Computed tomography for the diagnosis of hepatocellular carcinoma in chronic advanced liver disease

Nadarevic, Tin; Giljača, Vanja; Colli, Agostino; Fraquelli, Mirella; Casazza, Giovanni; Miletić, Damir; Štimac, Davor

Source / Izvornik: **Cochrane Database of Systematic Reviews, 2019, 6, 1 - 16**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1002/14651858.cd013362

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:892984

Cochrane Library

Cochrane Database of Systematic Reviews

Computed tomography for the diagnosis of hepatocellular carcinoma in chronic advanced liver disease (Protocol)

Nadarevic T, Giljaca V, Colli A, Fraquelli M, Casazza G, Miletic D, Štimac D

Nadarevic T, Giljaca V, Colli A, Fraquelli M, Casazza G, Miletic D, Štimac D.
Computed tomography for the diagnosis of hepatocellular carcinoma in chronic advanced liver disease.
Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD013362.
DOI: 10.1002/14651858.CD013362.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Diagnostic Test Accuracy Protocol]

Computed tomography for the diagnosis of hepatocellular carcinoma in chronic advanced liver disease

Tin Nadarevic[1], Vanja Giljaca[2], Agostino Colli[3], Mirella Fraquelli[4], Giovanni Casazza[5], Damir Miletic[1], Davor Štimac[6]

[1]Department of Radiology, Clinical Hospital Centre Rijeka, Rijeka, Croatia. [2]Directorate of Surgery, Department of Gastroenterology, Heart of England NHS Foundation Trust, Birmingham Heartlands Hospital, Birmingham, UK. [3]Department of Internal Medicine, A Manzoni Hospital ASST Lecco, Lecco, Italy. [4]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda - Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy. [5]Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Università degli Studi di Milano, Milan, Italy. [6]Department of Gastroenterology, Clinical Hospital Centre Rijeka, Rijeka, Croatia

Contact address: Agostino Colli, Department of Internal Medicine, A Manzoni Hospital ASST Lecco, Via dell'Eremo, 9/11, Lecco, 23900, Italy. colliagostino@gmail.com.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 6, 2019.

Citation: Nadarevic T, Giljaca V, Colli A, Fraquelli M, Casazza G, Miletic D, Štimac D. Computed tomography for the diagnosis of hepatocellular carcinoma in chronic advanced liver disease. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No.: CD013362. DOI: 10.1002/14651858.CD013362.

ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

To assess the diagnostic accuracy of multidetector, multiphasic contrast-enhanced computed tomography (CT) for the diagnosis of hepatocellular carcinoma (HCC) of any size and at any stage in people with chronic advanced liver disease.

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm, usually developing in the setting of chronic liver disease. It represents the third most common cause of death from cancer worldwide, with exceedingly high rates in East and Southeast Asia, several areas of Africa and Southern Europe (Bertuccio 2017). In the last decade, HCC was one of the few cancers that showed increasing incidence and mortality trends in several areas of the world including Europe, and North and Latin America (Bosetti 2013; Hashim 2016; Ryerson 2016). Mortality rates, even with a recently downward reported trend, are reported to be still two to five times higher in Japan, Hong Kong, and Korea than in most European countries, and the Americas, (Bertuccio 2017). Most common risk factors include liver cirrhosis, severe liver fibrosis, chronic infections with hepatitis B and C, heavy alcohol intake, tobacco use, diabetes, metabolic syndrome, aflatoxins (poisonous carcinogens produced by *Aspergillus flavus* and *Aspergillus parasiticus*, which grow in soil, decaying vegetation, hay, and grains), nonalcoholic fatty liver disease, and being overweight (Yang 2011; Bosetti 2014; Stanaway 2016; Bertuccio 2017); however, cases of HCC without known risk factors have been reported (Bralet 2000; Young 2012).

Clinically, HCC is frequently diagnosed in the late stages of liver disease because of the absence of specific symptoms, other than those related to chronic liver disease. Only less than 20% of patients are eligible for curative treatment — such as liver resection, transplantation or ablation — due to advanced tumour stage, liver dysfunction, or shortage of liver donors (Davila 2012). Furthermore, curative treatment options are unfeasible in most cases due to severe clinical deterioration at the moment of diagnosis, or due to the inaccuracy of the preoperative clinical evaluation and staging procedure.

Despite the poor initial prognosis (the mortality-to-incidence overall ratio has been reported as 0.95) (Ferlay 2012), a five-year survival rate of more than 50% can be achieved if the HCC is detected at an early stage (Forner 2012). According to the Barcelona Clinic Liver Cancer (BCLC) staging system, only patients with early-stage HCC are eligible for curative treatment (Llovet 1999). Therefore, accurate and early diagnosis of HCC is of high importance.

Prior to advancements in medical imaging, biopsy and cytologic examination of the liver specimen were used to make a definitive diagnosis of HCC (Tao 1984). With the development of advanced imaging techniques, HCC has become unique among tumours in that its characteristics can be accurately detected using imaging, thus reducing the need for invasive biopsy (Forner 2008; Sangiovanni 2010; Manini 2014). Currently, biopsy is not preferred for the diagnosis of HCC due to concerns regarding tumour seeding, bleeding, and rate of false-negative results (Silva 2008; Pomfret 2010). However, it is reserved for lesions with atypical appearance and when imaging results are equivocal (Bruix 2011).

Computer tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) have been established as the non-invasive imaging modalities for detection and evaluation of liver lesions (Lee 2012; O'Neill 2015). In comparison with single-detector CT, multidetector computed tomography (MDCT) is superior due to greater speed, thinner slices, and multiphasic scanning; these factors improve spatial and temporal resolution and provide more precise evaluation of liver tumour haemodynamics, and consequentially, the diagnostic accuracy (O'Neill 2015). The ability of a CT to detect HCC rests on characterising the enhancement patterns in arterial, portal venous, and subsequent phases relative to the surrounding liver tissue. The differences in blood flow and extracellular volume between HCC and normal liver tissue lead to main radiological hallmarks of HCC (Hennedige 2012; Choi 2014; Shah 2014; LI-RADS 2018).

According to American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) guidelines, a single contrast enhanced imaging study (CT or MRI), performed in centres of excellence with sophisticated radiological equipment showing typical radiological hallmarks in patients with cirrhosis, is valid to diagnose HCC (Bruix 2011; EASL-EORTC 2012; EASL 2018). However, if a detected lesion presents with some (but not all) of the hallmarks of HCC, another imaging study or biopsy is warranted.

According to current relevant guidelines, there are some differences in recommendations for management with regards to the size of a suspected focal liver lesion. In AASLD guidelines, lesions with a diameter less than 1 cm and those with a diameter more than 1 cm without HCC hallmarks are labelled as indeterminate lesions and require follow-up (Heimbach 2018). EASL guidelines propose a diagnostic algorithm for management of suspected focal liver lesions and group lesions in two categories (with a diameter less than 1 cm, and more than 1 cm) (EASL 2018). Asian Pacific Association for the Study of the Liver (APASL) diagnostic pathways focus more on lesion characteristics than on size (Omata 2017).

Previous systematic reviews have assessed the performance of CT in detecting HCC, and they have included different studies and yielded different results (Colli 2006; Chen 2013; Floriani 2013; Chou 2015; Lee 2015; Ye 2015; Guo 2016; Hanna 2016; Roberts 2018). These reviews are comparative reviews that compare two or more tests (ultrasound, CT, MRI) and include studies conducted before 2016, when CT diagnostic criteria were clearly defined (LI-RADS 2016). Evaluation of risk of bias and definition of inclusion criteria, type of studies, and reference standards are often inconsistent and questionable. Furthermore, these reviews did not put the index tests into context and did not define clearly their role, instead comparing all the available tests as they were used simultaneously. The aim of this systematic review and meta-analysis is to use Cochrane methodology to determine the accuracy of CT for the diagnosis of HCC of any size, as well as the diagnosis of resectable HCC in people with chronic advanced liver disease.

Target condition being diagnosed

Hepatocellular carcinoma is the most common primary liver cancer which occurs mostly in people with chronic liver disease. The incidence of HCC increases in individuals with hepatitis B and C, alcohol use, and nonalcoholic fatty liver disease, and in those with liver cirrhosis of various aetiologies (Bruix 2011). There is no definite threshold in the definition of lesion size, although literature tends to classify lesions with a diameter equal to or less than 2 cm as "small" (Hussain 2002; Choi 2014; Park 2017).

In clinical practice, and according to pertinent guidelines, multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) with intravascular contrast allow for a highly accurate diagnosis of HCC without an invasive biopsy. The diagnosis of HCC is usually obtained on the basis of cross-sectional CT or MR imaging

features, and liver histology is required only for undefined lesion (Omata 2017; EASL 2018; Heimbach 2018; LI-RADS 2018).

A number of staging systems for HCC have been proposed and developed; however, there is no globally applicable staging system (Kinoshita 2015). Among different staging protocols, the BCLC staging system has a notable feature of treatment recommendations for each stage, based on the best treatment options currently available (Llovet 1999; Llovet 2003; Llovet 2008). It is comprised of four elements: tumour extension, liver functional reserve, physical status, and cancer-related symptoms. According to the BCLC, only patients with early-stage HCC are eligible for curative treatment such as surgical resection or percutaneous treatment. Orthotopic liver transplantation is reserved for patients with decompensated cirrhosis, and is considered a definite curative treatment for HCC. When orthotopic liver transplantation for HCC was initially introduced in the 1980s, it was associated with poor five-year survival rates and high recurrence rates, which led to the treatment being contraindicated for HCC (Yokoyama 1990). In 1996, specific criteria, known as Milan criteria (Mazzaferro 1996), were developed for the selection of patients for liver transplantation. These criteria have been repeatedly validated and their value is considerable (EASL 2018). With their implementation, overall five-year survival of post-orthotopic liver transplantation patients exceeded 70% (Mazzaferro 2011). The criteria for patients eligible for orthotopic liver transplantation include: a single HCC lesion with a diameter equal to or less than 5 cm, or up to three HCC lesions, each with a diameter equal to or less than 3 cm; no vascular invasion; and no extrahepatic involvement (no metastasis).

Index test(s)

Contrast-enhanced multidetector and multiphasic CT is an advanced imaging modality which involves the rapid administration of contrast material in combination with fast acquisition of data using ionising radiation. Since its invention in the 1970s, significant technological advancements have led to improvement of hardware and software resulting in multidetector image acquisition (today, up to 320-slice CT scanners exist).

Minimal CT requirements for the detection of HCC include use of an eight-detector row CT scanner and 5 mm slice thickness to obtain high-quality images. Iodine contrast agent needs to be administered intravenously at the minimum recommended concentration of 300 mg /mL. After the injection of contrast, the following dynamic phases need to be acquired: late arterial (35 to 40 seconds after contrast injection or 15 to 20 seconds after bolus-tracking), portal venous (70 to 80 seconds after contrast injection or 50 to 60 seconds after bolus-tracking), and delayed phase (6 to 10 minutes after contrast injection or 6 to 10 minutes after bolus-tracking). The bolus-tracking technique and use of an automated power injector are recommended to obtain properly timed phases (Wald 2013). Injection of saline is strongly recommended because it reduces the dose of residual contrast and its arrival time to hepatic arteries (Bae 2010).

Acute adverse reactions to iodine contrast occur within one hour of contrast medium injection and are categorised into mild (nausea, mild vomiting, urticaria, and itching), moderate (severe vomiting, marked urticaria, bronchospasm, facial/laryngeal edema, and vasovagal attack), and severe (hypotensive shock, respiratory arrest, cardiac arrest, and convulsion). Late adverse reactions occur one hour to one week after contrast medium injection and include maculopapular rashes, erythema, swelling, and pruritus. Most skin reactions are mild to moderate and self-limiting. Very late adverse reaction occurs more than one week after contrast medium injection and includes thyrotoxicosis. The most important adverse reaction following iodine contrast injection is contrast-induced nephropathy (CIN), a decrease in renal function within three days of the intravascular administration of a contrast medium. An increase in serum creatinine by more than 25% or 44 µmol/L (0.5 mg/dL) indicates CIN (Thomsen 2014). The American College of Radiology (ACR) only recognises relative contraindications for the use of iodined contrast which include allergy to iodine, acute thyroid storm, and planned or ongoing radioiodine treatment of the thyroid gland. According to present evidence, it is controversial whether myasthenia gravis should be considered a relative contraindication (Davenport 2018).

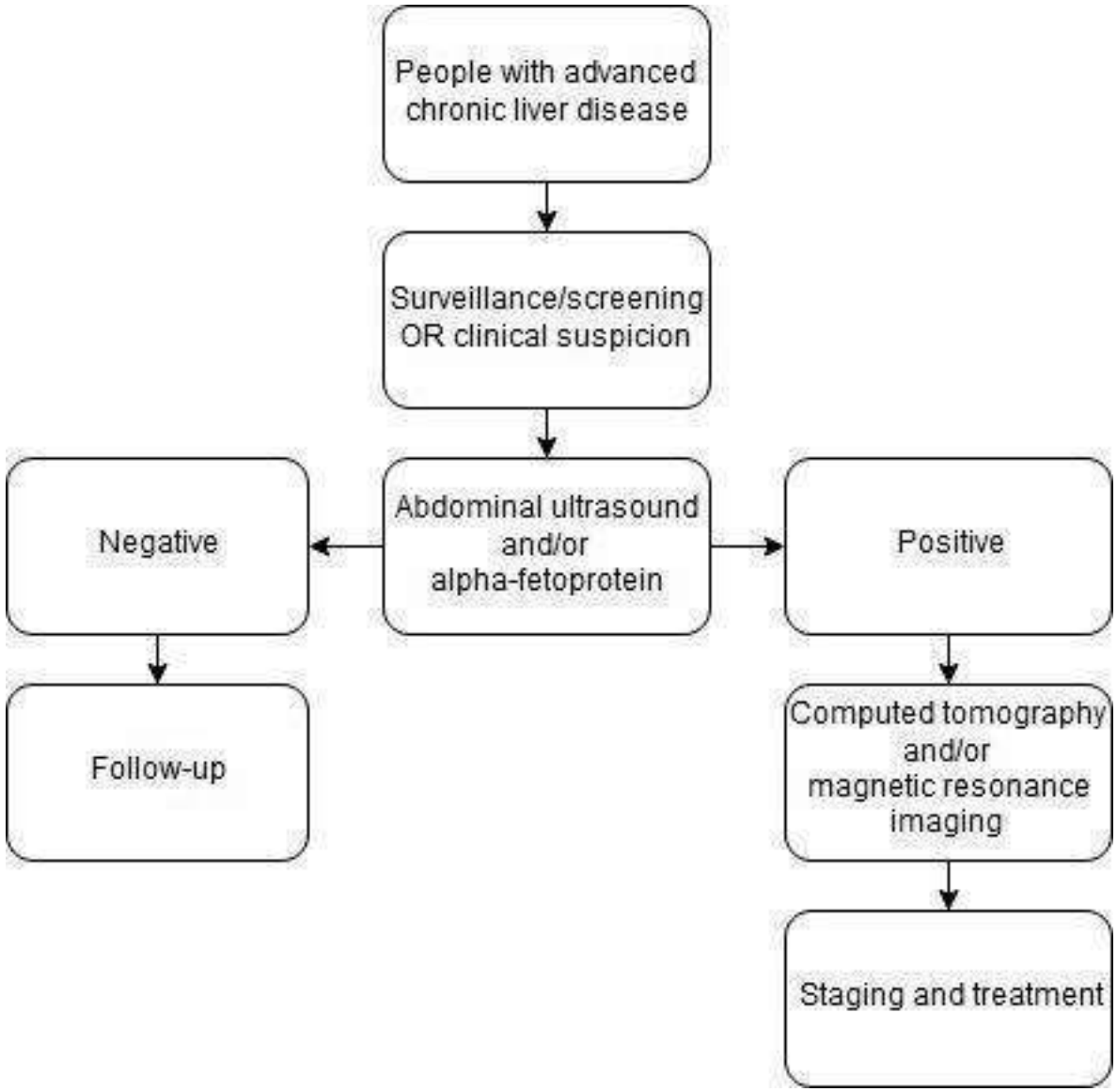
Ionising radiation produced by CT scanners is, by definition, harmful to the molecular structure of human tissue. It can damage DNA molecules directly by ionising them, or indirectly by producing free radicals (electrons from atoms or molecules are knocked out from their orbit, thereby creating ions which interact with nearby DNA, causing breaks in its strands or base damage). Most radiation-induced damage is quickly repaired; however, occasional misrepair can induce mutations, gene fusion, and chromosomal translocations, all of which could lead to the development of cancer (Mitelman 2018). Biological effects of ionising radiation can be divided into deterministic and stochastic. Deterministic effects occur when an x-ray dose exceeds a specific threshold; they are immediate and predictable, and include alopecia, burning sensations, ulcerative skin lesions, cataract formation, and cardiovascular disease (Einstein 2012). These effects are uncommon, although cases of hair loss in patients undergoing CT angiography/perfusion studies of the brain have been reported (Wintermark 2010). Stochastic effects are probabilistic: they occur with a probability that is believed to increase as the dose increases. They are the main concern with medical imaging tests, and include the risk of developing cancer (Einstein 2012). Many technological improvements, dose reduction strategies, and radiation effect campaigns have been made for the benefit of reducing radiation risks in patients undergoing a CT exam.

According to the American College of Radiology Liver Reporting and Data System (LI-RADS), typical hallmarks of HCC on contrast-enhanced imaging modalities (contrast enhanced ultrasound, CT, MRI) are detected and reported. In the case of CT, these include nonrim-like hyperenhancement in late arterial phase (defined as arterial phase hyperenhancement (APHE)) and subsequent nonperipheral washout on portal venous or delayed phases (or both). Not all lesions are typical; therefore, different diagnostic grades are reported (LR 3, LR 4, or LR 5), which take into account other factors including lesion size, enhancing capsule, and threshold growth (LI-RADS 2018).

Clinical pathway

Surveillance of HCC (that is, screening performed at regular intervals) in the at-risk population, i.e. patients with advanced chronic liver disease regardless of etiology, is carried out by abdominal ultrasound for detection of nodules. Once a suspected nodule has been detected, other imaging methods are considered according to the size of the nodule and appropriate guidelines. For a flow diagram of the clinical pathway and placement of tests, see Figure 1.

Figure 1. Flow diagram of the diagnostic pathway for the diagnosis of hepatocellular carcinoma



American Association for the Study of Liver Disease (AASLD) diagnostic guidelines

According to the AASLD guidelines, the cut-off value for size characterisation of liver nodules is 1 cm. If a suspected nodule smaller than 1 cm is detected, a follow-up ultrasound at three months is recommended to determine whether the lesion is stabile in size or growing. If a change in character or growth is observed, further workup is warranted; otherwise, further follow-up is recommended. In nodules larger than 1 cm, a four-phase MDCT or contrast-enhanced MRI is recommended to evaluate hallmarks for HCC. If no hallmarks are detected, a second contrast-enhanced study (CT or MRI) is warranted. If no imaging hallmarks of HCC are detected, biopsy is recommended (Bruix 2011).

European Association for the Study of the Liver (EASL) diagnostic guidelines

In cirrhotic liver disease, the diagnostic algorithm proposed by the EASL divides suspected focal liver lesions in two categories: lesions smaller than 1 cm, and those larger than 1 cm. Lesions smaller than 1 cm are to be followed up by ultrasound every four months: if the size of the lesion does not increase, then further ultrasound follow-up is recommended; otherwise, multiphasic contrast-enhanced CT, multiphasic contrast-enhanced MRI, or gadoxetic-enhanced MRI is required. Lesions larger than 1 cm directly require to be evaluated by CT or MRI. If at least one of these imaging modalities is positive, i.e. proves the existence of HCC hallmarks, diagnosis of HCC is considered certain. If the results are equivocal, the use of other multiphasic imaging modality is required: multiphasic contrast-enhanced CT or multiphasic contrast-enhanced MRI, gadoxetic-enhanced MRI or contrast-enhanced ultrasound. If these studies prove the hallmarks of HCC, the diagnosis is certain; otherwise,

biopsy is warranted. If biopsy appears to be unclear, re-biopsy is to be considered or a repeat ultrasound follow-up every four months (EASL 2018).

Asian Pacific Association for the Study of the Liver (APASL) diagnostic guidelines

Under the APASL guidelines, a single dynamic contrast-enhanced MRI or CT is warranted regardless of the size of suspected liver nodule. If typical hallmarks of HCC are shown (presence of arterial hyperenhancement, followed by washout in the portal venous or delayed phases, or both), diagnosis is confirmed. If the lesion is hypervascular but shows no washout, another contrast-enhanced MRI study is needed. If the lesion proves to be hypointense, HCC diagnosis is confirmed. However, if the lesion is isointense or hyperintense, biopsy is warranted. If the lesion on the first dynamic MRI or CT study is non-hypervascular, a dynamic MRI study in hepatobiliary phase is needed. If the lesion is isointense or hyperintense, surveillance by ultrasound is recommended every six months, and if the lesion is hypointense, contrast-enhanced ultrasound of the liver nodule is warranted. Depending on lesion features on contrast-enhanced ultrasound, biopsy or another dynamic CT or MRI study is recommended every three to six months (Omata 2017).

Prior test(s)

For surveillance purposes, abdominal ultrasound is recommended as a first-line imaging modality in patients with advanced chronic liver disease, regardless of aetiology, who are at risk of developing a HCC (Omata 2017; EASL 2018; Heimbach 2018). It is also used as a diagnostic tool in patients with clinical suspicion of HCC for detecting liver lesions. Alpha-fetoprotein (AFP) has been used as a diagnostic biomarker even before technological advancements (Kew 1975). However, its role as a screening tool is still a matter of debate. The diagnosis of chronic advanced liver disease is based on clinical judgement derived from history, laboratory testing, physical examination, imaging, liver stiffness measurement, liver histology, or a combination of the aforementioned. Due to the accuracy of non-invasive tests, liver histology is reserved to only a minority of patients with unclear diagnosis and a non-invasive diagnosis of chronic advanced liver disease is considered equivalent to a histological diagnosis of cirrhosis (de Franchis 2015).

Role of index test(s)

Computer tomography is used as an add-on test after ultrasound detection of liver lesions suspected for HCC in surveillance programmes or hospital settings in patients with clinical suspicion. Based on CT findings, biopsy and other imaging modalities could be avoided, therefore further testing could be reserved for a minority of cases.

Alternative test(s)

An alternative imaging modality in detecting HCC is contrast-enhanced dynamic MRI with extracellular and cell-specific gadolinium-based contrast agents. A recent meta-analysis aimed to determine the diagnostic benefit between multiphasic contrast-enhanced CT, extracellular contrast-enhanced MRI, and cell-specific gadoxetate-enhanced MRI for detection of HCC in patients with cirrhosis (Roberts 2018). No definitive recommendation could be made for the systematic use of gadolinium-enhanced MRI over CT, although other previous meta-analyses reported a preference for MRI (Lee 2015; Ye 2015; Guo 2016).

Contrast-enhanced ultrasound is an advanced form of ultrasound examination in which images are acquired using intravenously injected microbubble contrast agent. Dynamic contrast-enhanced ultrasound images are obtained similarly to contrast-enhanced CT and MR studies: depending on the time of image acquisition after intravenous contrast injection, the study differentiates arterial and portal venous phases in which sonographic hallmarks for HCC, such as arterial hyperenhancement and subsequent washout appearance, are investigated (Chung 2015; LI-RADS 2016). Unlike CT and MRI contrasts, ultrasound contrast agent is a purely intravascular agent; therefore, it is highly accurate in detecting tumour angiogenesis (Schirner 2004).

Lipiodol computerised tomography (lipiodol-CT) was used in the past as a diagnostic modality for the detection of HCC. The method included intra-arterial injection of iodised oil (lipiodol) through the hepatic arterial supply, following which lipiodol was deposited within the HCC nodule. The HCC was visualised as a hyperattenuating nodule on the subsequent CT, and it showed high sensitivity in detecting small HCC (Takayasu 1990). In the context of transarterial chemoembolisation, lipiodol may be used as an intraprocedural diagnostic modality (C-arm lipiodol CT) for additional detection of small-size HCC (Li 2015).

Rationale

Hepatocellular carcinoma is currently detected by liver ultrasound in patients with normal or high alpha-fetoprotein during surveillance programmes in patients with chronic liver disease. Following ultrasound, the diagnosis is usually confirmed with high levels of alpha-fetoprotein or contrast enhanced ultrasound (or both), CT, or MRI. The latter two imaging modalities are also appropriate for staging and allow the choice of the most appropriate treatment. There is no clear evidence of the benefits of surveillance programmes in terms of overall survival: the conflicting results can be a consequence of an inaccurate detection, ineffective treatment, or both. Assessing the diagnostic accuracy of CT, the most used confirmatory test after first-line tests, may clarify whether the absence of benefit in surveillance programmes might be related to underdiagnosis or understaging. Furthermore, an assessment of the accuracy of CT for the diagnosis of HCC is needed for either ruling out, diagnosing, or supporting further testing in people with chronic liver disease who are not included in surveillance programmes.

This review represents a part of a series of reviews about the diagnostic accuracy of the most commonly used modalities for diagnosing HCC in patients with chronic liver disease. The first part will include assessment of the diagnostic accuracy of ultrasound and alpha-fetoprotein levels, which are used as triage tests in the surveillance. The second part will focus on the diagnostic accuracy of contrast-enhanced ultrasound in characterising suspected lesions as HCC as a second-line diagnostic modality. The present review will focus on the assessment of CT as a third-line imaging modality in assessing focal liver lesions detected on ultrasound suspected for HCC. A review assessing the accuracy of MRI for diagnosing HCC is in progress (Tang 2017). We are planning to produce an overview of the reviews that assess abdominal ultrasound and alpha-fetoprotein, contrast-enhanced ultrasound, CT, and MRI for the diagnosis of HCC.

OBJECTIVES

To assess the diagnostic accuracy of multidetector, multiphasic contrast-enhanced computed tomography (CT) for the diagnosis of hepatocellular carcinoma (HCC) of any size and at any stage in people with chronic advanced liver disease.

Secondary objectives

- To assess the diagnostic accuracy of multidetector, multiphasic contrast-enhanced computed tomography for the diagnosis of resectable HCC in people with chronic advanced liver disease. The definition of resectable HCC is a neoplasm amenable to surgical radical resection according to the current guidelines (Milan Criteria): a single lesion with a maximum diameter of less than 5 cm, or fewer than three lesions with a maximum diameter of 3 cm (Mazzaferro 1996).
- To investigate the following predefined sources of heterogeneity:
  * study date (studies published before the year 2005 compared to studies published after the year 2005, due to advancements in technology);
  * study date (studies published before 2016 compared to studies published after 2016, due to changes in diagnostic criteria);
  * inclusion of participants without cirrhosis (studies including more than 10% participants without cirrhosis compared to studies including less than 10% participants without cirrhosis);
  * study location (population differences): studies conducted in the Americas compared to Europe compared to Asia;
  * participant selection (participants recruited from planned screening programmes compared to clinical cohorts);
  * different HCC stage (studies in which 20% or more of participants have resectable HCC compared to studies in which less than 20% of participants have resectable HCC);
  * different reference standard (histology of the explanted liver compared to liver biopsy compared to another reference standard);
  * different liver cirrhosis aetiology (hepatitis C or hepatitis B virus associated cirrhosis compared to all other aetiologies);
  * number of CT detector rows (exams conducted on 64-slice or fewer compared with more than 64-slice, due to advancements in technology);
  * HCC mean diameter;
  * prevalence of the target condition.

We chose the variables listed above for the following reasons. Due to advancements in technology and change in diagnostic criteria, we considered the date of study publication. The proportion of participants without cirrhosis is relevant because HCC in absence of cirrhosis has different CT characteristics, prognosis, and treatment. There are differences in epidemiology and clinical and radiological characteristics of HCC in Asia and in western countries. Selection of participants can induce variability of results: participants recruited from screening or surveillance programmes may be different mainly in severity of the underlying liver disease and consequently in radiological characteristics of the liver. The HCC prevalence in included studies can change according to selection and epidemiology. The proportion of resectable HCC found in the studies reflects different epidemiology and participant selection. The clinical and radiological characteristics of HCC varies according to the aetiology of the underlying liver disease, mainly in the case of chronic infection with hepatitis C or hepatitis B, compared to other aetiologies. The accuracy of CT may vary according to the diameter of the neoplastic lesion and the number of detector rows in the CT equipment.

METHODS

Criteria for considering studies for this review

Types of studies

We will aim to include studies that, irrespective of publication status and language, have evaluated the diagnostic accuracy of multidetector, multiphasic contrast-enhanced computed tomography for the diagnosis of hepatocellular carcinoma in people with chronic liver disease. These studies should have used one of the acceptable reference standards (see Reference standards).

We will consider studies of cross-sectional design which include participants with clinical suspicion of HCC. We plan to exclude studies of case-control design that compared people with known HCC to matched control as these are considered to have high risk of bias due to inflated accuracy estimates (Colli 2014). We will include studies assessing CT if all the participants have undergone at least one of the acceptable reference standards. We plan to exclude studies that analysed data only per-lesion, rather than per-participant, unless participant data are made available by study authors.

Participants

Participants will include adults of any age and sex with chronic liver disease, irrespective of aetiology, severity of disease, and duration of illness, with suspicion of having HCC on the basis of prior tests, ultrasound, and alpha-fetoprotein. The review will focus on diagnostic questions related to people with a first diagnosis of HCC. People with previous diagnosis and treatment of HCC make up a distinct group for which the diagnosis or natural history of HCC has been modified. These people are not the focus of this review; therefore, we will exclude studies that included such participants unless they represent less than 5% of all the included participants, or if investigators had presented data in such a way as to allow this group of participants to be isolated from the remaining included participants.

Index tests

We will include multiphasic contrast-enhanced CT for the detection of HCC in people with advanced chronic liver disease. CT is considered positive when a suspected liver lesion shows all the following characteristics: nonrim-like arterial hyperenhancement, subsequent nonperipheral washout appearance in later phases, lesion size greater than 10 mm, enhancing capsule, and threshold growth (LI-RADS 2018).

Target conditions

- Hepatocellular carcinoma of any size and at any stage.
- Resectable hepatocellular carcinoma (see Secondary objectives).

Reference standards

We will accept as a reference standard for the diagnosis of HCC one of the following.

- The pathology of the explanted liver in case of transplantation.
- The histology of resected focal liver lesion(s), or the histology of resected or biopsied focal liver lesion(s) with a follow-up period of at least six months to exclude the presence of focal lesions not detected by the index test.

All these reference standards, even if commonly used in clinical practice, are not perfect. The pathology of the explanted liver is possible only in the case when all the included patients undergo liver transplantation; therefore, the setting does not correspond to the clinical question that only people with advanced and decompensated liver disease are candidates for orthotopic liver transplantation. In the case of histology of resected focal lesion and histology of biopsied liver lesions, the negative result can be confirmed only with an adequate follow-up period. Differential verification is therefore unavoidable in this context.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register and the CHBG Diagnostic Test of Accuracy Studies Register (both registers are maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web), the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index - Expanded (Web of Science), and Conference Proceedings Citation Index – Science (Web of Science) (Royle 2003).

We will not apply any restrictions on language or document type.

Searching other resources

We will try to identify additional references by manually searching articles retrieved from digital databases and relevant review articles. We will seek information on unpublished studies by contacting experts in the field. In addition, we will hand-search abstract books from meetings of the AASLD, the EASL, and APASL held over the past 10 years. We will also search for other kinds of grey literature in the System for Information on Grey Literature in Europe "OpenGrey" (www.opengrey.eu/).

Data collection and analysis

We will follow available guidelines as provided in the*Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (DTA Handbook 2013).

Selection of studies

We will use Covidence to manage the selection of studies (Covidence 2017). Two review authors (VG and TN) will independently scrutinise titles and abstracts identified by electronic literature searching to identify potentially eligible studies. We will select any citation, identified by either of the two review authors, as potentially eligible for full-text review. The same review authors will independently assess full-text papers for study eligibility, using predefined inclusion and exclusion criteria. We will resolve any discrepancies by discussion. We will record all studies after full-text assessment, and their reasons for exclusion, in the 'Characteristics of excluded studies' table and illustrate the study selection process using a PRISMA diagram (Moher 2009).

Data extraction and management

Two review authors (VG and TN), working as a pair , will complete a piloted data extraction form for each included study. Each review author will independently extract study data. In cases of disagreement, we will reach consensus through discussion.

We will extract the following data.

- General information: title, journal, year, publication type, and study design (prospective versus retrospective), surveillance programme or clinical cohorts.
- Sample size: number of participants meeting the criteria and total number of participants included and tested.
- Baseline characteristics: baseline diagnosis, age, sex, race, and presence of cirrhosis and mean diameter of HCC.
- Index test with predefined positivity criteria.
- Reference standard tests.
- Numbers of true positive, true negative, false positive, and false negative findings. We will extract these data for the two target conditions (HCC of any size and stage and resectable HCC).

We will summarise the data from each study in 2 × 2 tables (true positive, false positive, false negative, true negative), according to the index test considered, and we will enter the data into Review Manager 5 software.

Missing data

We will contact primary authors by email to ask for missing data which are needed to design the 2 × 2 tables. If we receive no reply, we will send a second email after two weeks. If no reply is received, we will exclude the study in question.

Assessment of methodological quality

Two review authors (VG and TN) will independently assess the risk of bias of included studies and applicability of their results using QUADAS-2 (revised tool for quality assessment of diagnostic accuracy studies) (Whiting 2011). In cases of disagreement, we will reach a consensus through discussion. We will address aspects of study quality involving the participant spectrum, index tests, target conditions, reference standards, and flow and timing. A number of inadequate results should be reported and those should be assessed according to intention-to-diagnose (Schuetz 2012) . If not all participants are included in the analyses , we will consider the study to be at high risk of bias. We will classify a study as having a high risk of bias if at least one of the domains of QUADAS-2 is judged as being high risk .

Statistical analysis and data synthesis

We will carry out statistical analyses according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (DTA Handbook 2013). Firstly, we will perform a graphical descriptive analysis of the included studies. We will report forest plots (sensitivity and specificity separately, with their 95% confidence intervals (CIs)), and we will provide a graphical representation of studies in the receiver operating characteristic (ROC) space (sensitivity against 1 - specificity). Secondly, we will perform a meta-analysis using the

bivariate model and will provide estimates of summary sensitivity and specificity. We will use the pooled estimates obtained from the fitted models to calculate summary estimates of positive and negative likelihood ratios (LR+ and LR-, respectively).

In case of non-evaluable index test results, we plan to analyse data according to the intention-to-diagnose principle (Schuetz 2012), also described as worst-case scenario in Cohen 2015. Participants with indeterminate index test results will be classified as false positive if they had a negative reference standard or a false negative for patients with a positive reference standard . If data for the intention-to-diagnose analyses are not retrievable from the text, we will contact publication authors with provided email addresses. If we receive no reply, the study will be included in the analyses with data retrievable from the published manuscript and we will consider it as having a high risk of bias.

We will perform all statistical analyses using SAS statistical software, release 9.4 (SAS Institute Inc., Cary, NC, USA) and macro METADAS (DTA Handbook 2013).

Investigations of heterogeneity

The list of potential sources of heterogeneity we plan to explore is reported in Secondary objectives. We will estimate effects by adding covariates to the bivariate or to the HSROC models. We will assess the statistical significance of the covariate effect by using the log-likelihood ratio test for comparison of models with and without the covariate term. We will consider P values of less than 0.05 as two-sided and statistically significant.

Sensitivity analyses

We plan to assess effects of risk of bias of included studies on diagnostic accuracy by performing a sensitivity analysis in which we exclude studies classified as having high or unclear risk of bias in at least one of the domains of QUADAS-2 (Appendix 2). In addition, we have defined the following signalling questions as most relevant, and plan to conduct a sensitivity analyses in which we exclude studies with answers of 'no' or 'unclear'.

- “Were the positivity criteria defined?"
- "Were the reference standard results interpreted without the knowledge of the results of the index test?"

We also plan to conduct a sensitivity analysis in which studies published only in abstract or letter form are excluded.

Assessment of reporting bias

We do not plan to test for publication bias due to the lack of validated methods for diagnostic test accuracy reviews.

ACKNOWLEDGEMENTS

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of The Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. Disclaimer: The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

Peer reviewers: to be obtained from the Cochrane Diagnostic Accuracy Reviews Editorial Team, UK.
Contact Editor from the Cochrane Diagnostic Accuracy Reviews Editorial Team: Karen Steingart, UK.
Contact editor (CHBG): Christian Gluud, Denmark.
Sign-off editor (CHBG): Christian Gluud, Denmark.

REFERENCES

Additional references

Bae 2010

Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. *Radiology* 2010;**256**(1):32-61.

Bertuccio 2017

Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, et al. Global trends and predictions in hepatocellular carcinoma mortality. *Journal of Hepatology* 2017;**67**(2):302-9.

Bosetti 2013

Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Cancer mortality in Europe, 2005–2009, and an overview of trends since 1980. *Annals of Oncology* 2013;**24**:2657-71.

Bosetti 2014

Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. *Best Practice & Research. Clinical Gastroenterology* 2014;**28**:753-70.

Bralet 2000

Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000;**32**(2):200-4.

Bruix 2011

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;**53**(3):1020.

Chen 2013

Chen L, Zhang L, Bao J, Zhang J, Li C, Xia Y, et al. Comparison of MRI with liver-specific contrast agents and multidetector row CT for the detection of hepatocellular carcinoma: a meta-analysis of 15 direct comparative studies. *Gut* 2013;**62**:1520-1.

Choi 2014

Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology* 2014;**272**:635-54.

Chou 2015

Chou R, Cuevas C, Fu R, Devine B, Wasson N, Ginburg A, et al. Imaging techniques for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Annals of Internal Medicine* 2015;**162**:697-711.

Chung 2015

Chung YE, Kim KW. Contrast-enhanced ultrasonography: advance and current status in abdominal imaging. *Ultrasonography* 2015;**34**(1):3-18.

Cohen 2015

Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016;**6**:e012799.

Colli 2006

Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and apha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *American Journal of Gastroenterology* 2006;**101**:513-23.

Colli 2014

Colli A, Fraquelli M, Casazza G, Conte D, Nikolova D, Duca P, et al. The architecture of diagnostic research: from bench to bedside - research guidelines using liver stiffness as an example. *Hepatology* 2014;**60**(1):408-18.

Covidence 2017 [Computer program]

Veritas Health Innovation. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 19 June 2019.

Davenport 2018

Davenport MS, Asch D, Cavallo J, Cohan R, Dillman JR, Ellis JH, et al. ACR Manual on Contrast Media. 10.3. American College of Radiology, 2018.

Davila 2012

Davila JA, Duan Z, McGlynn KA, El-Serag HB. Utilization and outcomes of palliative therapy for hepatocellular carcinoma: a population-based study in the United States. *Journal of Clinical Gastroenterology* 2012;**46**:71-7.

de Franchis 2015

de Franchis R. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *Journal of Hepatology* 2015;**63**:743–52.

DTA Handbook 2013

Deeks JJ, Bossuyt PM, Gatsonis C, editor(s). Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. The Cochrane Collaboration, 2013. Available from srdta.cochrane.org.

EASL 2018

Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *Journal of Hepatology* 2018;**69**(1):182-236.

EASL-EORTC 2012

European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology* 2012;**56**(4):908-43.

Einstein 2012

Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data?. *Journal of the American College of Cardiology* 2012;**59**(6):553-6.

Ferlay 2012

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0IARC CancerBase No. 11. publications.iarc.fr/Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012 (accessed 22 February 2019).

Floriani 2013

Floriani I, D'Onofrio M, Rulli E, Chen MH, Li R, Musicco L. Performance of imaging modalities in the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Ultraschall in der Medizin* 2013;**34**:454-62.

Forner 2008

Forner A, Vilana R, Ayuso C, Bianchi L, Sole M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;**47**:97-104.

Forner 2012

Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;**379**(9822):1245-55.

Guo 2016

Guo J, Seo Y, Ren S, Hong S, Lee D, Kim S, et al. Diagnostic performance of contrast-enhanced multidetector computed tomography and gadoxetic acid disodium-enhanced magnetic resonance imaging in detecting hepatocellular carcinoma: direct comparison and a meta-analysis. *Abdominal Radiology* 2016;**41**:1960-72.

Hanna 2016

Hanna RF, Miloushev VZ, Tang A, Finklestone LA, Brejt SZ, Sandhu RS, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdominal Radiology* 2016;**41**:71-90.

Hashim 2016

Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, et al. The global decrease in cancer mortality: trends and disparities. *Annals of Oncology* 2016;**27**:926-33.

Heimbach 2018

Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;**67**:358-80.

Hennedige 2012

Hennedige T, Venkatesh SK. Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. *Cancer Imaging* 2012;**12**(3):530-47.

Hussain 2002

Hussain SM, Zondervan PE, IJzermans JNM, Schalm SW, de Man RA, Krestin GP. Benign versus malignant hepatic nodules: MR imaging findings with pathologic correlation. *Radiographics* 2002;**22**:1023–39.

Kew 1975

Kew MC. Alpha-fetoprotein. In: Read AE editor(s). Moderntrends in Gastroenterology. Vol. **5**, London: Butterworths, 1975:91.

Kinoshita 2015

Kinoshita A, Onoda H, Fushiya N, Koike K, Nishino H, Tajiri H. Staging systems for hepatocellular carcinoma: current status and future perspectives. *World Journal of Hepatology* 2015;**7**(3):406–24.

Lee 2012

Lee JM, Yoon JH, Kim KW. Diagnosis of hepatocellular carcinoma: newer radiological tools. *Seminars in Oncology* 2012;**39**:399-409.

Lee 2015

Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging - a systematic review and meta-analysis. *Radiology* 2015;**275**:97-109.

Li 2015

Li JJ, Zheng JS, Cui SC, Cui XW, Hu CX, Fang D, et al. C-arm Lipiodol CT in transcatheter arterial chemoembolisation for small hepatocellular carcinoma. *World Journal of Gastroenterology* 2015;**21**(10):3035-40.

LI-RADS 2016

American College of Radiology. Liver imaging reporting and data system. www.acr.org/quality-safety/resources/LIRADS (accessed 7 July 2018).

LI-RADS 2018

American College of Radiology. Liver imaging reporting and data system. www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?la=en 2018 (accessed 10 October 2018).

Llovet 1999

Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Seminars in Liver Disease* 1999;**19**:329-38.

Llovet 2003

Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;**362**:1907-17.

Llovet 2008

Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *Journal of the National Cancer Institute* 2008;**100**:698–711.

Manini 2014

Manini MA, Sangiovanni A, Fornari F, Piscaglia F, Biolato M, Fanigliulo L, et al. Clinical and economical impact of 20120

AASLD guidelines for the diagnosis of hepatocellular carcinoma. *Journal of Hepatology* 2014;**60**:995-1001.

Mazzaferro 1996

Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New England Journal of Medicine* 1996;**334**:693-9.

Mazzaferro 2011

Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence based analysis of 15 years of experience. *Liver Transplantation* 2011;**17**:S44-S57.

Mitelman 2018

Mitelman F, Johansson B, Mertens F, editors. Database of chromosome aberrations and gene fusions in cancer. cgap.nci.nih.gov/Chromosomes/Mitelman (accessed 22 February 2019).

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

O'Neill 2015

O'Neill EK, Cogley JR, Miller FH. The ins and outs of liver imaging. *Clinics in Liver Disease* 2015;**19**:99-121.

Omata 2017

Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatology International* 2017;**11**:317–70.

Park 2017

Park HJ, Choi BI, Lee ES, Park SB, Lee JB. How to differentiate borderline hepatic nodules in hepatocarcinogenesis: emphasis on imaging diagnosis. *Liver Cancer* 2017;**6**:189–203.

Pomfret 2010

Pomfret EA, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transplantation* 2010;**16**(3):262-78.

Roberts 2018

Roberts LR, Sirlin CB, Zaiem F, Almasri J, Prokop LJ, Heimbach JK, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatology* 2018;**67**(1):401-21.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591–603.

Ryerson 2016

Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016;**122**(9):1312-37.

Sangiovanni 2010

Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 2010;**59**:638-44.

Schirner 2004

Schirner M, Menrad A, Stephens A, Frentzel T, Hauff P, Licha K. Molecular imaging of tumor angiogenesis. *Annals of the New York Academy of Sciences* 2004;**1014**:67-75.

Schuetz 2012

Schuetz GM, Schlattmann P, Dewey M. Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies. *BMJ (Clinical Research Ed.)* 2012;**345**:e6717.

Shah 2014

Shah S, Shukla A, Paunipagar B. Radiological features of hepatocellular carcinoma. *Journal of Clinical and Experimental Hepatology* 2014;**4**:63-6.

Silva 2008

Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 2008;**57**(11):1592-6.

Stanaway 2016

Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016;**388**:1081-8.

Takayasu 1990

Takayasu K, Moriyama N, Muramatsu Y, Makuuchi M, Hasegawa H, Okazaki N, et al. The diagnosis of small hepatocellular carcinomas: efficacy of various imaging procedures in 100 patients. *AJR. American Journal of Roentgenology* 1990;**155**:49-54.

Tang 2017

Tang A, McInnes M, Hope TA, Vu KN, Amre D, Wolfson T, et al. Magnetic resonance imaging performed with gadoxetate disodium for the diagnosis of hepatocellular carcinoma in cirrhotic and non-cirrhotic patients. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: 10.1002/14651858.CD012766]

Tao 1984

Tao LC, Ho CS, McLoughlin MJ, Evans WH, Donat EE. Cytologic diagnosis of hepatocellular carcinoma by fine-needle aspiration biopsy. *Cancer* 1984;**53**:547-52.

Thomsen 2014

Thomsen H, Webb J. Contrast Media Safety Issues and ESUR Guidelines. 3rd Edition. Berlin: Springer, 2014.

Wald 2013

Wald C, Russo MW, Heimbach JK, Hussain HK, Pomfret EA, Bruix J. New OPTN/UNOS policy for liver transplant allocation: standardization of liver imaging, diagnosis, classification, and reporting of hepatocellular carcinoma. *Radiology* 2013;**266**(2):376-82.

Whiting 2011

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8):529-36.

Wintermark 2010

Wintermark M, Lev MH. FDA investigates the safety of brain perfusion CT. *American Journal of Neuroradiology* 2010;**31**(1):2-3.

Yang 2011

Yang JD, Harmsen WS, Slettedahl SW, Chaiteerakij R, Enders FT, Therneau TM, et al. Factors that affect the risk for hepatocellular carcinoma and effects of surveillance. *Clinical Gastroenterology and Hepatology* 2011;**9**(7):617-23.

Ye 2015

Ye F, Liu J, Ouyang H. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging and multidetector-row computed tomography for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Medicine* 2015;**94**:e1157.

Yokoyama 1990

Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. *Hepato-gastroenterology* 1990;**37**(2):188-19.

Young 2012

Young AL, Adair R, Prasad KR, Toogood GJ, Lodge JP. Hepatocellular carcinoma within a noncirrhotic, nonfibrotic, seronegative liver: surgical approaches and outcomes. *Journal of the American College of Surgeons* 2012;**214**(2):174-83.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET) AND (((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) AND (advanc* and chronic and (liver* or hepat*))
The Cochrane Hepato-Biliary Group Diagnostic Test of Accuracy Studies Register	Date will be given at review stage.	(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET) AND (((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) AND (advanc* and chronic and (liver* or hepat*))
The Cochrane Library	Latest issue	#1 MeSH descriptor: [Tomography, Emission-Computed] explode all trees #2 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees #3 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees #4 (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET) #5 #1 or #2 or #3 or #4 #6 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #7 MeSH descriptor: [Liver Neoplasms] explode all trees #8 (((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) #9 #6 or #7 or #8

(Continued)

		#10 (advanc* and chronic and (liver* or hepat*)) #11 #5 and #9 and #10
MEDLINE Ovid	1946 to the date of search	1. exp Tomography, Emission-Computed/ 2. exp Tomography, X-Ray Computed/ 3. exp Magnetic Resonance Imaging/ 4. (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 5. 1 or 2 or 3 or 4 6. exp Carcinoma, Hepatocellular/ 7. exp Liver Neoplasms/ 8. (((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 9. 6 or 7 or 8 10. (advanc* and chronic and (liver* or hepat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 11. 5 and 9 and 10
Embase Ovid	1974 to the date of search	1. exp computer assisted tomography/ 2. exp positron emission tomography/ 3. exp nuclear magnetic resonance imaging/ 4. (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 5. 1 or 2 or 3 or 4 6. exp liver cell carcinoma/ 7. exp liver tumor/ 8. (((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 9. 6 or 7 or 8 10. (advanc* and chronic and (liver* or hepat*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

(Continued)

		11. 5 and 9 and 10
LILACS (Bireme)	1982 to the date of search	(computed tomograph$ or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET) [Words] and (((liver or hepato$) and (carcinom$ or cancer$ or neoplasm$ or malign$ or tumo$)) or HCC) [Words] and (advanc$ and chronic and (liver$ or hepat$)) [Words]
Science Citation Index Expanded	1900 to the date of search	#4 #3 AND #2 AND #1 #3 TS=(advanc* and chronic and (liver* or hepat*)) #2 TS=(((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) #1 TS=(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET)
Conference Proceedings Citation Index – Science	1990 to the date of search	#4 #3 AND #2 AND #1 #3 TS=(advanc* and chronic and (liver* or hepat*)) #2 TS=(((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) #1 TS=(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET)

Appendix 2. QUADAS 2

Domain	1. Participant selection	2. Index test	3. Reference standard	4. Flow and timing
Signalling questions and criteria	Q1: "*Was a consecutive or random sample of participants enrolled?*" Yes - If the study reports on a consecutive or a random selection of participants. No - if the study reports on another form of selection of participants. Unclear - if the study does not report on how the participants were enrolled. Q.2: "*Did the study avoid inappropriate exclusions*?" Yes - if definitions of exclusion criteria are appropriate (i.e. previous surgery or treatment for hepatocellular carcinoma; patients with cholangiocarcinoma) and all exclusions are reported.	Q1: "*Were the index test results interpreted without knowledge of the results of the reference standard?*" Yes - if the study reports that the results of the index test were interpreted without the knowledge of the results of the reference standard. No - if the study reports that results of the index test were interpreted with the results of the reference standard. Unclear - if the study does not report information about blinding of the results of the index test and reference standard. Q2: "*Were positivity criteria clearly defined?*"	Q1: "*Is the reference standard likely to correctly classify the target condition?*" Yes - if the reference standard correctly defines the presence/absence of HCC (pathology of explanted liver in a transplant cohort). No - if other reference tests than pathology of explanted liver were used. Unclear - if the study does not report on the reference standard used. Q2: "*Were the reference standard results interpreted without the knowledge of the results of the index test?*"	Q1: "*Was there an appropriate interval between the index test and the reference standard?*" Yes - if the interval between the index test and the reference standard was less than 3 months. No - if the interval was longer than 3 months. Unclear - if the study does not report the interval between the index test and the reference standard. Q2: "*Did all participants receive the same reference standard?*" Yes - if the study has only one reference standard for all the participants No - if the study has more than one reference stan-

(Continued)

	No - if exclusion criteria are inappropriate and exclusions are not reported. Unclear - if the study does not report causes of exclusions.	Yes - if the study clearly reports positivity criteria (i.e. the minimum diameter of a detectable lesion, exclusion of benign criteria). No - if the study does not report the positivity criteria. Unclear - if the study does not report information about the definition of positivity criteria	Yes - if the study reports that the results of the reference standard were interpreted without the knowledge of the results of the index test. No - if the study reports that the results of the reference standard were interpreted with the knowledge of the results of the index test. Unclear - if the study does not report information about blinding of the results of the reference standard and the index test.	dard.(histology of resected focal liver lesion(s), or the histology of focal liver lesion(s) with a follow-up period of at least six months in the participants with a negative result of the index test) Unclear - if the study information regarding the use of reference standard are unclear Q3: "*Were all participants included in the analysis and analysed according to intention to diagnose principle (non-evaluable results considered as false)?*" Yes - if all enrolled participants were included in the analysis and non-evaluable index test results were analysed according to the intention to diagnose principle). No - if any participant was excluded from the analysis for any reason or non-evaluable index test results were not analysed according to intention to diagnose principle. Unclear - if the exclusion of participants from the analysis is unclear.
Risk of bias	*Could the selection of participants have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" for at least one signalling question.	*Could the conduct or interpretation of the index test have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" for at least one signalling question or "Unclear" for the Q 2.	*Could the reference standard, its conduct, or its interpretation have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" for at least one signalling question or "Unclear" for the Q 2.	*Could the participant flow have introduced bias?* Low risk: "Yes" for all signalling questions. High risk: "No" for at least one signalling question.
Concerns about applicability	*Are there concerns that included participants and setting do not match the review question?* Low concern: the participants included in the review represent the participants in whom the tests is used in clinical practice (i.e.	*Are there concerns that the index test, its conduct, or interpretation differ from the review question?* Low concern: the index test, its conduct or its interpretation does not differ from the way it is used in clinical practice.	*Are there concerns that the target condition as defined by the reference standard does not match the question?* High concern: the definition of the target condition as defined by the reference standard does not	

(Continued)

	surveillance programme in patients with chronic advanced liver disease; clinical cohort of patients with chronic advanced liver disease). High concern: the participants included in the review differ from the participants in whom the tests is used in clinical practice (cohort of patients with advanced and decompensated liver disease, candidates for orthotopic liver transplantation).	High concern: the index test, its conduct or its interpretation differs from the way it is used in clinical practice.	match the question (i.e. pathology of the explanted liver is feasible only in the case of liver transplant; the natural history and prognosis of HCC detected in explanted liver might be different). Low concern: the definition of the target condition as defined by the reference standard does match the question for all included patients.

CONTRIBUTIONS OF AUTHORS

TN wrote the protocol and will perform searches for references, evaluate references for obtaining the full reports, evaluate studies for inclusion, extract data from studies, assess the risk of bias, and write the final review.
VG commented on the protocol and will perform searches for references, evaluate references for obtaining the full reports, evaluate studies for inclusion, extract data from studies, assess the risk of bias, and write the final review.
AC co-ordinated the protocol design and will design the final review.
MF will perform searches for references and critically comment on the review.
GC wrote the protocol, provided statistical expert opinion and will critically comment on the final review.
DM commented on the protocol and will critically comment on the final review.
DŠ critically commented on the protocol, will act as arbiter if review authors cannot reach a consensus, and will critically comment on the final review.

All authors approved the publication of the protocol.

DECLARATIONS OF INTEREST

TN: none known.
VG: none known.
AC: none known.
MF: none known.
GC: none known.
DM: none known.
DŠ: none known.