave ablation.

**Results:** It is found that computer fusion is the possible alternative to the present mental registration.

**Conclusions:** Although computer fusion is the best alternative to use radio wave ablation, there have been a few open-ended questions to further explore.

**Keywords:** Liver, US, CT, Hepatocellular carcinoma, Image fusion

## Introduction

Liver disease is a leading cause of mortality; statistically, hepatic cancer remains the eighth-most and fifth-most common malignancy in women and men, respectively [1, 2]. Among those malignant neoplasms of the liver, primary hepatocellular carcinoma (HCC) and colorectal metastasis are the most frequent and amount to 500,000 and 700,000 new cases per year, respectively. Primary liver cancer is the sixth-most common cancer in the world and the third leading cause of death due to cancer, after lung and colorectal; its incidence is the highest in Asia and Africa [3]. Hepatocellular carcinoma is the most common type of liver cancer, accounting for 75% globally [4].

### Hepatocellular carcinoma (HCC)

HCC is the most common primary liver cancer [5]. The major risk factors for HCC include hepatitis B, hepatitis C, chronic alcohol consumption, nonalcoholic fatty liver disease, obesity, diabetes mellitus, and aflatoxin. Other causes are increased iron overload, hereditary hemochromatosis, Wilson's disease, primary biliary cirrhosis, alpha1-antitrypsin deficiency, and autoimmune hepatitis [6]. It occurs more often in men than in women and is usually diagnosed in people 50 years or older, reaching a peak at 70 years [7]. HCC may be asymptomatic in the early

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stages, making it harder to diagnose [8]. As it grows, it may cause right upper quadrant pain of the abdomen, feeling of a lump, nausea, loss of appetite, unintentional weight loss, jaundice, swelling or bloating of the abdomen, and easy bruising. The overall prognosis for survival is poor, especially in symptomatic patients. Survival length depends on the degree of cirrhosis in the liver; cirrhotic patients have shorter survival times and lesser therapeutic options. Portal vein occlusion leads to even shorter survival [3]. A comparable number of patients die of liver failure as they do from tumour progression. The course of action for treating HCC depends on its size, number, location of tumours, presence or absence of cirrhosis and its extent, portal vein patency, and presence or absence of metastatic disease [3].

In addition to primary cancer, the liver is also the most commonly affected organ by metastasis. Among liver metastasis, colorectal cancer is the most frequent and accounts for 150,000 cases per year in the USA and around 700,000 cases worldwide.

## Diagnostics and treatments

The treatment of HCC requires a multidisciplinary approach, including hepatologists, transplant and hepatobiliary surgeons, medical oncologists, interventional radiologists, and palliative care specialists. While there are several treatment options available for HCC, there are only two possible curative options available—surgical resection and liver transplantation [9]. The two main factors used for determining resection are tumour size and liver function. The Milan criteria is used for checking liver transplantation eligibility [10, 11]. Only about 5% of HCC patients fit the criteria; most of these patients have longer survival lengths and lower rates of recurrence after the transplantation (Fig. 1) [12].

### Liver transplantation

Liver transplantation is possibly one of the best curative treatment options available for HCC. There has been an improvement in the prognosis of HCC patients after the introduction of the Milan criteria; 75% of patients had a 5-year overall survival rate and less than 15% had tumour

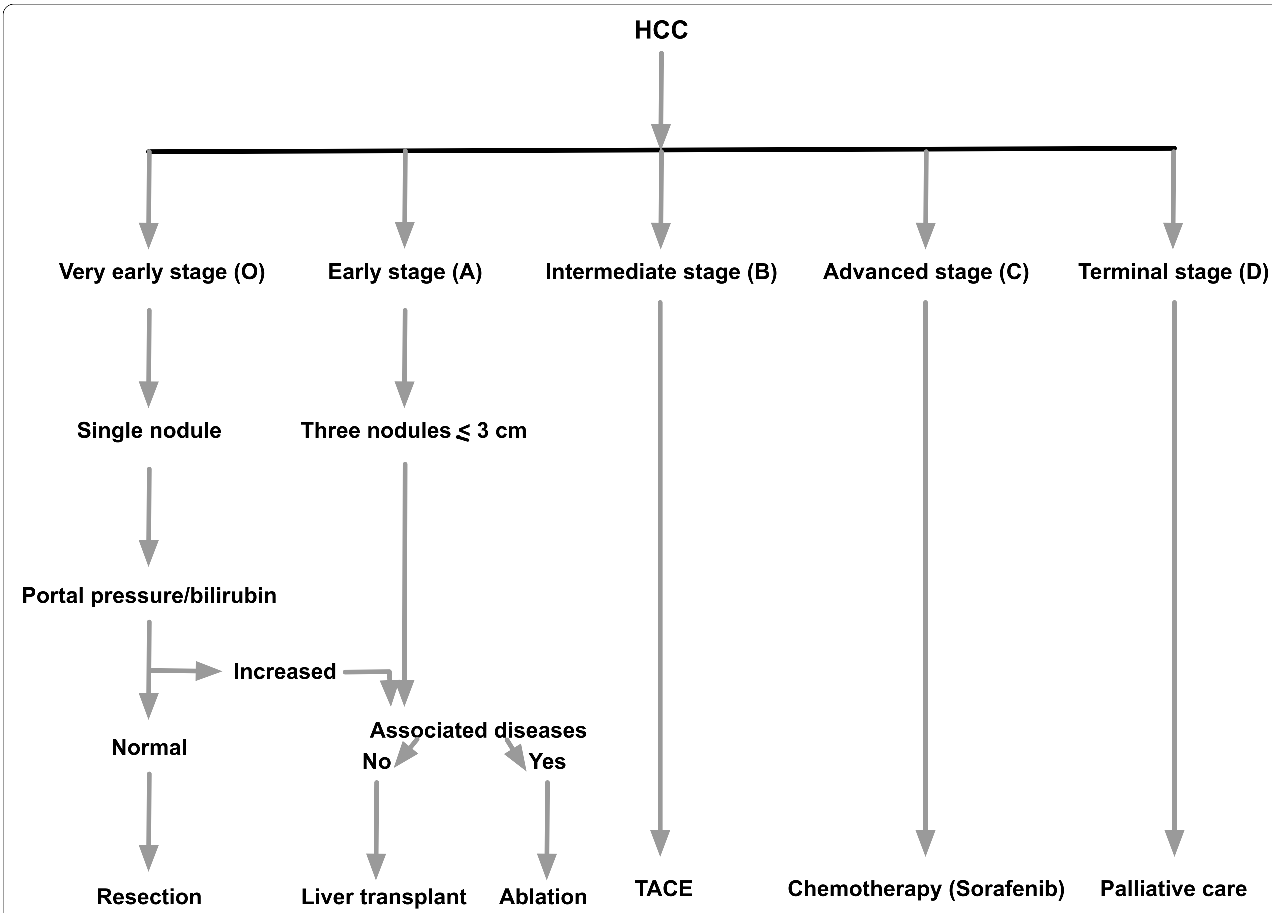


**Fig. 1** Treatment options for HCC

recurrence [13]. Milan criteria for liver transplant are (a) one lesion ≤ 5 cm, (b) 2–3 lesions ≤ 3 cm, (c) no extrahepatic metastasis, and (d) no vascular invasion.

Living donor liver transplant is done for (1) patients that do not fit the Milan criteria, enabling them to undergo the liver transplant, and for (2) patients that fit the Milan criteria to decrease their wait time. It is used as a life-saving procedure; however, it has a higher HCC recurrence rate than a deceased liver donor. For patients with very early-stage HCC or Child-Pugh A cirrhosis, i.e. preserved liver function, a liver transplant is not as beneficial as liver resection or ablation.

### Surgical resection

Surgical resection is generally performed on certain patients eligible for transplantation, leaving liver transplantation for HCC patients with severely impaired liver functions [14]. Surgical resection is preferred for patients with a single nodule, good liver function, and no underlying cirrhosis. This results in a narrow range of patients eligible for the procedure, only Child-Pugh class A patients. Although surgical resection has a good 5-year prognosis, it has a high recurrence rate due to microscopic vascular invasion [7]. Early recurrence occurs due to local invasion and intrahepatic metastasis, whereas late recurrence is mainly due to de novo tumour formation. The surgical approach is chosen subject to the availability and response to local ablative therapies like radiofrequency ablation [15, 16].

### Transcatheter arterial chemoembolization

Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure used in interventional radiology to block the blood supply to the lesion [17]. It is done by injecting the chemotherapy through the catheter directly into the artery supplying the tumour and then plugging the artery with an embolus to get a targeted effect. This spares the patient many side effects that they would get in the systemic chemotherapy. TACE is the chosen method of treatment for intermediate HCC; it is used in case of unresectable HCC without microvascular invasion and some preserved liver function. It is contraindicated in patients with poor liver function as the chemoembolization may worsen the hepatic function. Patients with allergy to the dye, coagulopathy, severe cytopenia, kidney impairment, or cardiac dysfunction are also not advised to undergo TACE [18].

### Systemic targeted therapy

Carcinogenesis occurs due to genetic modifications affecting various signalling cascades resulting in mutations that lead to uncontrolled cellular growth [19]. There is also overexpression of certain signalling pathways such as vascular endothelial growth factor (VEGF), epidermal growth factor, insulin-like growth factor, Ras/MAPK, etc. Systemic therapy aims to target these specific signalling pathways, limiting systemic therapy [20, 21]. Nevertheless, HCC is resistant to most chemotherapy and the application of chemotherapy is limited due to the underlying liver disease [14]. Sorafenib, a multi-kinase inhibitor, is now approved for use against advanced unresectable HCC, but its use in intermediate HCC treatment is not clear yet [22].

In 15–25% of patients, these hepatic metastases are uncovered with colon cancer, while hepatic tumours are developed metachronously in 20–25% of patients [23]. The 5-year survival rates for metastatic liver cancer are 5–8% if untreated and 35–58% if surgically treated. However, only 10–20% of patients are fortunate to get treated by surgical procedure, because of the associated cirrhosis orientation complexity preventing the surgery [24]. Thus, other potential alternative treatments are usually adopted such as radiation therapy, chemotherapy, and ablation for those patients by extrahepatic clinicians. Thermal ablation, being a less invasive procedure, is now well preferred as one of the curative treatments for early-stage HCC patients. It is needless to say that every present ablation procedure has merits and demerits, but recently, it is found that radiofrequency ablation can be recommended as the standard treatment for HCC, where surgery is not suitable [25]; furthermore, it has relatively less complications [26].

### Radiofrequency ablation (RFA)

Radiofrequency (RF) is an ablation method that uses heat resulting in the formation of zones of coagulative necrosis [27, 28]. An alternating current (AC) is applied to the cathode that is grounded on the skin. As a result, the ions around the electrode vibrate aligning with the AC leading to resistive tissue heating. This direct heating gets conducted to the adjacent tissues through thermal diffusion. Thus, both the indirect and direct heating results in the final ablation [29].

RFA has been in use since last three decades [30] and the clinicians (interventional radiologists) prefer it over others in locoregional treatment. In small lesions (size ≤3 cm), the RFA relatively needs lesser sessions than percutaneous ethanol injection (PEI) and has a higher rate of complete necrosis [31]. The antitumour effect is influenced by tumour location, blood flow, and tumour size. Moreover, it can also be used as a bridge before the liver transplant or as a palliative care method to prevent tumour progression and extend survival length.

## Liver radiofrequency ablation

Certain measures are required to determine if RFA is needed for early-stage HCC, such as tumour background, liver function, and patient's performance status. RFA is used as per the guidelines set by the Barcelona Clinic Liver Cancer (BCLC) staging system in treating patients with very early stage of HCC (stage 0 and stage A). It has already been established that RFA can be used for the patients with stage 0, Child-Pugh class A or B liver profile, and HCC lesions ≤ 3 cm [30]. It may be noted that heat-based RFA is considered as the primary treatment for the patients with liver dysfunction, who have stage 0 or stage A HCC [32]. The following are some of the indications of radiofrequency ablation: (a) usually <3 cm lesions, (b) <3 cm tumour diameter, (c) colorectal metastases isolated to the liver, (d) proximity to blood vessels—heat sink effect if vessels are too close, and (e) limited extrahepatic lesions, multiple lesions (diffuse and sparring)—if all can be cured. RFA can lead to small ablation zone size in a single treatment session. More patients with HCC can be benefited from RFA if its indication included increases in the sizes up to 5 cm [19].

### Clinical and technical challenges of RFA

It may be noted that there are several complications, where RFA cannot be used, for instance, haemorrhage is one of them [30]. Patients with coagulopathies are usually excluded due to the risk of haemothorax or portal vein thrombosis. The benchmark of the platelet count for abnormal coagulability is set as $<40–50 \times 10^9$/L and/or INR > 1.5 [33]. Gastrointestinal perforation is another major complication. Any history of biliary surgery increases the risk of higher liver abscess. There is also a chance of hepatic decompensation and liver failure. It may cause thermal organ damage to nearby organs. The rare biliary interventional procedures could also lead to the formation of bacteraemia and sepsis [34]. RFA has witnessed very little success while treating large tumours. Additionally, the RFA is not suitable for the tumours in highly perfused tissue regions because of the heat sink effect, where there is poor conductive heating and limited cooling within perfusion-mediated tissues. As a result, an undesirably high rate of local tumour progression is evolved in large tumours [32]. The following are the contraindications of RFA: (a) tumour location <1 cm from main bile duct (delayed stenosis due to fibrosis), (b) dilated intrahepatic bile duct, (c) anterior exophytic lesion—tumour seeding, and (d) bilioenteric anastomosis—could lead to fibrosis, hence, obstruction, unmanageable coagulopathies.

Despite the above, RFA has been popular; obtaining the complete tumour necrosis and a disease-free margin of ~ 1 cm is the primary objective of RFA [35, 36]. However, there are some technical challenges associated with RFA: (1) there is a significant increase in lesion reoccurrence [37], (2) there is a risk of increasing tumour seeding and thermal injury of perihepatic structures [38, 39], and (3) complex tumour location (e.g. diaphragm, colon, proximity to the biliary tree), portal hypertension, and obesity of the patient; these can alter the results substantially [17]. The main reason of these may be linked to (1) the inability of drawing an appropriate safety margin along the local tumour [38, 39] and (2) improper visualization of the tumour in completing the tumour necrosis.

### Role of computer vision

Computer vision and image processing are needed to improve the visualization of the lesions that are complex to identify with the human naked eye. Thus, computer vision helps in 3 key aspects: (1) speed—helps complete a task faster, (2) accuracy—helps obtain the outcomes with better accuracy, and (3) urgency—whenever there needs immediate attention. Various liver imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are processed to localize the lesion(s) in the input liver image. US is considered to be the first line of imaging due to its easy accessibility, real-time capabilities, and low cost. Most importantly, it does not have any radiation hazard. However, it has certain limitations: (1) it is equipment and operator dependent and (2) image resolution is low. Thus, other imaging methods such as CT and MRI are considered to confirm the lesion site. Appropriate delineation of tumour boundary is possible by a robust *image segmentation* method [40–43]. The image segmentation can also help set the appropriate safety margin.

Visualization is key in removing the liver lesions. Since the imaging methods such as CT/MRI cannot be performed during the actual intervention, the clinicians have to depend only on the liver US images and mentally register with the pre-operative CT images. However, *image fusion* (by fusing two different imaging modalities) could provide improved visualization of the liver lesions that individual imaging modalities are incapable of, enabling the radiologist\interventional radiologist to set a needle route to the lesion, pinpoint the exact lesion location, minimize mistargeting, and help in checking for recurrences [44, 45]. Sometimes, flexible physical 3D liver models are built from the corresponding liver images (CT\MRI) using robust computer vision algorithms for procedural rehearsal [46, 47].

## Image fusion

As discussed, US is usually the preferred method of imaging because of many factors such as (1) it does not have any radiation hazards, (2) it has real-time capability, (3) it is easily accessible, and (4) its cost is low. The clinicians usually perform mental registration between pre-operative CT with intra-operative ultrasound during US-guided interventional procedures. This is quite challenging because the liver cannot be scanned in the same planes like CT or MR images [48]. In addition, the liver gets deformed and displaced because of the patient's breathing and heartbeats. Furthermore, a lower resolution of US limits the visualization of small lesions, especially when they are sparse (not focused). Air present in the lung parenchyma, bones, hollow organs, calcifications (gallstones), or biliary tract may limit the acoustic window and interfere with the ultrasound. Sometimes, the lesions and their margins are also not clearly evident in B-mode ultrasound in the case of inhomogeneous and cirrhotic livers even after the contrast agent is injected. Thus, confusion with cirrhotic nodules, poor conspicuity of the target lesion, and poor acoustic window are bound to happen [49]. Therefore, inappropriate intervention may be resulted hurting the patient and wasting the effort of the clinicians, para-medical staff increasing the country/hospital burden socially and economically. Citing these problems, a sophisticated tool, Image Fusion, is needed to facilitate the integration of the US images with CT/MR increasing the visualization of lesions from these imaging modalities, when applied alone [50]. The fusion can efficiently combine the merits of the individual imaging modalities increasing the quality of visualization and improving the confidence of the clinician.

## Image fusion procedure

The image fusion procedure is described as follows: (a) acquire the pre-operative CT/MRI of the liver lesion; (b) segment the liver for localizing of the lesion [51–55]; (c) take the intra-operative US of the liver; (d) perform image fusion—convert the images into the same format and spatially align the images; (e) image fusion is then performed integrating the display of the registered images, either side-by-side or overlay them; (f) determine the needle route to the lesion; (g) augment the lesion on the liver; and (h) perform radio wave ablation of the lesion with a 5-mm safety margin. Hepatic and portal veins are used as anatomical markers after dividing the liver into segments. The specific anatomical landmarks for image fusion and ablation are chosen based on the location of the lesions.

## Clinical applications

Image fusion helps combine various modalities of imaging and compare them to one another which helps with precise localization and characterization of the liver lesion. This does not only help with diagnosis, but also the intervention and follow-up, especially for lesions with low conspicuity on B-mode ultrasound. It is used for the following: (a) diagnosis and treatment of small liver cancer, (b) evaluation of minimally invasive treatment techniques—transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA), and (c) early diagnosis and treatment of new or recurrent liver cancers or liver metastasis after surgery (Fig. 2).

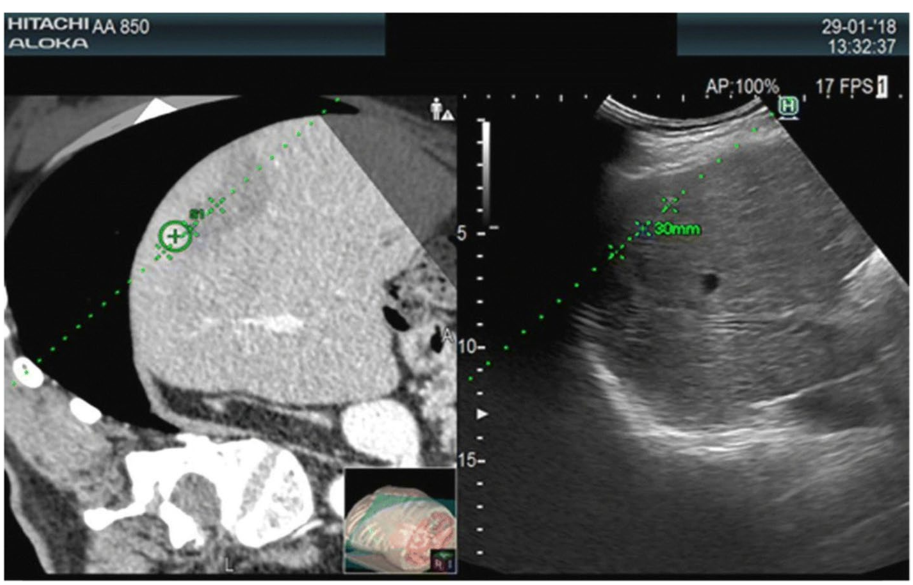


**Fig. 2** CT-US image fusion of small hyper-vascular nodular recurrent HCC close to a previously ablated area [14]

## Potential challenges of image fusion and prospects

The imminence of mistargeting a lesion is one of the main concerns in image fusion. This could be due to two reasons: (1) the lesion is usually small in size or (2) the adjacent pseudo-lesions are confused with a lesion (regenerative nodules in a cirrhotic liver). Lesions may also be missed due to their location (subphrenic or subcapsular areas) or poor conspicuity.

It is also challenging to synchronize a static image (pre-operative CT) with a dynamic image (intra-operative US) due to the patient's breathing motion affecting the liver. The liver itself is also a dynamic organ in the sense that the periphery expands more widely than the core during the breathing cycle, including translations and rotations. There are also fewer vessels present in the periphery, making the image fusion difficult due to fewer anatomical landmarks. The patient may also be positioned differently during the two imaging procedures.

Contrast-enhanced US (CEUS), which is the use of ultrasound after injection of contrast media, may be used in combination with image fusion to alleviate some of the limitations since it has better conspicuity than the B-mode US.

Image fusion aims to determine the spatial correspondence between two image sets minimizing their difference. For instance, there are a static image *St(x)* and a moving image *Mv(x)*; an optimal transform *Tr(x)* is determined by the image fusion algorithm that minimizes the difference between *St(x)* and *Mv(x)*. The fusion algorithms can either be rigid or non-rigid; the operations such as rotation and translation are uniform in rigid image fusion so that all the pixel-to-pixel relationships remain equal even after the transformation, whereas, in the case of non-rigid fusion (also called deformable fusion), the pixel-to-pixel relationships change keeping *St(x)* and *Mv(x)* aligned on the same reference coordinate. However, a pixel in either image set may not necessarily represent the same anatomical structure. Thus, local distortions either due to self or neighbouring dynamic organs\tissues or patient breathing are bound to occur.

Several challenges can complicate the fusion accuracy; they are real-time fusion, tissues located in the abdomen/thorax, and respiratory motion causing tissue deformation. Furthermore, intra- and inter-fractional anatomical variations in the image sets can cause dissimilarities. The plain physiological changes such as tumour growth, patient weight loss, bladder filling, etc., can cause soft tissue deformation. The image fusion should not be dependent on the medical instruments in the ultrasound images.

Although the deformable fusion can manage most of these challenges, it would certainly need high computational power and time that may affect the real-time aspect. There are three key functionary blocks in a deformable fusion: the deformation model, the optimization method, and the objective function. The similarity definition between *St(x)* and *Mv(x)* is needed for the objective function that can be feature-based, intensity-based, or a combination of the two. The type of similarity metric depends on the fusion accuracy desired and the type of images along with the amplitude of misalignment. The intensity-based objective functions are most suitable for the single modality images, while the feature-based objective function needs the image feature definition that is independent of image intensity. However, it can be time-consuming and difficult to construct the features while introducing intra- and inter-observer dependencies.

From a medical standpoint, the real-time US-CT fusion is certainly challenging, which is due to the fact that the information in the modalities originates from different physical processes and properties. The changes in the acoustic impedance, various artefacts, and speckle noise are all included in US images, whereas CT uses X-ray attenuation. With regard to image quality, US images are relatively limited with image information due to overlying structures and subcutaneous fat or gas-containing organs. Additionally, the US images are acquired in arbitrary planes.

The fusion outcome may be better visualized by using augmented reality (AR), whereas there is a substantial drop in the cost incurred [56]. Although virtual reality is another option, it is not appropriate to be used since it isolates the clinicians from the surroundings. AR has the ability to integrate real objects with virtual ones in a real environment. Importantly, since the virtual and the real objects are aligned and run interactively, AR could be more advantageous for image-guided systems. Thus, operating on HCCs could also be made easier by using AR, where the lesion is projected onto the patient's liver at the exact location and depth. We have provided a possible workflow as in Fig. 3, which could be explored further. We believe that this solution could improve the lesion visualization indirectly reducing the patient's exposure to radiation. Furthermore, it could also be time- and cost-effective, and much more clinically applicable.

The system overview can further be imagined as shown in Fig. 4. This system aims at fusing pre-operative CT images with intra-operative US images for hepatobiliary procedures in Interventional Radiology with a complete visualization in augmented

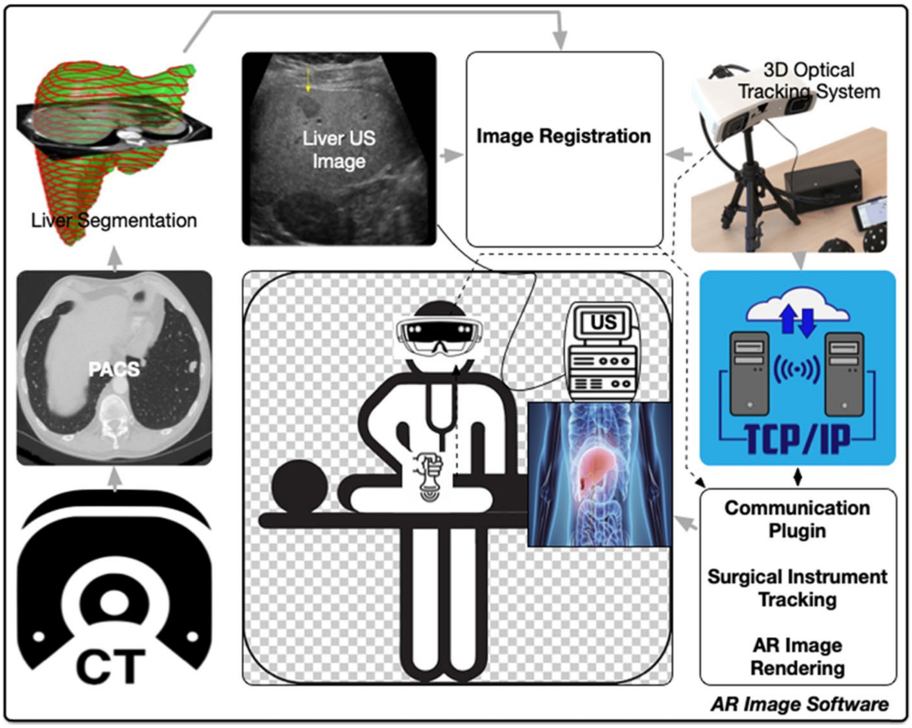


**Fig. 3** Projection of CT-US image fusion in AR to highlight sparse lesions

reality (AR). As described in Fig. 4, the pre-operative CT images of the same patient can be retrieved from the picture archiving and communication system (PACS) server and US images can be sent from the ultrasound machine to the Image Fusion system in real time. The Image Fusion PC can run a set of image processing algorithms (including image segmentation [40–43] and image registration [57]) rendering the processed 3D images via augmented reality (AR) providing an enhanced visualization to the clinician.

Figure 4 describes the hardware architecture of the entire system. The system mainly consists of the following major hardware components: fusion PC (personal computer) is the core of the system. This PC is responsible for communicating with all other hardware components and running all software components in it, including querying CT images from PACS, receiving real-time ultrasound images from the ultrasound scanner, running all image processing algorithms, receiving scanner position via optical marker, and running AR rendering server to render AR images via AR device. The PACS server is responsible for storing DICOM CT images, whereas the ultrasound scanner is responsible for acquiring real-time ultrasound images of the patient and sending those images to the fusion PC. Finally, Hololens renders the processed images in augmented reality. In this setup, the optical tracker tracks the position of the body part being scanned in the 3D space. The proposed system can certainly be helpful, if some concerns are properly addressed: (1) most of the ultrasound machines available in the hospitals do not have provision to export raw data (videos), say to the computer; (2) latency at the computer in receiving the raw data from the US machine; (3) accuracy of real-time fusion; (4) privacy in using AR; and (5) adaptation of an AR-based system by the clinicians, who are not technology friendly.

## Conclusion

Image fusion of pre-operative US and postoperative CT/MRI increases the conspicuity of HCC that is not visible on the conventional B-mode US. Integrating two different imaging modalities further helps in differentiating the true index of the tumour from nearby pseudo-lesions or previous ablated zones. In this paper, we have summarized and reviewed the existing treatments for hepatocellular carcinoma. We have shown how this helps the clinicians in successfully

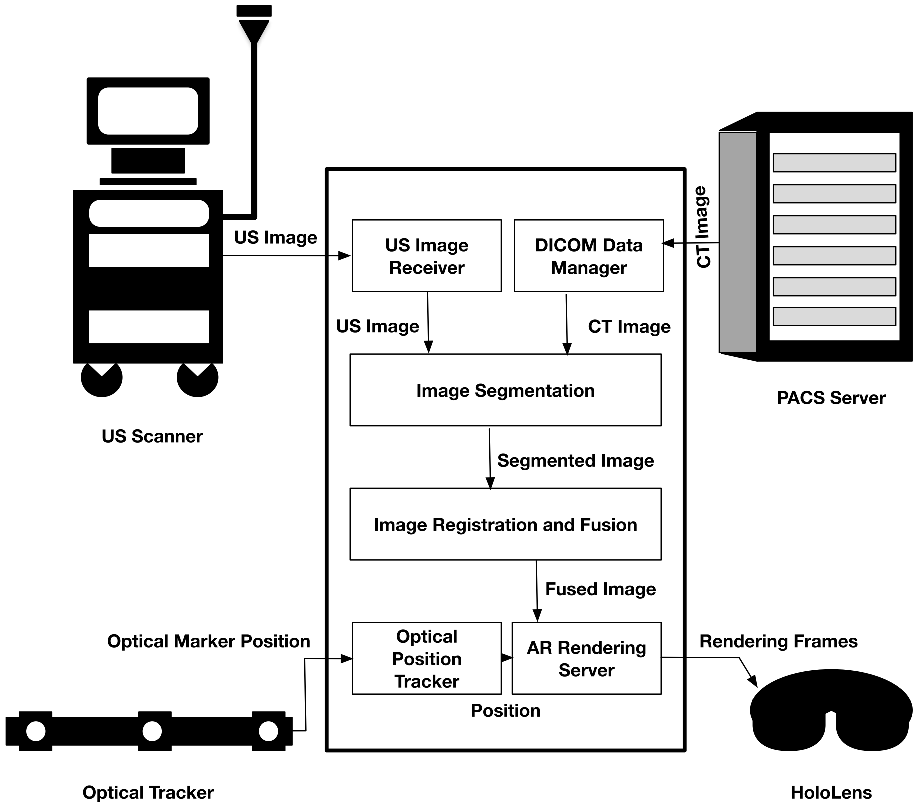


**Fig. 4** Illustration of a possible solution

targeting the liver lesion and ablating it. Although the technology for image fusion has come a long way, there is still scope for further advancements in the field. We have highlighted the potential limitations and have presented some open questions for the researchers. We believe that this review would help the clinical researchers gain some technical knowledge along with clinical ones.

**Acknowledgements**
Not applicable.

**Authors' contributions**
Sarada has conceptualized the study and participated in the design of the study, data analysis, manuscript preparation, manuscript editing, and manuscript review, while Anchal has participated in the manuscript preparation, literature search, data analysis, and manuscript review. The author(s) read and approved the final manuscript.

**Funding**
This publication was made possible by NPRP-11S-1219-170106 from the Qatar National Research Fund (a member of the Qatar Foundation). The findings herein reflect the work and are solely the responsibility of the authors. The Open Access funding was provided by the Qatar National Library.

**Availability of data and materials**
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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Received: 20 January 2022 Accepted: 9 April 2022
Published online: 27 April 2022

**References**
1. McGlynn KA, Petrick JL, El-Serag HB (2001) Epidemiology of hepatocellular carcinoma. Hepatology 73(Suppl 1):4–13. https://doi.org/10.1002/hep.31288
2. Bosch FX, Ribes J, Díaz M, Cléries R (2004) Primary liver cancer: worldwide incidence and trends. Gastroenterology 127(5 Suppl 1):S5–S16. https://doi.org/10.1053/j.gastro.2004.09.011
3. Gelband H et al (2015) Liver cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S (eds) Cancer: disease control priorities, third edition (volume 3). The International Bank for Reconstruction and Development

/ The World Bank, Washington (DC) Available: http://www.ncbi.nlm.nih.gov/books/NBK343640/. Accessed 28 Mar 2022
4. Llovet JM et al (2021) Hepatocellular carcinoma. Nat Rev Dis Primers 7(1):6. https://doi.org/10.1038/s41572-020-00240-3
5. Sung H et al (2021) Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209CI49. https://doi.org/10.3322/caac.21660
6. Hamed MA, Ali SA (2013) Non-viral factors contributing to hepatocellular carcinoma. World J Hepatol 5(6):311–322. https://doi.org/10.4254/wjh.v5.i6.311
7. Govalan R et al (2021) Comparison of surgical resection and systemic treatment for hepatocellular carcinoma with vascular invasion: National Cancer Database Analysis. LIC 10(5):407–481. https://doi.org/10.1159/000515554
8. Lencioni R et al (2005) Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 234(3):961–967. https://doi.org/10.1148/radiol.2343040350
9. Sandhu DS, Tharayil VS, Lai J-P, Roberts LR (2008) Treatment options for hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2(1):81–92. https://doi.org/10.1586/17474124.2.1.81
10. Mazzaferro V et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334(11):693–700. https://doi.org/10.1056/NEJM199603143341104
11. Mazzaferro V et al (2011) Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 17(S2):S44–S57. https://doi.org/10.1002/lt.22365
12. Vivarelli M et al (2002) Low recurrence rate of hepatocellular carcinoma after liver transplantation: better patient selection or lower immunosuppression? Transplantation 74(12):1746–1751. https://doi.org/10.1097/00007890-200212270-00017
13. Sapisochin G et al (2016) The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. Hepatology 64(6):2077–2088. https://doi.org/10.1002/hep.28643
14. Lurje I et al (2019) Treatment strategies for hepatocellular carcinoma—a multidisciplinary approach. Int J Mol Sci 20(6):6. https://doi.org/10.3390/ijms20061465
15. Crocetti L, de Baere T, Lencioni R (2010) Quality improvement guidelines for radiofrequency ablation of liver tumours. Cardiovasc Intervent Radiol 33(1):11–17. https://doi.org/10.1007/s00270-009-9736-y
16. Lin S-M, Lin C-J, Lin C-C, Hsu C-W, Chen Y-C (2004) Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma ≤4 cm. Gastroenterology 127(6):1714–1723. https://doi.org/10.1053/j.gastro.2004.09.003
17. Hennedige T, Kundapur Venkatesh S (2013) Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. Cancer Imaging 12(3):530–547. https://doi.org/10.1102/1470-7330.2012.0044
18. Iyonaga T et al (2015) A case of Kounis syndrome associated with transcatheter arterial chemoembolization for hepatocellular carcinoma. J Cardiol Cases 12(4):106–109. https://doi.org/10.1016/j.jccase.2015.05.007
19. Alqahtani A, Khan Z, Alloghbi A, Said Ahmed TS, Ashraf M, Hammouda DM (2019) Hepatocellular carcinoma: molecular mechanisms and targeted therapies. Medicina 55(9):9. https://doi.org/10.3390/medicina55090526
20. Karaman B, Battal B, Sari S, Verim S (2014) Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol 20(47):18059–18060. https://doi.org/10.3748/wjg.v20.i47.18059
21. Wilhelm S et al (2006) Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 5(10):10. https://doi.org/10.1038/nrd2130
22. Escudier B, Worden F, Kudo M (2019) Sorafenib: key lessons from over 10 years of experience. Expert Rev Anticancer Ther 19(2):177–189. https://doi.org/10.1080/14737140.2019.1559058
23. Pawlik TM, Schulick RD, Choti MA (2008) Expanding criteria for resectability of colorectal liver metastases. Oncologist 13(1):51–64. https://doi.org/10.1634/theoncologist.2007-0142
24. Kirstein MM, Wirth TC (2020) Multimodale Therapie des hepatozellulären Karzinoms. Internist 61(2):164–169. https://doi.org/10.1007/s00108-019-00722-x
25. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu and European Association for the Study of the Liver (2018) EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 69(1):182–236. https://doi.org/10.1016/j.jhep.2018.03.019
26. Zheng H et al (2022) Microwave ablation versus radiofrequency ablation for subcapsular hepatocellular carcinoma: a propensity score-matched study. Eur Radiol. https://doi.org/10.1007/s00330-022-08537-5
27. Zhu F, Rhim H (2019) Thermal ablation for hepatocellular carcinoma: what's new in 2019. Chin Clin Oncol 8(6):6. https://doi.org/10.21037/cco.2019.11.03
28. Carriero S et al (2021) Role of fusion imaging in image-guided thermal ablations. Diagnostics 11(3):3. https://doi.org/10.3390/diagnostics11030549
29. Hui TC, Kwan J, Pua U (2021) Advanced techniques in the percutaneous ablation of liver tumours. Diagnostics 11(4):4. https://doi.org/10.3390/diagnostics11040585
30. Yamakado K et al (2014) Radiofrequency ablation for hepatocellular carcinoma. Gastrointest Interv 3(1):35–39. https://doi.org/10.1016/j.gii.2014.04.002
31. Ansari D, Andersson R (2012) Radiofrequency ablation or percutaneous ethanol injection for the treatment of liver tumors. World J Gastroenterol 18(10):1003–1008. https://doi.org/10.3748/wjg.v18.i10.1003
32. Wells SA, Hinshaw JL, Lubner MG, Ziemlewicz TJ, Brace CL, Lee FT (2015) Liver ablation: best practice. Radiol Clin North Am 53(5):933–971. https://doi.org/10.1016/j.rcl.2015.05.012
33. Alvaro D et al (2021) Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia. Eur J Clin Investig 51(6):e13508. https://doi.org/10.1111/eci.13508
34. Huang SY, Philip A, Richter MD, Gupta S, Lessne ML, Kim CY (2015) Prevention and management of infectious complications of percutaneous interventions. Semin Intervent Radiol 32(02):078–088. https://doi.org/10.1055/s-0035-1549372
35. Izzo F et al (2019) Radiofrequency ablation and microwave ablation in liver tumors: an update. Oncologist 24(10):e990–e1005. https://doi.org/10.1634/theoncologist.2018-0337
36. Weinstein JL, Ahmed M (2018) Percutaneous ablation for hepatocellular carcinoma. AJR Am J Roentgenol 210(6):1368–1375. https://doi.org/10.2214/AJR.17.18695
37. Ito T et al (2016) Outcomes of laparoscopic hepatic resection versus percutaneous radiofrequency ablation for hepatocellular carcinoma located at the liver surface: a case–control study with propensity score matching. Hepatol Res 46(6):565–574. https://doi.org/10.1111/hepr.12592
38. Kang TW et al (2016) Long-term therapeutic outcomes of radiofrequency ablation for subcapsular versus nonsubcapsular hepatocellular carcinoma: a propensity score matched study. Radiology 280(1):300–312. https://doi.org/10.1148/radiol.2016151243
39. Liu F et al (2017) Comparison of ultrasonography-guided percutaneous microwave ablation for subcapsular and nonsubcapsular hepatocellular carcinoma. Eur J Radiol 91:93–98. https://doi.org/10.1016/j.ejrad.2017.04.002
40. Dakua SP, Sahambi JS (2009) LV contour extraction using difference of Gaussian weighting function and random walk approach. In: 2009 annual IEEE India conference, pp 1–4. https://doi.org/10.1109/INDCON.2009.5409483
41. Dakua SP (2017) Towards left ventricle segmentation from magnetic resonance images. IEEE Sensors J 17(18):5971–5981. https://doi.org/10.1109/JSEN.2017.2736641
42. Dakua SP, Sahambi JS (2010) Automatic left ventricular contour extraction from cardiac magnetic resonance images using cantilever beam and random walk approach. Cardiovasc Eng 10(1):30–43. https://doi.org/10.1007/s10558-009-9091-2
43. Dakua SP (2015) LV segmentation using stochastic resonance and evolutionary cellular automata. Int J Patt Recogn Artif Intell 29(03):1557002. https://doi.org/10.1142/S0218001415570025
44. Minami Y, Kudo M (2020) Ultrasound fusion imaging technologies for guidance in ablation therapy for liver cancer. J Med Ultrasonics 47(2):257–263. https://doi.org/10.1007/s10396-020-01006-w
45. Minami Y, Kudo M (2021) Image guidance in ablation for hepatocellular carcinoma: contrast-enhanced ultrasound and fusion imaging. Front Oncol 11:234 Available: https://www.frontiersin.org/article/10.3389/fonc.2021.593636. Accessed 28 Mar 2022
46. Vikram Singh A, Laux P, Luch A, Balkrishnan S, Prasad Dakua S (2019) Bottom-UP assembly of nanorobots: extending synthetic biology to

complex material design. Front Nanosci Nanotech 5(1). https://doi.org/10.15761/FNN.1000S2005
47. Akhtar Y et al (2021) Risk assessment of Computer-Aided diagnostic software for hepatic resection. In: IEEE transactions on radiation and plasma medical sciences, pp 1–1. https://doi.org/10.1109/TRPMS.2021.3071148
48. Lee MW (2014) Fusion imaging of real-time ultrasonography with CT or MRI for hepatic intervention. Ultrasonography 33(4):227–239. https://doi.org/10.14366/usg.14021
49. D'Onofrio M et al (2019) Abdominal applications of ultrasound fusion imaging technique: liver, kidney, and pancreas. Insights Imaging 10(1):6. https://doi.org/10.1186/s13244-019-0692-z
50. Li C, Zhu A (2020) Application of image fusion in diagnosis and treatment of liver cancer. Appl Sci 10(3):3. https://doi.org/10.3390/app10031171
51. Dakua SP (2013) Use of chaos concept in medical image segmentation. Comput Methods Biomech Biomed Eng Imaging Vis 1(1):28–36. https://doi.org/10.1080/21681163.2013.765709
52. Dakua SP, Abinahed J, Al-Ansari AA (2016) Pathological liver segmentation using stochastic resonance and cellular automata. J Vis Commun Image Represent 34:89–102. https://doi.org/10.1016/j.jvcir.2015.10.016
53. Dakua SP et al (2019) Moving object tracking in clinical scenarios: application to cardiac surgery and cerebral aneurysm clipping. Int J CARS 14(12):2165–2176. https://doi.org/10.1007/s11548-019-02030-z
54. Dakua SP, Sahambi JS (2011) Detection of left ventricular myocardial contours from ischemic cardiac MR images. IETE J Res 57(4):372–384. https://doi.org/10.4103/0377-2063.86338
55. Dakua SP, Sahambi JS (2011) Weighting function in random walk based left ventricle segmentation. In: 2011 18th IEEE international conference on image processing, pp 2133–2136. https://doi.org/10.1109/ICIP.2011.6116031
56. Halabi O, Balakrishnan S, Dakua SP, Navab N, Warfa M (2020) Virtual and augmented reality in surgery. In: Doorsamy W, Paul BS, Marwala T (eds) The disruptive fourth industrial revolution: technology, society and beyond. Springer International Publishing, Cham, pp 257–285. https://doi.org/10.1007/978-3-030-48230-5_11
57. Mohanty S, Dakua SP (2022) Toward computing cross-modality symmetric non-rigid medical image registration. IEEE Access 10:24528–24539. https://doi.org/10.1109/ACCESS.2022.3154771

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