Practical Utility of Liver Segmentation Techniques in Clinical Surgeries and Interventions

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RESEARCH

Practical Utility of Liver Segmentation Techniques in Clinical Surgeries and Interventions

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Abstract

Medical images (e.g., magnetic resonance imaging (MRI) and computed tomography (CT)) provide critical information to the clinicians in order to diagnose pathology and plan interventions. Image segmentation is the first and foremost step taken by the clinicians while optimizing analytic diagnosis and treatment planning for interventions (e.g., transplantation and complete resection) and therapeutic procedures (e.g., radiotherapy, PVE, and embolization approaches), especially in hepatocellular carcinoma. Thus, segmentation techniques certainly impact the diagnosis and treatment outcomes. This paper studies the literature during the year 2012 until 2021 and reviews the segmentation methods classifying them into three categories based on their clinical utility (i.e., surgical and radiological interventions). The classification is based on the parameters such as precision, accuracy, location, liver condition, and other clinical considerations.

Keywords: Liver; Tumor; Segmentation; Surgery; Intervention

1 Introduction

The World Health Organization (WHO) has reported that hepatocellular carcinoma (HCC) is the leading cause of cancer deaths worldwide. In 2020, liver cancer caused 830,000 lives, and HCC has accounted for about 80% of primary liver cancers [1]. Surgeons, radiologists, and oncologists study liver texture anomalies, shape, and lesions from CT/MRI images utilizing computer-aided diagnoses (CAD) to evaluate liver conditions. Segmentation of CT/MRI liver images can greatly augment current clinical practice because it plays an essential role in CAD systems allowing the surgeons to analyze small lesions that have similar gray-level intensities as the liver. Therefore, precise and reliable segmentation methods with a swift time-frame are

crucial for boundary and volumetric assessments for staging of liver tumors (e.g., Response Evaluation Criteria in Solid Tumor (RECIST) protocol) [2].

Treatment of HCC requires accurate delineation of liver and tumor to direct appropriate planning. For this reason, liver and tumor segmentation plays a critical role in conventional treatment methods such as surgical intervention, Radiofrequency Ablation (RFA), Percutaneous Ethanol Injection (PEI), Transcatheter Arterial Chemoembolization (TACE), and the use of targeted agents [3]. For example, controlled radiation dosage is mandatory for Selective Radiation Therapy (SIRT) to minimize excessive radiation exposure [3]. Additionally, liver tumor segmentation is a prerequisite for several treatment such as surgical resection [4], thermal percutaneous ablation [5], PEI [6], and arterial embolization [7]. Segmentation is also needed in post-treatment tracking of ablated/resected zones of the liver, allowing the clinician to evaluate the procedure's success rate. Thus, liver and tumor segmentation is vital for the diagnosis, treatment, and post-treatment analysis of HCC [3].

Segmentation methods are usually classified based on the needs. Here, they have been divided into two categories based on the extent of human intervention; semi-automatic and automatic segmentation methods. The semi-automatic methods require the surgeon's assistance to produce consistent results. For instance, a surgeon's opinion may be needed in a region-growing algorithm for seed selection or in the post-processing step of a segmentation algorithm to refine the segmentation masks [8]. These semi-automatic methods provide more control to the surgeons during the procedure but are prone to user errors. On the other hand, the automatic methods have minimal user errors due to lack of external interventions. However, the automatic segmentation techniques are biased towards the statistical distribution of the training data. Over the past few decades, many semi-automatic and automatic techniques including, region growing [9], active contours [10], graph cuts [11], statistical shape models [12], support vector machines [13], neural network-based [14] have been proposed for liver and lesion segmentation. Deep learning-based methods have recently gained popularity because of the state-of-the-art accuracy, robustness, and generalization provided by the neural networks [14].

The development of accurate liver and tumor segmentation methods is challenging because of varying liver volumes and shapes in different CT/MRI images orienta-

tions. Additionally, the contrast media injections alter the grey level values of the liver, making its intensity similar to neighboring organs such as the stomach, the spleen, and abdominal wall, thus adding complexity to the segmentation process [15]. Furthermore, diverse liver pathologies may deform liver structure and modify signal intensity. Figure 1 shows the challenge faced by the segmentation algorithms due to ambiguous anatomical boundaries of the liver. Liver lesion segmentation is challenging due to variable contrast levels (i.e., hyper-/hypo-intense tumors) and broad-spectrum abnormalities (inconsistent size and shape of lesions) [3].

The segmentation methods are compared with respect to consistency, reliability, and segmentation performance depending on the spread of HCC and its diagnoses. Bilic et al. [3] assess over 24 state-of-the-art liver and tumor segmentation techniques; they conclude that a single segmentation algorithm might not always be the best fit for segmenting the liver and its tumors in all clinical scenarios. Therefore, judging the feasibility of a segmentation method for a specific clinical use or intervention remains challenging because of abundant methods with limited clinical assessments. This paper attempts to overcome the limitation of insufficient clinical assessments of segmentation methods and presents them in a structured manner based on their clinical utility. It is established that the diagnosis of HCC is a complex procedure that may be impacted by the tumor size [16], intensity [17], malignant or benign nature [18], and other liver diseases (e.g., liver cirrhosis) [19]. There has been extensive research and case studies in the literature that aims to classify and detect tumors [20, 21, 22]. In this work, we recommend liver and tumor segmentation methods for different clinical pathways for HCC, aiming to serve as a knowledge base for the radiologist for expediting their segmentation tool selection. We have extensively reviewed the algorithms in the literature and have classified them based on critical parameters such as accuracy, texture, automation, and precision. Specifically, this work discusses the state-of-the-art segmentation methods for surgical and nonsurgical interventions for the treatment of HCC.

This paper is structured as follows; Section II provides an overview of the liver and tumor segmentation methods. Section III and IV present the segmentation techniques for surgical and radiological interventions, respectively. Section V discusses the technical and clinical challenges facing the segmentation algorithms and treatment of HCC. Section VI concludes the paper and provides critical future directions related to the liver and lesion segmentation.

2 Literature Review

Liver segmentation in CT and MRI scans is challenging due to variability in liver dimensions and comparable gray-level intensity of its neighboring organs (e.g., heart and kidney). Furthermore, the blurry anatomical boundaries, poor contrast of the medical images, partial volume effects resulting from patient movement, spatial averaging, and reconstruction artifacts make liver segmentation daunting. Figure 2 describes the application of the segmentation methods to the various components of the liver.

Generally, the conventional image segmentation methods are either model-based (e.g., active contours, and snake algorithms) [23], [24], [25], [26], [27] or intensity-based (e.g., thresholding). Some algorithms utilize primitive image features, e.g.,

pixels intensities in region-growing/thresholding based approaches [28], [29], [24], [30]. Fuzzy segmentation techniques have also been utilized for multi-channel image segmentation and extended for single-channel images [31], [32]. Zhang et al. [12], and Nuzillard et al. [33] have shown that model-based statistical approaches achieve expected results relative to the conventional segmentation methods based on image intensities. Mahr et al. [34] evaluated several segmentation methods and concluded that model-based techniques are the potential futures for liver segmentation. However, the statistical models are limited by constraints and require additional parameter tuning and initialization, resulting in high computational time. If the models are considered to be evaluated without the constraints, they misclassify or under-segment the region of interests.

There has been also a different classification of the segmentation techniques that is based on the extent of human intervention; some of them are automatic [35], [36], [37], [38], [39], [40], [41], [42] that do not require human intervention for the generation of segmentation masks and some are semi-automatic requiring human assistance, say for seed selection or segmentation mask refinement [43], [44], [45], [46], [47]. Linguraru et al. [36] suggest an automatic segmentation approach for the liver segmentation based on an affine invariant shape formulation. The paper makes a point-to-point comparison of various 3D surface features in the affine parameter space. Another automatic method proposed by Seo et al. [48] follows a multi-stage approach by utilizing an optimal threshold value to segment liver, hepatic vessels, and tumors sequentially. Chartrand et al. [43] introduce a semi-automatic liver segmentation technique that generates an approximate liver model and deforms it by using a Laplacian mesh optimization to obtain accurate liver segmentation. Peng et al. [46] utilize semi-automatic level sets that integrate the likelihood energy and anatomical boundary information to segment the liver. Zhang et al. [44] propose a semi-automatic method based on Couinaud's theory to segment the liver with varying clinical conditions. Zhao et al. [49] report a semi-automatic region-growing method that avoids over-predictions of the surrounding tissues and organs using shape constraints. The primary shortcoming of semi-automatic implementations is user intervention that interrupts the segmentation process and results in subjective outcomes. From this standpoint, it is essential to note that automated segmentation techniques are preferred in time-constrained clinical applications.

Segmentation of vessels, tumors, and bile duct also plays an important in the diagnosis, treatment, and post-treatment evaluation of HCC [50], [51]. Segmentation of these relatively minute components of the liver is challenging because of artifacts, poor contrast, and distortions in the standard image at the native scale/resolution. Specific denoising and image enhancement techniques have improved images with high noise levels and artifacts (e.g., Wavelet and Ridgelet transform). These methods transform the image to a different domain in order to segregate the image noise [34], [52]. Shang et al. [42] propose an active contour-based method that uses a Gaussian mixture model to segment major liver vessels. Next, the vascular vector field centerline segments thin vessels with lower visibility. Kirbas et al. [53] present a comprehensive review to understand the conventional vessel segmentation algorithms. Wang et al. [54] suggest a model-based algorithm to detect and segment bile duct carcinoma. Similar model-based approaches have been proposed for detecting and segmenting liver malignancies (e.g., HCC) [36], [37].

In recent years, machine learning and deep learning have vigorously gained popularity in medical image segmentation. Specifically, the U-net architecture proposed for biomedical image segmentation has been modified for segmentation of organs in CT/MRI images [55]. Although the deep learning algorithms provide acceptable reliability and accurate results, they require large datasets and dedicated hardware (i.e., GPU). The challenges related to limited data and computation cost have been mitigated using data augmentation and efficient network layers. Alexey et al. [56] present a hybrid convolutional LSTM architecture that merges time distributed convolutions, bi-directional C-LSTM blocks, and pooling operations to work with partial input volumes. The resultant hybrid network is competitive in terms of computational power, memory consumption, and inference times for the liver segmentation.

3 Segmentation for Surgical Intervention

Clinicians utilize multiple staging systems to predict HCC prognosis, such as Okuda system, Tumor, Node, Metastasis (TNM) staging, Cancer of the Liver Italian Pro-

gram (CLIP) score, Barcelona staging classification (BCLC), Albumin-Bilirubin (ALBI) score, etc. [57], [58], [59], [60], [61]. Of these, BCLC staging offers the most algorithmic approach to plan interventions, accounting for extent of hepatic lesion, vascular invasion, hepatic function status, and spread outside the liver [61]. It establishes a prognosis based on first-line treatment linked stages as per current scientific evidence. Several studies have reported BCLC system to outperform other models in predicting HCC prognosis [62], [63]. Clinicians utilize BCLC to decide the most appropriate therapeutic intervention for patients suffering from HCC. Figure 3 showcases the staging and treatment recommendations according to the BCLC criteria. Studies have shown that patients diagnosed with large multifocal tumors or advanced stage HCC are less likely to benefit from transplantation, liver resection, and ablation therapy [64], [65], [66], [67]. Nevertheless, the patients diagnosed with the early or initial stage of HCC with no liver diseases can be treated by surgical liver resection [68]. Figure 4 summarizes the role of segmentation and volumetry in surgical and radiological interventions of the liver.

3.1 Transplant

A liver transplant is recommended for treating patients with very early stages of HCC and increased portal pressure or bilirubin levels 3. However, clinicians need to ensure that the transplanted liver is well matched as this may impact the functional capabilities of the liver. In liver transplant surgeries, accurate segmentation and calculation of liver volume are critical, as the success of the donor and recipient operations depends heavily on the graft size [69]. The accepted standard for liver segmentation and volume calculation is manual delineation, which requires a highly experienced surgeon to manually trace the boundaries of the liver on CT/MRI images. However, manual tracing of organs is time-consuming and idiosyncratic. Therefore, reliable and automated segmentation techniques with fast inference times can reduce the complexity of the liver transplantation procedure. It has been shown

Table 1 Summary of methods for liver segmentation and volume estimation

Title	Method	Test Dataset	Performance
Lu et. al. [70]	3D-CNN	LiTs + 3DIRCADB	5.9 9.36 (VOE)
Wang et. al. [71]	U-Net-CNN	Custom Dataset	0.94 ± 0.06 (DSC)
Nakayama et. al. [72]	Vivo Hepatic Automated Volumetry	Custom Volumetric Dataset	0.96 (ICC)
Allir et. al. [73]	FCN	LiTs IRCAD	95.2% 95.6% (DSC)
Yasaka et. al. [74]	CNN	Custom Dataset (55536 Pictures)	0.84 (Median Accuracy)
Vorontsov et. al. [75]	FCN	Custom Dataset	0.68 (DSC)

that structure-based, machine learning, and deep learning techniques are suitable for liver delineation and volume estimation because of their robustness and ability to achieve high segmentation accuracy [8],[70]. These methods learn to identify variations of the liver shapes that may be missed by conventional segmentation algorithms, allowing for robust and consistent boundary delineation and volume calculation.

3.1.1 Liver Segmentation

Liver segmentation in 3-D medical scans is a crucial pre-requisite for the calculation of liver volume and liver/tumor ratio (i.e., tumor burden) [76], [77]. Liver segmentation techniques with high precision and accuracy (comparable to manual delineation) are highly desirable in clinical workflows. As discussed earlier, the deep learning-based approaches have recently provided robust and accurate liver segmentation techniques that may assist in liver transplantation. Alirr et al. [73] employ a region-based level set function with convolutional networks for liver and tumor segmentation. The FCN architecture has been tested on the IRCAD and LiTS dataset and resulted in 95.2%, 95.6% dice coefficient on the liver, and 76.1 %, 70% dice coefficient on the tumor, respectively. Yasaka et al. [74] introduce a CNN model to differentiate between liver masses during dynamic contrast agent-enhanced CT. The model is trained using 55,536 image sets (from 460 patients) to learn accurate and precise differentiation between liver regions. Results indicate that the median accuracy is above 0.84 for differential diagnosis of liver masses on the test dataset. Vorontsov et al. [75] propose an FCN architecture for detecting and segmenting liver lesions in CT images for patients with Colorectal Liver Metastases (CLMs). Results show that the network produces high dice coefficients for increasing lesion size. Specifically, the FCN achieves Dice Similarity Coefficient (DSC) of 0.14 (size<10 mm), 0.53 (size 10-20 mm), and 0.68 (size>20 mm). Altogether, these state-of-the-art methods could serve as an effective second opinion for interventional radiologists responsible for delineating livers in medical scans.

3.1.2 Calculation of Liver Volume

Liver and lesion volumetry, followed by a tumor burden analysis, provide valuable information to the surgeons in predicting the success of liver transplantation [3], [78]. Over the years, several automated segmentation methods have been proposed to segment the liver in CT and MRI imaging. Recently, Lu et al. [70] introduced

a 3D convolutional neural network (CNN) with graph cut to delineate the liver and predict its volume. The model's evaluation of the MICCAI-Sliver07 (LiTs) and 3Dircadb datasets indicates a volumetric overlap error (VOE) of 5.9% and 9.36%, respectively. Wang et al. [71] present a computationally light 2D U-Net variant for liver segmentation and volumetry. The model is trained using 330 abdominal CT examinations in two stages, allowing coarse fine segmentation. Results show that the proposed model reaches over 95% agreement with the ground truth. In [72], a comparison of Vivo hepatic automated volumetry with manual volumetry is performed to assess the effectiveness and margin of error for automated segmentation methods in liver transplantation scenarios. These neural network-based systems could provide viable information to the clinicians for deciding donor-patient compatibility based on liver volume estimation. Table 1 provides a summary of liver segmentation and volume estimation methods along with the datasets and performance.

3.2 Resection

3.2.1 Importance of Segmentation in Resection

BCLC staging system recommends liver resection for patients suffering from early or initial stage HCC with a single tumor, normal portal pressure, and bilirubin levels. For physicians, tumor information plays a critical role in surgical planning and image-guided interventions. Specifically, the exact volume, morphology, shape, and location of tumors must be accurately determined to carry out a successful resection procedure. In a conventional setting, surgeons manually delineate liver lesions by relying on their experience and observations, which results in biased outcomes that lack in efficiency and robustness. Therefore, automated liver tumor segmentation techniques are considered as a crucial second-opinion for interventional radiologists and surgeons. However, performing automatic tumor segmentation is quite challenging due to the low intensity, poor contrast, and anatomical variation of liver and lesions between patients. Specifically, sometimes the tumors vary in shape, size, and location, making the algorithm challenging to generalize for a diverse patient population. In addition, unclear boundaries of some lesions (as seen in Fig. 5) make it difficult for edge-based algorithms to perform effectively. Furthermore, the variations in anisotropic dimensions of the medical scans (i.e., voxel space ranging from 0.45 mm to 6.0 mm) may cause loss of critical volumetric information. Nevertheless, several conventional techniques, deformable models, and neural networks have been proposed to segment liver lesions [79], [80], [81].

3.2.2 Liver Tumor Segmentation

One significant challenge for the tumor segmentation algorithm is the inconsistency in tumor shapes and locations between patients. Deep learning models can overcome this challenge using data comprising of a diverse patient population with tumors of different shapes, sizes, and locations. It has been shown that neural networks' robustness and generalization capability increase with the data's quantity and variability. A few high-accuracy liver tumor segmentation models rely on different uses of renowned deep learning techniques. Zhang et al. [80] propose a level-set technique for CT-based liver tumor segmentation that incorporates an edge indicator and an automatically computed initial curve. The method employs a 2D-slice-based U-net

to localize the liver, followed by a 3D patch-based FCN to refine the liver segmentation and locate the tumor. The model's evaluation of the MICCAI 2017 Liver Tumor Segmentation (LiTS) Challenge has resulted in an average DSC of 96.31%. Xi et al. [81] present two cascading U-ResNets for end-to-end liver and lesion segmentation. Results on the LiTS highlight that the model achieves a dice score of 94.9%. Bai et al. [82] utilize a multi-scale candidate generation method (MCG) and 3D fractal residual network (3D FRN) for liver and tumor segmentation in CT volumes. Initially, a U-Net segments the liver region in the 3-D space. Next, MCG is employed to mark the candidate regions for liver tumors. Finally, 3D FRN is used to mark the lesion accurately. It is known that post-processing removes minor mispredictions, enhances or refines segmentation masks, or interrupts a surgeon to validate the results, thus enhancing the generalization capabilities of the deep learning model. Bai et al. [82] use an active contour model (ACM) on the tumor predictions to refine tumor boundaries. The resultant method 3D MCG-FRN + ACM results in a dice coefficient of 0.67 on the 3DIRCADb dataset. Alternatively, Li et al. [45] propose a simple approach by combining a level set model with likelihood and boundary energies to segment liver tumors. The result highlights a Jaccard distance error of $14.4 \pm 5.3\%$ and a relative volume difference of $-8.1 \pm 2.1\%$ on a custom CT dataset with 18 patients.

After segmenting any existing liver tumors, surgeons and radiologists must recognize its type to determine the extent of cancer spread and malignancy. This classification process can be automated and embedded within the segmentation algorithm, efficiently providing physicians valuable secondary information. Trivizakis et al. [20] train a 3-D CNN using 130 DW-MRI scans to classify the tumor type. The network results in an 83% classification accuracy compared to 69.6% of a previously implemented 2-D CNN. Chen et al. [21] present an effective and efficient probabilistic neural network (PNN) trained using fractal information gray-level co-occurrence matrix to classify liver tumors into hepatoma and hemangioma. Balagourouchetty et al. [22] suggest an ensemble FCNet classifier trained using GoogLeNet features to classify six different classes of liver tumors. Recently, Dong et al. [83] proposed a Hybridized Fully Convolutional Neural Network (HFCNN) to detect cancer and segment liver tumors.

3.2.3 Automation

The heterogeneous shape of tumors, and inconsistent background, which creates high unpredictability between the liver and the lesions adds complexity to automatic tumor segmentation methods [8]. Most interactive or semi-automatic methods that involve input from a physician have shown better results and are used for critical hepatic operations like hepatic biopsies and hepatic therapeutic interventions [6]. Zhang et al. [84] present an interactive seed-selection strategy for liver tumor segmentation using support vector machines in CT scans. Lin et al. [85] propose an interactive implementation that places emphasis on region partition and boundary information. The tumor texture information and clear tumor boundary allow the model to segment tumors effectively. Moreover, the Lucas–Kanade algorithm selects the seed pixel for initiating model training, and user inputs are utilized to incorporate the data variations. The collaborative model obtains promising results and an average segmentation accuracy of 80%. On the other hand, fully automated techniques lack performance because of the complex and volatile nature of surgeries and complications [86]. Nonetheless, complete automation is being consistently pursued to achieve performance that is comparable to semi-automatic methods. A fully automated deep learning approach based on an Attention Hybrid Connection (AHC) Network architecture is implemented by [87], giving notable results. The network is tested using 20 cases from the 3DIRCADb dataset and 117 cases from a clinical dataset, achieving a global Dice coefficient of 0.62 ± 0.07 in tumor segmentation. Seo et al. [88] proposes a modified U-Net (mU-Net), which combines object-dependent high-level features to improve liver-tumor and liver segmentation from CT scans. The model’s evaluation on the (LiTS) dataset results in a dice similarity coefficient (DSC) of 89.72 % for liver tumors. Vivanti et al. [89] present an automatic method for liver tumors segmentation in post-treatment CT studies that use a CNN to image patches. Next, a voxel classifier is employed to generate the refined tumor segmentation mask. The model’s evaluation on a custom dataset results in an average of 16.05% VOE and a 2.05 mm average symmetric surface distance (ASSD), giving a success rate of 90.5%. Table 2 provides a summary of liver tumor segmentation techniques along with the datasets and performance.

4 Segmentation for Radiological Intervention

Interventional radiology has opened new avenues for treatment of liver cancers. BCLC staging system recommends radiological interventions (e.g., ablation) for patients not suited for transplant or with livers with associated diseases. Radiological treatments can be performed by an endovascular approach or by direct transcapsular access [90]. Endovascular treatments include TACE, Stereotactic Body Radiation Therapy (SBRT), Transarterial Radioembolization (TARE), and portal vein embolization (PVE). Direct transcapsular access treatments involve microwave thermal ablation (MWA), RFA, and PEI [91].

TARE and TACE block the hepatic artery to treat the liver cancer segment by cutting off its blood supply. TARE is a selective internal radiation therapy that requires an intra-arterial supply of microspheres packed with radioactive compounds such as tritium90, iodine131, or rhenium188 [92]. In comparison, TACE is a type of chemoembolization that involves chemotherapy. CT or MRI imaging is used to

Table 2 Summary of available techniques for liver tumor segmentation

Title	Method	Test Dataset	Method Result
Lin et al. [85]	Lucas-Kanade Algorithm	LiTs	80% (Avg. Segmentation Accuracy)
Zhang et al. [80]	2D-Slice Based U-Net + 3D Patch-Based CNN	LiTs	96.31% (DSC)
Xi et al. [81]	Two Cascading U-ResNets	LiTs + 3DIRCADb	94.9% (DSC)
Jiang et al. [87]	AHC	3DIRCADb + Clinical Dataset (117 cases)	0.62 ± 0.07 (DSC)
Seo et. al. [88]	Modified U-Net (mU-Net)	LiTs	89.72% (DSC)
Vivanti et. al. [89]	CNN	Manual Dataset (67 Tumor Scans)	16.05% (VOE)
Bai et al. [82]	3D MCG-FRN + ACM	3DIRCADb	0.67 (DSC)

predict whether or not extra-hepatic arteries augment tumors. All of the feeding arteries of a tumor, including any possible extra-hepatic arteries, are examined by angiographic images. TACE can treat liver tumors larger than 5 cm, but it may take 2 or 3 treatments [93]. Furthermore, CT scans must be taken 2 to 3 months after TACE to ensure treatment success [94]. Liver tumor segmentation techniques may provide crucial secondary information to monitor treatment progress and success.

PVE increases the volume of the Future Liver Remnant (FLR) for extended hepatectomy by embolizing a portal vein region, resulting in hepatic regeneration. PVE is performed when a large FLR is required for a post-operative liver recovery as determined by liver volumetry. Often this is due to the extent of the liver resection or the underlying liver disease [95]. Segmentation and volumetry of CT scans provide crucial pre-requisite information for the success of PVE. SBRT has been used in the treatment of primary HCC (with slight metastases) that require radiation in less than 25% [96].

RFA and MWA use image guidance intervention, where a probe is utilized for heat generation, resulting in coagulation necrosis to destroy the cancer cells [90]. PEI is performed for tumors less than or equal to 3 cm. PEI injects highly concentrated alcohol using a thin needle, leading to complete ablation of up to 70% of lesions. Ultrasound guidance is generally utilized for performing ablation, and the treatment requires 4-6 sessions. Real-time segmentation of the captured images can assist the radiologist in carrying out the procedure and improve treatment success.

4.1 Tumor Segmentation and Volumetry

FLR, Total Liver Volume (TLV), and liver burden are all important volumetry metrics needed for radiological intervention treatment planning [97]. CT or MRI segmentation and volumetry can provide crucial secondary information for radiologists to carry out radiological interventions. Advancements in radiation therapy procedures and segmentation technology effectively reduce GI toxicity (i.e., toxicity in small intestine and stomach) and spinal cord toxicity caused by inadequate/inaccurate dosage determination, leading to more liver dysfunction. For example, radiation-induced liver disease can result from inadequate treatment SBRT

Table 3 Segmentation methods for radiation therapy (RT) in liver treatment

Title	Method	Test Dataset	Method Result
Li et al. [99]	Adaboosted classifiers	LiTs	0.015 (RMSE)
Wang et al. [100]	Adaptive Mesh Expansion Model (AMEM)	LiTs	0.016 (RMSE)
Wu et al. [11]	Supervoxel based graph cuts	LiTs	0.016 (RMSE)

planning [98]. Having an accurate liver tumor segmentation enables the secure computation of chemical and radio dosages. Therefore, accuracy and precision are essential considerations for segmentation methods for these applications.

Deep-learning approaches that involve cascaded U-Net derived architectures are accurate performance and are recommended for radiological interventions [3]. The top three ranked methods according to tumor burden estimation includes works of Li et al., which employs Adaboosted to identify tumor boundaries [99], Wang et al.'s adaptive mesh expansion model (AMEM) for segmentation of liver [100], and Wu et al.'s supervoxel-based graph cuts [11]. These methods accurately predict the tumor volume with a root mean square error (RMSE) in tumor burden of 0.0150, 0.0160, and 0.0160, respectively [3]. In general, these methods also achieve good area-overlap with the ground truth with dice scores of 0.9650, 0.9590, and 0.962, respectively [3]. Despite the state-of-the-art performance, automatically segmenting small liver tumors remains a difficult task. This limitation suggests that future improvements can be made by investigating methods that segment a broad spectrum of liver tumors. Table 3 summarizes the methods, datasets, and performance metrics, for radiation therapy of the liver.

5 Discussion

The diagnosis and treatment planning of hepatic diseases (like HCC) are decided by the location and spread of liver lesions, the severity of underlying liver dysfunction, availability of medical technology, and expertise. The choice of segmentation methods for a particular operation or therapy is determined by the method's robustness, segmentation accuracy and precision, the extent of automation, and generalizability. For this reason, we have categorized the popular segmentation methods based on their clinical utility. The classification allows the clinicians to select effective techniques for varying treatment pathways, subsequently decreasing the complexity of diagnosis and treatment planning and likely improving procedure outcomes. Specifically, we recommend segmentation methods for liver transplantation, resection, and radiological intervention. Next, we subclassify the papers based on their aim to address automation, volume estimation, and segmentation. For instance, models presented by Alirri et al. [73] and Vorontsov et al. [75] use FCNs to achieve high accuracy and precision results for liver segmentation. Wang et al. [71] propose a two-dimensional U-Net CNN to estimate liver volumes in CT scans. Vivanti et al. [89] present a automatic method for liver and tumors segmentation using deep CNNs.

Over the past few decades, a significant articles have been published to assist the treatment of hepatic diseases (e.g., liver cancer) by proposing novel methods for liver and tumor segmentation in CT and MRI scans. However, medical image

Figure 6 Technical and clinical challenges facing diagnosis and treatment of HCC

segmentation of the liver still faces unaddressed challenges in technical and clinical settings. Figure 6 summarizes the clinical and technical challenges for HCC and liver segmentation algorithms, respectively. Some technical challenges still lack unified benchmarks, reliance on conventional segmentation methods, and usage of first-generation deep learning architectures. Similarly, clinical challenges include shortage of compatible liver donors, lengthy diagnosis and treatment planning periods, limited understanding of tumor shapes and biology.

5.1 Outlook on Technical Challenges

Comparative studies are critical for discovering state-of-the-art treatment methods for any disease. Many such studies aim to determine the ideal technique for liver segmentation but rely on private, or custom datasets [89], [71], [72], [74], [75]. The datasets often have built-in biases (e.g., subjects diagnosed with a particular disease) and do not cover more than a few hundred patients. Furthermore, the comparison of these works in literature is challenging due to their differing performance measure metrics. This variability in research due to custom datasets and varying performance metrics add to the challenge of evaluating different methods based on their claimed results, reinforcing the need to create benchmark datasets.

Benchmark datasets and their evaluation using standard metrics are crucial for fair quantitative comparison of the existing techniques. It should be ensured that the datasets satisfy both technical and clinical standards. A reliable technical benchmark should contain samples from many patients (with minimal bias) and several scans volumes for each patient. From a clinical standpoint, multiple experts should medically validate and annotate datasets to account for subjective annotation differences. These guidelines would allow the creation of well-rounded datasets that could aid both technical and clinical challenges facing liver and tumor segmentation.

Robust and accurate segmentation methods are a necessity for clinicians performing Liver transplant or Liver resection [101]. After evaluating several works, we have observed that the conventional methods and first-generation neural networks (like plain U-nets and FCNs) have undesirable sensitivity to segment the liver and its tumors, high computation time, over-segmentation, and lack of generalizability. These shortcomings highlight the need for sophisticated deep learning models with optimizations to help reduce the networks' parameter count, memory footprint, and computation time. To address generalizability and enhance performance, we propose exploring two main avenues in supervised deep learning. First,

employing transfer learning and larger benchmark datasets to tackle overfitting in neural networks. Second, using preprocessing techniques on the datasets to enhance anatomical boundaries and contrast of the images. The preprocessing in CT images is critical due to image noise, poor contrast, and organs with overlapping boundaries. Researchers have utilized conventional denoising algorithms for enhancing CT images. However, new deep learning-based architectures that could simultaneously denoise and segment CT images will be an asset for clinicians to diagnose and treat HCC.

5.2 Outlook on Clinical Challenges

RFA has shown promising results in treating HCC and metastatic diseases such as colorectal cancer (CRC) [102]. However, the current use of RFA is limited to treating livers with inadequate residual functionality and inoperable liver tumors due to their distribution, co-morbidity, [103], [104]. This limited use of RFA is primarily due to the high chance of post-treatment complications. Specifically, RFA may cause liver failure, biliary tract damage, and local tumor relapse [105]. Furthermore, the clinical and technical challenges like insufficient ablation of tumors due to constraints of ablation needles, cooling of tissue by the adjacent blood vessels, large tumor mass, and tumors in the surroundings of heat-sensitive organs adds complexity to the RFA procedure [105]. Nevertheless, we think that RFA will soon promote its clinical standing in treating advanced-stage liver tumors, primarily because of its potential to be used with multi-model imaging modalities.

The tumor location and the affected liver segment determine the nature of the radiological intervention and the prescribed segmentation method. It is recommended to use graph cut and gradient vector flow methods instead of active contour segmentation when the tumor is near the surface. This suggestion is because the active contours can easily stream into the neighboring organs and cause over-segmentation, while gradient vector flow methods have demonstrated effective performance even for broken edges and subjective contours [15]. Furthermore, the liver segment location is vital in radiological interventions, because it can affect the dose and dose constraints in treatment planning [96]. For example, if the tumor is located in the caudate lobe, necessary safety precautions should be taken for positioning accuracy and quality assurance to avoid harming the gastrointestinal track [96]. A high degree of accuracy in target delineation and the use of image-guided radiotherapy (IGRT) can provide tighter margins that will minimize induced toxicity. Therefore, it is also recommended to segment the patient's liver according to the Chouinard classification to recognize the risks associated with every segment. For future work, liver sub-segmentation is crucial and can improve the success of radiological interventions and prevent harm to healthy portions of liver.

Recurrence of HCC after resection is a frequent postoperative complication [106]. There is a difference in opinion among clinicians on the precise chance for recurrence after partial or complete resection. Some papers claim that over 50-80% of patients following resection develop recurrences (over the first two years) [107], [108], while others claim that only over 20% of patients are at the risk of developing tumor relapse [106]. Nevertheless, studies emphasize mandatory postoperative surveillance and regular screening [109]. Several key medical indicators (like the presence of

microscopic venous invasion, slow growth of small and inactive tumors) are signs for HCC recurrence [110]. It may be noted that the detection of tumor relapse relies heavily on the postoperative imaging modality and segmentation tools. Thus, accurate and precise segmentation tools are required to detect minute lesions for early diagnosis of recurrent HCC. Models proposed by Alirri *et al.* [73], Wang *et al.* [71], and Vorontsov *et al.* [75] are well-suited for this task. Moreover, a combination of precise segmentation models with other clinical treatment methods like nucleic acid analogs and interferon (IFN) [111] can potentially become a robust curative option for HCC.

It is realized in clinical practice that RFA, liver resection, and transplantation are the possible remedying measures for treating HCC and most other hepatic diseases. One critical goal of future clinical work should be to evaluate a combination of surgical and radiological interventions. Targeting numerous pathways in the HCC cascade with a variety of treatments can help in accomplishing personalized care aimed to improve overall survival [112]. Clinicians hope that combination therapies would have higher treatment efficacy and efficiency. Some promising compound treatment methods blend direct cytotoxicity from chemotherapeutic agents and ischemia from selective embolization to cause tumor necrosis. In addition, embolization results in reducing washout and systemic chemotherapy toxicity [113].

In addition to the patient's clinical history, the diagnosis of HCC relies on multiple technical (such as the choice of contrast, imaging modality, etc.) and pathological (liver heterogeneity, liver diseases, tumor size, and intensity) factors [16, 17, 19]. Due to this, the optimum course of treatment depends on many contextual factors and differs from patient to patient. Currently, well-established clinical guidelines and protocols attempt to account for these contextual factors to assist treatment decisions. They oversee detection of small lesions and classification of benign (regenerative nodule) or pre-malignant nodules from HCC [18]. Our current work aims to supplement these established clinical guidelines. The work in this manuscript is intended as a guiding adjunct for essential segmentation methods in different clinical pathways for the treatment of HCC. Our work is not without its limitations, though, as 1) it does not try to overcome the existing challenges in segmentation methods, and 2) imaging modalities due to heterogeneity in liver texture. Nevertheless, we strive to establish a knowledge base of segmentation methods to serve as an adjunct to an existing clinical decision and expedite the segmentation tool selection.

6 Conclusion

This paper reviews a plethora of state-of-the-art segmentation techniques and classifies them among three types of clinical intervention: Complete Resection, Partial Resection, and Radiological Interventions. This classification is based on critical technical requirements or expectations from the algorithm to provide the best possible segmentation needed by the surgeon for a specific type of intervention. For instance, in a specific type of intervention, the clinician might be more interested in the liver volume, tumor location, and in some other instances, they are only interested in the tumor size only. Considering the applications (Preoperative Planning or Image-guided Intervention) have their requirements in terms of Accuracy,

Automation, and Time-cost, we have provided a table summarizing the methods matching to their most appropriate corresponding clinical applications and types of intervention, where they are expected to perform the best. We have observed that no single algorithm provides a fit-all solution. Therefore, we believe that the classification could help the clinicians in choosing the appropriate algorithms on a case-by-case basis ensuring optimized healthcare [114, 115].

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Abbreviations

magnetic resonance imaging (MRI), computed tomography (CT), World Health Organization (WHO), hepatocellular carcinoma (HCC), computer-aided diagnoses (CAD), Response Evaluation Criteria in Solid Tumor (RECIST), Radiofrequency Ablation (RFA), Percutaneous Ethanol Injection (PEI), Transcatheter Arterial Chemoembolization (TACE), Tumor, Node, Metastasis (TNM), Barcelona staging classification (BCLC), Cancer of the Liver Italian Program (CLIP), Colorectal Liver Metastases (CLMs), Dice Similarity Coefficient (DSC), convolutional neural network (CNN), volumetric overlap error (VOE), Liver Tumor Segmentation (LiTS), multi-scale candidate generation method (MCG), active contour model (ACM), probabilistic neural network (PNN), Hybridized Fully Convolutional Neural Network (HFCNN), modified U-Net (mU-Net), Attention Hybrid Connection (AHC), average symmetric surface distance (ASSD), Stereotactic Body Radiation Therapy (SBRT), Transarterial Radioembolization (TARE), and portal vein embolization (PVE), microwave thermal ablation (MWA), Future Liver Remnant (FLR), Total Liver Volume (TLV), adaptive mesh expansion model (AMEM), root mean square error (RMSE), image-guided radiotherapy (IGRT), interferon (IFN).

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

Not applicable

Competing interests

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Authors' contributions

Mohammed Yusuf Ansari: Literature Review, Surgical Intervention, Radiological Interventions Clinical Perspectives, Manuscript Planning, Manuscript Preparation, Manuscript Review, Future Directions.

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References

1. Organization, W.H., et al.: Who report on cancer: setting priorities, investing wisely and providing care for all (2020)
2. Campadelli, P., Casiraghi, E., Esposito, A.: Liver segmentation from computed tomography scans: a survey and a new algorithm. *Artificial intelligence in medicine* **45**(2-3), 185–196 (2009)
3. Bilic, P., Christ, P.F., Vorontsov, E., Chlebus, G., Chen, H., Dou, Q., Fu, C.-W., Han, X., Heng, P.-A., Hesser, J., et al.: The liver tumor segmentation benchmark (lits). *arXiv preprint arXiv:1901.04056* (2019)
4. al., K.S.A.: Radiotherapy plus chemotherapy with or without surgical resection for stage iii non-small-cell lung cancer: a phase iii randomised controlled trial. *Lancet* **374**(9687), 379–386 (2009)
5. al., S.R.: Percutaneous rf interstitial thermal ablation in the treatment of hepatic cancer. *Am. J. Roentgenol.* **167**(3), 759–768 (1996)
6. al., T.L.: Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* **197**(1), 101–108 (1995)
7. Yamada, R., Sato, M., Kawabata, M., Nakatsuka, H., Nakamura, K., Takashima, S.: Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* **148**(2), 397–401 (1983)
8. Moghbel, M., Mashohor, S., Mahmud, R., Saripan, M.I.B.: Review of liver segmentation and computer assisted detection/diagnosis methods in computed tomography. *Artif. Intell. Rev* **50**(4), 497–537 (2018)
9. Thakur, P., Madaan, N.: A survey of image segmentation techniques. *International Journal of Research in Computer Applications and Robotics* **2**(4), 158–165 (2014)
10. Guo, X., Schwartz, L.H., Zhao, B.: Automatic liver segmentation by integrating fully convolutional networks into active contour models. *Medical physics* **46**(10), 4455–4469 (2019)
11. Wu, W., Zhou, Z., Wu, S., Zhang, Y.: Automatic liver segmentation on volumetric ct images using supervoxel-based graph cuts. In: *Comput. Math. Methods Med*, vol. 2016 (2016)
12. Zhang, X., Tian, J., Deng, K., Wu, Y., Li, X.: Automatic liver segmentation using a statistical shape model with optimal surface detection. In: *IEEE Trans*, pp. 2622–2626. *Biomed. Eng*, vol. 57, no. 10 (2010)
13. Luo, S., Hu, Q., He, X., Li, J., Jin, J.S., Park, M.: Automatic liver parenchyma segmentation from abdominal ct images using support vector machines. In: *2009 ICME International Conference on Complex Medical Engineering*, pp. 1–5 (2009). IEEE
14. Hosny, A., Parmar, C., Quackenbush, J., Schwartz, L.H., Aerts, H.J.W.L., Edu, H.H.: Artificial intelligence in radiology. *Nat Rev Cancer* **18**(8), 500–510 (2018)
15. Khan, N., Ahmed, I., Kiran, M., Adnan, A.: Overview of technical elements of liver segmentation. *Int. J. Adv* **7**(12), 271–278 (2016)
16. Liver, E.A.F.T.S.O.T., et al.: Easl–eortc clinical practice guidelines: management of hepatocellular carcinoma. *Journal of hepatology* **56**(4), 908–943 (2012)
17. Ye, S., Chen, R.: Comments on management of hepatocellular carcinoma: an update. *Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology* **19**(4), 251–253 (2011)
18. Rhee, H., Kim, M., Park, M., Kim, K.: Differentiation of early hepatocellular carcinoma from benign hepatocellular nodules on gadoteric acid-enhanced mri. *The British journal of radiology* **85**(1018), 837–844 (2012)
19. Reynolds, A.R., Furlan, A., Fetzer, D.T., Sasatomi, E., Borhani, A.A., Heller, M.T., Tublin, M.E.: Infiltrative hepatocellular carcinoma: what radiologists need to know. *Radiographics* **35**(2), 371–386 (2015)
20. Trivizakis, E., Manikis, G.C., Nikiforaki, K., Drevelegas, K., Constantinides, M., Drevelegas, A., Marias, K.: Extending 2-d convolutional neural networks to 3-d for advancing deep learning cancer classification with application to mri liver tumor differentiation. *IEEE journal of biomedical and health informatics* **23**(3), 923–930 (2018)
21. Chen, E.-L., Chung, P.-C., Chen, C.-L., Tsai, H.-M., Chang, C.-I.: An automatic diagnostic system for ct liver image classification. *IEEE transactions on biomedical engineering* **45**(6), 783–794 (1998)
22. Balagourouchetty, L., Pragatheeswaran, J.K., Pottakkat, B., Ramkumar, G.: Googlenet-based ensemble fcnet classifier for focal liver lesion diagnosis. *IEEE journal of biomedical and health informatics* **24**(6), 1686–1694 (2019)
23. Dakua, S.P.: Use of chaos concept in medical image segmentation. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization* **1**(1), 28–36 (2013)
24. Dakua, S.P., Sahambi, J.S.: Automatic left ventricular contour extraction from cardiac magnetic resonance images using cantilever beam and random walk approach. *Cardiovascular Engineering* **10**(1), 30–43 (2010)
25. Dakua, S.P.: Performance divergence with data discrepancy: a review. *Artificial Intelligence Review* **40**(4), 429–455 (2013)
26. Dakua, S.P., Sahambi, J.S.: Detection of left ventricular myocardial contours from ischemic cardiac mr images. *IETE Journal of Research* **57**(4), 372–384 (2011)
27. Dakua, S.P.: Towards left ventricle segmentation from magnetic resonance images. *IEEE Sensors Journal* **17**(18), 5971–5981 (2017). doi:10.1109/JSEN.2017.2736641
28. Kennedy, D.N., Filipek, P.A., Caviness, V.S.: Anatomic segmentation and volumetric calculations in nuclear magnetic resonance imaging. In: *IEEE Trans*, pp. 1–7. *Med. Imaging*, vol. 8, no. 1 (1989)
29. Grady, L.: Random walks for image segmentation. *IEEE Trans. Pattern Anal* **28**(11), 1768–1783 (2006)
30. Dakua, S.P., Sahambi, J.S.: Weighting function in random walk based left ventricle segmentation. In: *2011 18th IEEE International Conference on Image Processing*, pp. 2133–2136 (2011). doi:10.1109/ICIP.2011.6116031
31. Ruan, S., Moretti, B., Fadili, J., Bloyet, D.: Fuzzy Markovian segmentation in application of magnetic resonance images. *Comput. Vis* **85**(1), 54–69 (2002)
32. Patwardhan, S.V., Dai, S., Dhawan, A.P.: Multi-spectral image analysis and classification of melanoma using fuzzy membership based partitions. In: *Comput*, pp. 287–296. *Med. Imaging Graph*, vol. 29, no. 4 (2005)
33. Nuzillard, D., Lazar, C.: Partitional clustering techniques for multispectral image segmentation. *J. Comput. -*

- JCP 2, 1–8 (2007)
34. AlZu'bi, S., Islam, N., Abbod, M.: Multiresolution analysis using wavelet, ridgelet, and curvelet transforms for medical image segmentation. In: Biomed, J. (ed.) *Int. Imaging*, vol. 2011, p. 136034 (2011)
 35. Mharib, A., Ramli, A., Mashohor, S., Mahmud, R.: Survey on liver ct image segmentation methods. *Artif. Intell. Rev* **37**, 83–95 (2012)
 36. al., M.G.L.: Tumor burden analysis on computed tomography by automated liver and tumor segmentation. In: *IEEE Trans.*, pp. 1965–1976. *Med. Imaging*, vol. 31, no. 10 (2012)
 37. al., S.C.: Fully automatic segmentations of liver and hepatic tumors from 3-d computed tomography abdominal images: Comparative evaluation of two automatic methods. *IEEE Sensors* **12**(3), 464–473 (2012)
 38. Ji, H., He, J., Yang, X., Deklerck, R., Cornelis, J.: Acm-based automatic liver segmentation from 3-d ct images by combining multiple atlases and improved mean-shift techniques. In: Biomed, I.J. (ed.) *Heal*, pp. 690–698. *informatics*, vol. 17 (2013)
 39. Li, G., Chen, X., Shi, F., Zhu, W., Tian, J., Xiang, D.: Automatic liver segmentation based on shape constraints and deformable graph cut in ct images. *IEEE Trans. Image Process* **24** (2015)
 40. al., Z.Y.: Atlas-based liver segmentation and hepatic fat-fraction assessment for clinical trials. In: *Comput.*, pp. 80–92. *Med. Imaging Graph*, vol. 41 (2015)
 41. al., X.W.: Liver segmentation from ct images using a sparse priori statistical shape model (sp-ssm). *PLoS One* **12**, 10 (2017)
 42. al., Y.S.: Vascular active contour for vessel tree segmentation. In: *IEEE Trans.*, pp. 1023–1032. *Biomed. Eng.*, vol. 58, no. 4 (2011)
 43. Chartrand, G., Cresson, T., Chav, R., Gotra, A., Tang, A., Guise, J.A.D.: Liver segmentation on ct and mr using laplacian mesh optimization. In: *IEEE Trans.*, pp. 2110–2121. *Biomed. Eng.*, vol. 64, no. 9 (2017)
 44. Zhang, Q., Fan, Y., Wan, J., Liu, Y.: An efficient and clinical-oriented 3d liver segmentation method. *IEEE Access* **1** (2017)
 45. al., C.L.: A likelihood and local constraint level set model for liver tumor segmentation from ct volumes. In: *IEEE Trans.*, pp. 2967–2977. *Biomed. Eng.*, vol. 60 (2013)
 46. Peng, J., Wang, Y., Kong, D.: Liver segmentation with constrained convex variational model. *Pattern Recognit. Lett.* **43**, 81–88 (2014)
 47. Foruzan, A.H., Chen, Y.-W.: Improved segmentation of low-contrast lesions using sigmoid edge model. *Int. J. Comput. Assist* **11** (2015)
 48. Seo, K.-S.: Automatic hepatic tumor segmentation using composite hypotheses. in *International Conference Image Analysis and Recognition* pp. 992–929 (2005)
 49. al., B.Z.: Shape-constraint region growing for delineation of hepatic metastases on contrast-enhanced computed tomograph scans. *Invest. Radiol.* **41**, 753–762 (2006)
 50. al., Y.S.: 3d multi-scale line filter for segmentation and visualization of curvilinear structures in medical images. *Lecture Notes in Computer Science*, 213–222 (2006)
 51. Hassouna, M.S., Farag, A.A.: Variational curve skeletons using gradient vector flow. *IEEE Trans. Pattern Anal* **31**(12), 2257–2274 (2009)
 52. Mahr, A., Levegrun, S., Bahner, M.L., Kress, J., Zuna, I., Schlegel, W.: Usability of semiautomatic segmentation algorithms for tumor volume determination. *Invest. Radiol.* **34**(2), 143–150 (1999)
 53. Kirbas, C., Quek, F.: A review of vessel extraction techniques and algorithms. *ACM Comput. Surv.* **36** (2002)
 54. Wang, J., Hu, M., Zhou, M., Sun, L., Li, Q.: Segmentation of pathological features of rat bile duct carcinoma from hyperspectral images. In: *2018 11th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI)*, pp. 1–5 (2018). *IEEE*
 55. Ronneberger, O., Fischer, P., Brox, T.: U-net: Convolutional networks for biomedical image segmentation. in *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015*, 234–241 (2015)
 56. Novikov, A.A., Major, D., Wimmer, M., Lenis, D., Buhler, K.: Deep sequential segmentation of organs in volumetric medical scans. In: *IEEE Trans.*, pp. 1207–1215. *Med. Imaging*, vol. 38, no. 5 (2019)
 57. Yu, S.J.: A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. *Clinical and molecular hepatology* **22**(1), 7 (2016)
 58. Pererrone, F., Daniele, B., Gaeta, G.B., Pignata, S., Gallo, C., Izzo, F., Cuomo, O., Capuano, G., Ruggiero, G., Mazzanti, R., et al.: Prospective validation of the clip score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology* **31**(4), 840–845 (2000)
 59. Yau, T., Tang, V.Y., Yao, T.-J., Fan, S.-T., Lo, C.-M., Poon, R.T.: Development of hong kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* **146**(7), 1691–1700 (2014)
 60. Okuda, K., Ohtsuki, T., Obata, H., Tomimatsu, M., Okazaki, N., Hasegawa, H., Nakajima, Y., Ohnishi, K.: Natural history of hepatocellular carcinoma and prognosis in relation to treatment study of 850 patients. *Cancer* **56**(4), 918–928 (1985)
 61. Llovet, J.M., Brú, C., Bruix, J.: Prognosis of hepatocellular carcinoma: the bclc staging classification. In: *Seminars in Liver Disease*, vol. 19, pp. 329–338 (1999). © 1999 by Thieme Medical Publishers, Inc.
 62. Vauthey, J.-N., Ribero, D., Abdalla, E.K., Jonas, S., Bharat, A., Schumacher, G., Lerut, J., Chapman, W.C., Hemming, A.W., Neuhaus, P.: Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. *Journal of the American College of Surgeons* **204**(5), 1016–1027 (2007)
 63. Kudo, M., Chung, H., Osaki, Y.: Prognostic staging system for hepatocellular carcinoma (clip score): its value and limitations, and a proposal for a new staging system, the japan integrated staging score (jis score). *Journal of gastroenterology* **38**(3), 207–215 (2003)
 64. al., Y.D.: Liver resection in selected patients with metastatic breast cancer: a single-centre analysis and review of literature. *J. Cancer Res* **139**(8), 1317–1325 (2013)
 65. Zhou, L., Rui, J.-A., Wang, S.-B., Chen, S.-G., Qu, Q.: Risk factors of poor prognosis and portal vein tumor thrombosis after curative resection of solitary hepatocellular carcinoma. *Hepatobiliary Pancreat. Dis* **12**(1),

- 68–73 (2013)
66. al., T.L.: Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* **47**(1), 82–89 (2008)
 67. al., A.A.: Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. *J. Gastrointest. Surg.* **17**(1), 66–77 (2013)
 68. Jia, C.-K., Weng, J., Chen, Y.-K., Fu, Y.: Anatomic resection of liver segments 6–8 for hepatocellular carcinoma. *World J. Gastroenterol.* **20**(15), 4433–4439 (2014)
 69. Health, U.: Living donor liver transplant: The facts. UCSF Health (2021). <https://www.ucsfhealth.org/education/living-donor-liver-transplant-the-facts>
 70. Lu, F., Wu, F., Hu, P., Peng, Z., Kong, D.: Automatic 3d liver location and segmentation via convolutional neural network and graph cut. *International journal of computer assisted radiology and surgery* **12**(2), 171–182 (2017)
 71. Wang, K., Mamidipalli, A., Retson, T., Bahrami, N., Hasenstab, K., Blansit, K., Bass, E., Delgado, T., Cunha, G., Middleton, M.S., et al.: Automated ct and mri liver segmentation and biometry using a generalized convolutional neural network. *Radiology: Artificial Intelligence* **1**(2), 180022 (2019)
 72. Nakayama, Y., Li, Q., Katsuragawa, S., Ikeda, R., Hiai, Y., Awai, K., Kusunoki, S., Yamashita, Y., Okajima, H., Inomata, Y., et al.: Automated hepatic volumetry for living related liver transplantation at multisection ct. *Radiology* **240**(3), 743–748 (2006)
 73. Alir, O.I.: Deep learning and level set approach for liver and tumor segmentation from ct scans. *Journal of Applied Clinical Medical Physics* **21**(10), 200–209 (2020)
 74. Yasaka, K., Akai, H., Abe, O., Kiryu, S.: Deep learning with convolutional neural network for differentiation of liver masses at dynamic contrast-enhanced ct: a preliminary study. *Radiology* **286**(3), 887–896 (2018)
 75. Vorontsov, E., Cerny, M., Régner, P., Di Jorio, L., Pal, C.J., Lapointe, R., Vandenbroucke-Menu, F., Turcotte, S., Kadoury, S., Tang, A.: Deep learning for automated segmentation of liver lesions at ct in patients with colorectal cancer liver metastases. *Radiology: Artificial Intelligence* **1**(2), 180014 (2019)
 76. Nordlinger, B., Guiguet, M., Vaillant, J.-C., Balladur, P., Boudjema, K., Bachellier, P., Jaeck, D.: Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **77**(7), 1254–1262 (1996)
 77. Jagannath, S., Velasquez, W.S., Tucker, S.L., Fuller, L.M., McLaughlin, P.W., Manning, J.T., North, L.B., Cabanillas, F.C.: Tumor burden assessment and its implication for a prognostic model in advanced diffuse large-cell lymphoma. *Journal of Clinical Oncology* **4**(6), 859–865 (1986)
 78. Blachier, M., Leleu, H., Peck-Radosavljevic, M., Valla, D.-C., Roudot-Thoraval, F.: The burden of liver disease in europe: a review of available epidemiological data. *Journal of hepatology* **58**(3), 593–608 (2013)
 79. Li, X., Chen, H., Qi, X., Dou, Q., Fu, C.W., Heng, P.A.: H-denseunet: Hybrid densely connected unet for liver and tumor segmentation from ct volumes. In: *IEEE Trans*, pp. 2663–2674. *Med. Imaging*, vol. 37, no. 12 (2018)
 80. Zhang, Y., Jiang, B., Wu, J., Ji, D., Liu, Y., Chen, Y., Wu, E.X., Tang, X.: Deep learning initialized and gradient enhanced level-set based segmentation for liver tumor from ct images. *IEEE Access* **8**, 76056–76068 (2020)
 81. Xi, X.-F., Wang, L., Sheng, V.S., Cui, Z., Fu, B., Hu, F.: Cascade u-resnets for simultaneous liver and lesion segmentation. *IEEE Access* **8**, 68944–68952 (2020)
 82. Bai, Z., Jiang, H., Li, S., Yao, Y.D.: Liver tumor segmentation based on multi-scale candidate generation and fractal residual network. *IEEE Access* **7**, 82122–82133 (2019)
 83. Dong, X., Zhou, Y., Wang, L., Peng, J., Lou, Y., Fan, Y.: Liver cancer detection using hybridized fully convolutional neural network based on deep learning framework. *IEEE Access* **8**, 129889–129898 (2020)
 84. Zhang, X., Tian, J., Xiang, D., Li, X., Deng, K.: Interactive liver tumor segmentation from ct scans using support vector classification with watershed. In: *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp. 6005–6008 (2011). IEEE
 85. Lin, L., Yang, W., Li, C., Tang, J., Cao, X.: Inference with collaborative model for interactive tumor segmentation in medical image sequences. *IEEE transactions on cybernetics* **46**(12), 2796–2809 (2015)
 86. Akhtar, Y., Dakua, S.P., Abdalla, A., Aboumarzouk, O.M., Ansari, M.Y., Abinshed, J., Elakkad, M.S.M., Al-Ansari, A.: Risk assessment of computer-aided diagnostic software for hepatic resection. *IEEE Transactions on Radiation and Plasma Medical Sciences* (2021)
 87. Jiang, H., Shi, T., Bai, Z., Huang, L.: Ahcnet: An application of attention mechanism and hybrid connection for liver tumor segmentation in ct volumes. *IEEE Access* **7**, 24898–24909 (2019)
 88. Seo, H., Huang, C., Bassenne, M., Xiao, R., Xing, L.: Modified u-net (mu-net) with incorporation of object-dependent high level features for improved liver and liver-tumor segmentation in ct images. *IEEE transactions on medical imaging* **39**(5), 1316–1325 (2019)
 89. Vivanti, R., Ephrat, A., Joskowicz, L., Karaaslan, O., Lev-Cohain, N., Sosna, J.: Automatic liver tumor segmentation in follow-up ct studies using convolutional neural networks. In: *Proc. Patch-Based Methods in Medical Image Processing Workshop*, vol. 2, p. 2 (2015)
 90. al., P.R.-M.: Other non-surgical treatments for liver cancer. *Reports Pract. Oncol. Radiother.* **22**(2), 181–192 (2017)
 91. Revel-Mouroz, P., Ota, P., Jaffro, M., Petermann, A., Meyrignac, O., Rabinel, P., Mokrane, F.-Z.: Other non-surgical treatments for liver cancer. *Reports of Practical Oncology and Radiotherapy* **22**(2), 181–192 (2017)
 92. al., R.S.: Transarterial radioembolization for hepatocellular carcinoma: An update and perspectives. *World J. Gastroenterol.* **21**(21), 6518–6525 (2015)
 93. Shin, S.W.: The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. *Korean J. Radiol.* **10**(5), 425–434 (2009)

94. Xia, J., Ren, Z., Ye, S., Sharma, D., Lin, Z., Gan, Y., Chen, Y., Ge, N., Ma, Z., Wu, Z., et al.: Study of severe and rare complications of transarterial chemoembolization (tace) for liver cancer. *European journal of radiology* **59**(3), 407–412 (2006)
95. al., A.G.: Liver segmentation: indications, techniques and future directions. *Insights Imaging* **8**(4), 377–392 (2017)
96. Wang, P.M., Chung, N.N., Hsu, W.C., Chang, F.L., Jang, C.J., Scorsetti, M.: Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve. *Reports Pract. Oncol. Radiother.* **20**(6), 417–424 (2015)
97. al., A.G.: Liver segmentation: a primer for interventional radiologists. *J. Vasc. Interv. Radiol.* **27**, 3 (2016)
98. al., M.-S.C.: High-dose iodized oil transcatheter arterial chemoembolization for patients with large hepatocellular carcinoma. *World J. Gastroenterol.* **8**(1), 74–78 (2002)
99. Li, Y., Hara, S., Shimura, K.: A machine learning approach for locating boundaries of liver tumors in ct images. In: 18th International Conference on Pattern Recognition (ICPR'06) Vol, pp. 400–403. 1, ??? (2006)
100. Wang, X., Yang, J., Ai, D., Zheng, Y., Tang, S., Wang, Y.: Adaptive mesh expansion model (amem) for liver segmentation from ct image. *PLoS One* **10**, 3 (2015)
101. Ambrogne, J.A.: Reduced-risk drinking as a treatment goal: what clinicians need to know. *Journal of substance abuse treatment* **22**(1), 45–53 (2002)
102. Künzli, B.M., Abitabile, P., Maurer, C.A.: Radiofrequency ablation of liver tumors: actual limitations and potential solutions in the future. *World journal of hepatology* **3**(1), 8 (2011)
103. McGrane, S., McSweeney, S.E., Maher, M.M.: Which patients will benefit from percutaneous radiofrequency ablation of colorectal liver metastases? critically appraised topic. *Abdominal imaging* **33**(1), 48–53 (2008)
104. Gillams, A., Lees, W.: Radio-frequency ablation of colorectal liver metastases in 167 patients. *European radiology* **14**(12), 2261–2267 (2004)
105. Jansen, M., Van Duijnhoven, F., Van Hillegersberg, R., Rijken, A., Van Coevorden, F., Van Der Sijp, J., Prevoo, W., van Gulik, T.: Adverse effects of radiofrequency ablation of liver tumours in the netherlands. *Journal of British Surgery* **92**(10), 1248–1254 (2005)
106. Lacaze, L., Scotté, M.: Surgical treatment of intra hepatic recurrence of hepatocellular carcinoma. *World journal of hepatology* **7**(13), 1755 (2015)
107. How common is recurrence of hepatocellular carcinoma (HCC)? (2021). <https://www.medscape.com/answers/197319-39257/how-common-is-recurrence-of-hepatocellular-carcinoma-hcc>
108. Kim, R.D., Reed, A.I., Fujita, S., Foley, D.P., Mekeel, K.L., Hemming, A.W.: Consensus and controversy in the management of hepatocellular carcinoma. *Journal of the American College of Surgeons* **205**(1), 108–123 (2007)
109. Min, J.H., Kim, Y.K., Choi, S.-Y., Kang, T.W., Jeong, W.K., Kim, K., Won, H.-J.: Detection of recurrent hepatocellular carcinoma after surgical resection: Non-contrast liver mr imaging with diffusion-weighted imaging versus gadoxetic acid-enhanced mr imaging. *The British journal of radiology* **91**(1090), 20180177 (2018)
110. Poon, R.T.-P., Fan, S.-T., Wong, J.: Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Annals of surgery* **232**(1), 10 (2000)
111. Takami, T., Yamasaki, T., Saeki, I., Matsumoto, T., Suehiro, Y., Sakaida, I.: Supportive therapies for prevention of hepatocellular carcinoma recurrence and preservation of liver function. *World journal of gastroenterology* **22**(32), 7252 (2016)
112. Couri, T., Pillai, A.: Goals and targets for personalized therapy for hcc. *Hepatology international* **13**(2), 125–137 (2019)
113. Bruix, J., Sala, M., Llovet, J.M.: Chemoembolization for hepatocellular carcinoma. *Gastroenterology* **127**(5), 179–188 (2004)
114. Norouzi, A., Rahim, M.S.M., Altameem, A., Saba, T., Rad, A.E., Rehman, A., Uddin, M.: Medical image segmentation methods, algorithms, and applications. *IETE Technical Review* **31**(3), 199–213 (2014)
115. Jayadevappa, D., Srinivas Kumar, S., Murty, D.: Medical image segmentation algorithms using deformable models: a review. *IETE Technical review* **28**(3), 248–255 (2011)