The Egyptian Journal of Hospital Medicine (July 2024) Vol. 96, Page 3045-3049

Screening Methods for Early Hepatic-Cellular Carcinoma as an Essential Part of Surgical Planning and for Follow-up after Surgical Intervention; by 320-d of CT Perfusion vs Triphasic-CT

Mohamed Abdel Aziz Ali Khalil*[1], Adel Mohamed Ismail[2]
[1]Department of General Surgery, Faculty of Medicine, Arish University, Egypt
[2]Department of Surgical Oncology, Ismailia Teaching Oncology Hospital, Ismailia, Egypt
***Corresponding author:** Mohamed Abdel Aziz Ali Khalil, **Mobile:** (+20)01099614514, **E-Mail:** mohamed76aziz@gmail.com

ABSTRACT

Background: Histologically confirmed hepatocellular carcinomas (HCC) account for 90% of allhepatic malignancies and are notoriously fatal. Because of neovascularization, its blood supply isgreater than that of the surrounding hepatic tissue. In order to diagnose HCC early and monitor itsprogress after surgery, a noninvasive technique called CTP, or computed tomography with perfusion imaging, measures the blood flow characteristics of the tumor and compares them to the surrounding tissue.

Objective: To assess if CTP is a useful diagnostic method for identifying HCC for early surgical intervention and post-therapeutic assessment.

Patients and Methods: Screening clinical trial study for patients who had HCC according to inclusion and exclusion criteria. 250 patients were included in the study.

Results: Triphasic yields invisible results lesions were (20%) and visible lesions were (80%) oftriphasic results. Regarding perfusion parameters, patients were (6%) negative and (94%) positive. CT perfusion was more sensitive and was 100% specific in the early detection of HCC lesions for early surgical intervention and also for follow-up after surgery to detect the recurrence if the positive predictive value was high, which means a high percent of true positive results and a small percent of false positive results.

Conclusion: When it comes to evaluating surgical interventional techniques for HCC and making an early diagnosis, CTP is a specialized and secure imaging method.

Keywords: CT perfusion, Hepatocellular carcinoma, Triphasic CT, Surgical intervention.

INTRODUCTION

An increasing number of cases of hepatocellular carcinoma (HCC) are causing alarm, and this cancer is mostly associated with cirrhosis and chronic liver disease. Surgical procedures, including liver transplantation or removal, are the mainstays of HCC curative treatment. Liver transplant and hepatobiliary surgeons, oncologists, and hepatologists are all part of the interdisciplinary team that must work together to make therapeutic decisions for patients with HCC [(1)].

Because 80% of lesions go undetected at first diagnosis, and because HCCs are hypervascular tumors where the degree of neovascularization is directly correlated to disease progression and prognosis, assessing tumor angiogenesis is crucial for disease management [(1)]. In order to evaluate pathologic angiogenesis, the various traditional CT, MRI, and US imaging techniques are insufficient [(2)]. CTP is a risk-free way to statistically evaluate tumor angiogenesis by utilizing many elements [(3)].

A noninvasive method that quantitatively assesses tumor vascularity using many factors is CT perfusion imaging, which stands for functional computed tomography with perfusion. When it comes to diagnosing and staging HCC, it is an invaluable tool. CT scans can identify liver tumorsand assess their extent, size, and location. If they find anything out of the ordinary with the liver's blood arteries, it could change the way the surgeon approaches the operation [(4,5)].

Patients suffering from untreated HCC have extremely bad outcomes. When dealing with hepatocellular carcinoma during surgery, a CT diagnosis is essential. It helps the surgeon determine the best way to remove the tumor by providing important details about its location and size. When individuals with HCC are diagnosed at an early stage, surgery is often the best course of treatment. Tumor vascularity is an essential trait for staging. Ultrasonography and conventional cross-sectional imaging methods such as MRI and CT may be inadequate for detecting tumor-associated vascularity. During carcinogenesis, a dysplastic lesion transforms into HCC over time. The number of neo-vascularized arteries grows little by little throughout this procedure. A recent advancement in noninvasive imaging techniques is CT perfusion imaging, which may assess tumor vascularity quantitatively and qualitatively [(2)]. Measurement of tissue blood flow utilizing many perfusion metrics in tissues that are both pathogenic and normal is made possible by the functional imaging technique using CT [(6)].

The technique necessitates a series of CT scans taken in rapid succession with very little time between them. Following the delivery of iodinated contrast material, CT perfusion imaging is carried out. As blood carries contrast material to the tissue, an exchange takes place between the interstitial area outside of the blood vessels and the intravascular region within them. Employing a color-coded graphic representation of information obtained from the portal blood flow, hepatic blood flow, and time-density curve may be computed from serial pictures acquired using CT

Received: 20/03/2024
Accepted: 19/05/2024

perfusion imaging, allowing for a detailed examination of liver hemodynamics. Cirrhosis, cancer, infectious liver disease, and other liver conditions have all been the subject of functional evaluations. When comparing normal tissue with malignant tissue, perfusion parameters were drastically different. Vascular neo-angiogenesis results in increased blood flow, volume, and permeability as a result of arterio-venous shunts, enlarged capillary beds, and hyper-permeable vessels [(4)].

The capacity to detect alterations in tumor vasculature and the usefulness of CT perfusion to track the effects of anticancer medications on the tumor vasculature were both discovered. Treatment efficacy can be more accurately measured by observing changes in tumor vascularity. As shown in rectal tumors, HCC, and various cancers of the body, another promising application of CT perfusion imaging is the prediction of antiangiogenic therapy response. According to **Sahani *et al.* [(2)],** CT perfusion imaging can be a helpful tool for evaluating angiogenesis and tumor vascularity in advanced HCC patients. The following variables: tissue blood volume, hepatic perfusion, hepatic perfusion index (HPI), arterial perfusion (AP), portal perfusion (PP), and time to peak (TTP) were all shown to be considerably changed in HCC, according to another research [(5)]**.** Early diagnosis of recurrent cancers after surgery following various Methods guided by imaging for both primary and secondary liver cancers is another crucial function of CT perfusion (CTP) [(7)]**.**

At now, there is a big study underway that evaluated 522 patients with HCC using diffusion-weighted MRI and CTP after they underwent loco regional treatments. In evaluating the efficacy of a treatment, they found that CTP and MRI with diffusion sequence were both moderately useful [(8)]**.**

Objectives: comparing 320-CT perfusion versus triphasic-CT approaches as a new modality in early identification of hepatic-cell carcinoma for early surgical intervention as well as the likelihood of recurrence following surgery. Also to prove that 320 MDCT perfusion methods are useful for the early detection and postoperative monitoring of HCC, in order to evaluate the aftermath of surgery and identify any recurrence.

PATIENTS AND METHODS

The 250 participants in this one-arm clinical trial; all have a history of HCC. The patients' ages varied from forty to seventy-nine, and the study ran from November 2020 through December 2020. In the triphasic CT scan, 30 lesions were evident, while 22 lesions with elevated alpha fetoprotein levels were non-visible.

Inclusion criteria: Patients of both genders over 40 years old, diagnosis of hepatocellular cancer in patients with elevated levels of alpha-fetoprotein, and normal renal function tests.

Exclusion criteria: Pregnant women, children, and nursing mothers, individuals diagnosed with advanced liver disease, individuals known to be allergic to contrast, and conditions affecting the kidneys in patients.

All cases had been subjected to the following: Every patient had to sign a permission form, accurate documentation of demographic information (age, sex, and clinical presentation), review the patient's medical history for any relevant tests, such as those measuring renal function (urea and creatinine) and laboratory analysis (tests for renal function, alpha-fetoprotein, and liver biochemical profile). review of prior histopathological findings (the study's gold standard) and radiological studies (US and triphasic CT) performed on study participants.

Classification of patients: Based on The Child-Pugh various sections make up the score: For total bilirubin, under 34: 1 point, between 34 and 50: 2 points, and over 50: 3 points. Serum albumin levels in milligrams per milliliter are as follows: >35: 1 point, 28–35: 2 points, <28: 3 points. INR<1.7: 1 point, 1.7–2.3: 2 points, >2.3: 3 points. 1 point for no ascites, 2 points for mild ascites, and 3 points for moderate to severe ascites. Regarding hepatic encephalopathy, scores are as follows: 2 points for grades I–II (or suppressed with medication), 3 points for grades III–IV (or refractory), and 1 point for no hepatic encephalopathy. Five to six points are awarded to Class A, seven to nine points to Class B, and ten to fifteen points to Class C [(9)]**.**

CT perfusion Technique: Pre-imaging preparation: The study was conducted in the Radio Diagnosis Department, using (TOSHIBA Aquilion ONE 320-DE MDC, USA). The patients were told to fast for four hours before to the procedure. Right at the base of the skull, an intravenous cannula of 18 or 16 gauge was inserted. A CT scan of the abdomen was performed with the patient in the standard supine and face-down positions. The patient was coached to perform “quiet respiration” during the scan. The quiet respiration should be shallow, even, and as slow as possible. Slow and steady breathing was crucial for accurate results. A wide immobilization strap was applied firmly across the abdomen. This was used to reduce abdominal movement and helped the patient perform “quiet respiration”.

Imaging technique: The patient was laid flat on the CT table, arms relaxed above his head. In order to get patients to cooperate during examinations, we trained them to hold their breath. The antecubital fossa was used to insert an 18-20-gauge catheter into a superficial vein. While the patient's arms were in the scanning position, the injector manually administered saline injections at a high flow rate before administering the

contrast material. In order to guarantee a successful vein cannulation, this was done [2].

Liver perfusion test bolus: We obtained AP and lateral scanograms. Either the middle of T12 or the liver hilum served as the location for the test bolus slice. We established the protocol for injecting the contrast medium, which must have an iodinated concentration of 350 mg/mL in order to comply with CT perfusion. It was imperative that the injection and scanning begin at the same time. The perfusion protocol requires the examination of test bolus pictures in order to establish the moment the contrast agent enters the aorta.

Ethical approval:

The study was authorized by the Ethics Committee of the Ismailia Teaching Oncology Hospital. Each participant received a full summary of the study's aims prior to completing an informed consent form. The Helsinki Declaration was observed at all stages of the study.

Statistical analysis:

Data analysis was done using the Statistical Package for the Social Sciences (SPSS) version 18.0. The numeric data were presented as the average plus or minus the standard deviation (SD). Frequency and percentage were used to express the qualitative data. Test's sensitivity and specificity were calculated.

RESULTS

For this research project, 250 patients were considered. The patients' average age was 46.33 years old, and their ages ranged from 40 to 79 years old. The study group consisted of male patients (58% of the total) and female patients (42%) (Table 1).

Table (1): Distribution of research participants' ages and sex.

Age (years)	No.	%
≤45 years	95	38
>45 years	155	62
Mean ± SD	46.33±5.75	
Sex		
Female	105	42
Male	145	58
Total	250	100.00

The study group included 62% of patients from Child A, as shown in table 2.

Table (2): The distribution of liver functions in the research group based on Child categorization

Liver function	No.	%
Child (A)	93	62
Child (B)	30	20
Child (C)	27	18
Total	250	100.00

The data in table 3 reveal that 60% of the patients in the study group had α-fetoprotein levelsabove 200 ngm/ml.

Table (3): Distribution of alpha fetoprotein in the research study group

Alpha-fetoprotein	No.	%
Less than 200 ngm/ml	100	40.0%
More than 200 ngm/ml	150	60.0%
Total	250	100.0%

Eighty percent of triphasic outcomes were visible lesions as seen in table 4.

Table (4): Comparison between triphasic results and CT perfusion result

Triphasic results	No.	%
Non-visible lesion	30	20.00
Visible lesion	120	80.00
Total	150	100.00

According to the data in table 6, 94% of patients tested positive for perfusion measures.

Table (5): Distribution of perfusion parameters for the research group.

Perfusion parameters	No.	%
Positive	141	94.00
Negative	9	6.00
Total	150	100.00

CT perfusion was more sensitive and it was 100% specific in the early detection of HCC lesions for early surgical intervention and also for follow-up after surgery to detect the likelihood of recurrence (Table 6).

Table (6): Comparing of perfusion parameters and triphasic data for diagnostic purposes of HCC

	Triphasic results	Perfusion parameters
Positive	120	141
Negative	30	9
Sensitivity	80%	94%
Specificity	100%	100%
+PV	45.98%	61.04%
-PV	23.08%	76.72%

DISCUSSION

It is possible to find primary or secondary liver tumors, some of which may be cancerous and others of which may be completely benign. Ultrasonography, magnetic resonance imaging (MRI) and computed tomography (CT) are the current gold standards for diagnosing focal masses; when additional characterization of these masses is required, MRI is preferable. CT perfusion imaging applications in

medicine for liver cancers have been steadily rising since **Miles *et al.*** [6] initially detailed the benefits of CT perfusion imaging for the liver in 1993. Known clinical uses of liver CT perfusion include early tumor diagnosis, early tumor recurrence following therapy, therapeutic efficacy monitoring of various treatment regimens (including antiangiogenic medications), and disease prognosis based on tumor vascularity.

Liver transplantation and partial liver resection are two surgical options for hepatocellular carcinoma (HCC). Strict criteria (one nodule <5 cm or two to three nodules <3 cm without macroscopic vascular invasion), unavailability of grafts, and high treatment costs mean that only about 30% of patients with small HCC are suitable for LT, even though it is the most efficient treatment [10].

As of now, LR is the sole therapeutic option that has the potential to cure big HCC. With a low mortality rate, LR is now a safer option. Improvements in surgical procedures, such as the anterior technique, intermittent clamping, and preoperative portal vein embolization to enhance the volume of liver leftover in the future, and selective preoperative morphological assessment, all contribute to LR's increased safety and tolerance. An excellent prognosis for the patient's long-term health can be attained with anatomical minor HCCs removed in individuals with intact liver function (Child-Pugh grade A). Because of its efficacy in treating minor HCC and the long wait times for LT candidates, LR is once again being considered as a bridge procedure prior to LT [10]. The key to a good prognosis and effective therapy for people with liver tumors is early cancer identification. For instance, while 85% of cirrhotic and HCC patients who fulfilled transplantation criteria survived for 4 years, the 5-year survival percentage for those who had liver transplants because of advanced, symptomatic HCC was fewer than 5% [11].

Based on this disparity, it appears that improved patient outcomes are achieved with early identification of HCC. In a similar vein, patients who do not have metastases may not need harmful treatment if hepatic micrometastasis is not present. However, because micrometastases do not manifest as visible morphologic alterations, conventional CT and MRI scans are insensitive to their presence [11].

In this work, the study population included 250 cirrhotic patients with male predominance (145 males, and 105 females). The majority of cases were diagnosed (by biopsy and pathological results) asmalignant HCC lesions.

In this work, the lesions were about 150 with some patients having (multifocal, multicenter HCC). A comparison with the triphasic results done for the cases revealed that about 20% of lesions (30 lesions) were not visualized (false negative) and about 80% of them (120 lesions) were visualized with the typical criteria of triphasic CT. So far CT perfusion has been found to be of great value in diagnosing hepatic hypervascular lesions with a true positive ratio (94%) and false negative (6%).

This method is easy to use and produces consistent results. Shorter acquisition times, better superior liver imaging with robust natural soft-tissue contrast, and the ability to recreate either thin or thick sections retrospectively from the same raw data are all benefits of this method. Renal insufficiency and hypersensitivity to intravenous contrast are relative contraindications.

Our findings are consistent with previous research on liver malignancies, where researchers wanted to determine CTP's function in therapy response prediction and evaluation. According to **Ippolito *et al.*** [12], CTP can evaluate the vascularity of HCC following radiofrequency ablation by utilizing perfusion, HAO, and HPI characteristics. Even though **Marquez *et al.*** [13] also included patients with liver metastases other than HCC in their investigation, they still observed similar outcomes. Patients with HCC who underwent chemoembolization had encouraging outcomes, according to **Yang *et al.*** [14]. After argon-helium knife therapy, **Wang *et al.*** [15] discovered that all CTP parameters they studied dramatically decreased in HCC. In three separate investigations, CTP measurements were used to gauge how well HCC patients responded to TACE [16-18].

In a study of patients with HCC receiving TACE, **Du *et al.*** [16] also discovered similar outcomes. **Popovic *et al.*** [19], reported that in patients receiving DEB-TACE for intermediate-stage HCC found that CTP might predict survival. The effectiveness of the treatment could not be determined using this method. In patients with hepatocellular carcinoma (HCC) who received sorafenib treatment, **Nakamura *et al.*** [20] discovered that CTP might predict overall survival.

Lastly, a number of CTP characteristics were determined to have diagnostic power and to be able to predict treatment response in three trials [7, 21-22]. No research on liver cancer grading was located.

CONCLUSION

The liver's dual vascular supply and significant non-uniform motion during respiration make it one of the most perfusion imaging-challenging organs. Compared to triphasic CT, CT perfusion is superior for diagnosing and monitoring HCC therapy outcomes. Integrating it into standard imaging methods is a breeze. CT perfusion of the liver shows great promise as a tool for evaluating surgical treatments, detecting primary or metastatic cancers early on, forecasting how well a patient will react to surgery, and tracking the return of malignancies following treatment.

Financial support and sponsorship: Nil.

Conflict of Interest: Nil.

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