Digestive and Liver Disease 47 (2015) 877–883

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Systematic review of guidelines for management of intermediate hepatocellular carcinoma using the Appraisal of Guidelines Research and Evaluation II instrument

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ARTICLE INFO

Article history:
Received 17 March 2015
Accepted 7 July 2015
Available online 15 July 2015

Keywords:
Appraisal of Guidelines Research and Evaluation II instrument
Clinical practice guidelines
Hepatocellular carcinoma
Transarterial chemoembolization

ABSTRACT

Background: Hepatocellular carcinoma is the second leading cause of cancer-related mortality worldwide. Multiple guidelines have been developed to assist clinicians in its management. We aimed to explore methodological quality of these guidelines focusing on treatment of intermediate hepatocellular carcinoma by transarterial chemoembolization.
Methods: A systematic search was performed for Clinical Practice Guidelines and Consensus statements for hepatocellular carcinoma management. Guideline quality was appraised using the Appraisal of Guidelines Research and Evaluation II instrument, which rates guideline development processes across 6 domains: 'Scope and purpose', 'Stakeholder involvement', 'Rigour of development', 'Clarity of presentation', 'Applicability' and 'Editorial independence'. Thematic analysis of guidelines was performed to map differences in recommendations.
Results: Quality of 21 included guidelines varied widely, but was overall poor with only one guideline passing the 50% mark on all domains. Key recommendations as (contra)indications and technical aspects were inconsistent between guidelines. Aspects on side effects and health economics were mainly neglected.
Conclusions: Methodological quality of guidelines on transarterial chemoembolization in hepatocellular carcinoma management is poor. This results in important discrepancies between guideline recommendations, creating confusion in clinical practice. Incorporation of the Appraisal of Guidelines Research and Evaluation II instrument in guideline development may improve quality of future guidelines by increasing focus on methodological aspects.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related mortality worldwide [1]. HCC is frequently associated with liver cirrhosis complicating therapeutic strategies. Overall, one-third of cirrhotic patients will develop HCC during their lifetime [2].

Prognosis and treatment of HCC is based on the Barcelona Clinic Liver Cancer (BCLC) staging system, which combines information about tumour, functional liver status, patient performance and presence of cancer-related symptoms. Early stage HCC (BCLC A), which is characterized by a preserved liver function (Child–Pugh A/B) and a solitary HCC nodule or up to 3 nodules less than 3 cm in size, is currently the only approved indication for curative treatment with liver transplantation or resection [3,4]. However, this condition represents only ~20% of patients with HCC [2,3]. Most patients present with advanced disease (BCLC B/C) for which variable therapeutic options are available, including percutaneous ablation, transarterial chemo-embolization (TACE) and treatment with sorafenib, which makes it difficult for the clinician to select the most optimal strategy. Clinical practice guidelines provide evidence-based recommendations to help with these therapeutic

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http://dx.doi.org/10.1016/j.dld.2015.07.005
1590-8658/

dilemmas. As HCC is a cancer type managed by different specialties as Oncology, Gastroenterology and Hepatology, there is currently a plethora of HCC management guidelines.

In most of these guidelines TACE is recommended as the preferred technique for management of intermediate HCC (BCLC B). TACE exploits the preferentially hepatic arterial blood supply of HCC lesions to transarterially deliver chemotherapeutic agents in proximity to the tumour followed by vessel embolization. This locally administrated chemotherapy is thought to work synergistically with the embolization-induced ischaemic damage.

However, TACE remains a controversial technique. Firstly, there is an important amount of heterogeneity between different TACE protocols and there is no well-defined gold standard. An essential source of variation is the chemotherapeutic agent used with doxorubicin being most frequently administrated, but cisplatin, epirubicin and mitoxantrone are also in use. Additionally, dosing is not clearly defined, with reported doses of doxorubicin ranging from 50 to 150 mg [5]. As a vehicle for these agents lipiodol is used in most but not all protocols, and, when used, its preparation is not standardized [6]. Product administration is followed by hepatic artery obstruction for which again multiple systems are used, including gelfoam particles, polyvinyl alcohol, starch microspheres, metallic coils and autologous blood cloths. Number of treatments necessary is not objectively defined, leading to a highly variable number of procedures per patient.

Secondly, evidence for therapeutic efficacy of TACE is inconsistent. Although initial studies demonstrated a survival benefit over best supportive care [7,8], there were important methodological issues [9]. Recent studies failed to show beneficial effects of TACE or suffered from similar methodological issues [10,11]. Accordingly, a recent Cochrane meta-analysis concluded that there was insufficient evidence to justify the prominent position of TACE in the management of intermediate HCC [9].

Lastly, TACE is a relatively expensive technique [12] and few studies provide information about cost-effectiveness.

In light of these controversies associated with TACE, we evaluated the quality of current HCC guidelines with primary focus on this therapeutic option, using the AGREE II instrument, a standardized and reliable technique for comparing methodological integrity between different guidelines [13,14]. Additionally, we planned a thematic analysis to elucidate discrepancies between guidelines and their underlying rationale.

2. Materials and methods

2.1. Criteria for study selection

Evidence-based clinical practice guidelines and consensus statements on treatment of HCC were included. Clinical practice guidelines were defined as statements that included recommendations intended to optimize patient care and were based on systematic review of published evidence [13]. Consensus statements were defined as documents containing recommendations based on the collective opinion of an expert panel [13]. We included English, French and Dutch publications. Guidelines related to diagnosis alone, conference or discussion papers, personal opinions and obsolete guidelines were excluded.

2.2. Search methods for guidelines and consensus statements

We searched MEDLINE (1946 to June 2015) and EMBASE (1980 to June 2015), combining vocabulary terms for HCC with terms related to clinical practice guideline. We also searched guideline databases, as well as selected specialist societies in Hepatology, Gastroenterology, Radiology and Oncology. YV, SR and TH independently screened titles and abstracts and discarded those that did not meet the inclusion criteria. Full texts for potentially relevant guidance documents were retrieved and examined for eligibility.

2.3. Data collection process and data items

We developed a template data extraction form to support the thematic analysis. Extracted data included document characteristics (e.g. year of publication, country, development team, funding source) and recommendations related to the treatment of intermediate HCC. YV, SR and TH extracted all data using a standardized data extraction form and resolved discrepancies by consensus.

2.4. Appraisal of guidelines and consensus statements

Five trained reviewers (HV, KG, YV, SR, and TH) independently rated guidelines using the AGREE II instrument [14], which is an internationally validated 23-item tool used to evaluate 6 domains of guideline development: 'Scope and purpose', 'Stakeholder involvement', 'Rigour of development', 'Clarity and presentation', 'Applicability' and 'Editorial independence' [15]. Reviewers rated each item on a Likert scale from 1 ('Strongly Disagree') to 7 ('Strongly Agree'). A total score for each domain was calculated as follows:

$$\frac{\textit{Obtained score} - \textit{Minimum possible score}}{\textit{Maximum possible score} - \textit{Minimum possible score}} \times 100\%$$

Minimum possible score for each domain equalled number of questions multiplied by number of reviewers, multiplied by 1 ('Strongly disagree'). Maximum possible score for each domain equalled number of questions multiplied by number of reviewers, multiplied by 7 ('Strongly agree'). To ensure standardization of each reviewer's approach, all reviewers completed the online training tutorial (http://www.agreetrust.org) before starting the appraisal.

In a consensus meeting, item scores that differed more than 2 points on the original seven-point scale were discussed. Reviewers explained the rationale for their score and had the opportunity to revise their score when they considered this appropriate.

3. Results

3.1. Search results

We identified 133 citations, of which we excluded 90 based on title and abstract (Fig. 1). The full text of the remaining 43 citations was assessed and 22 citations were excluded because they were not related to the management of HCC, were not clinical practice guidelines or consensus statements or were guidelines replaced by an updated version. Ultimately, 14 clinical practice guidelines [3,16–28] and 7 consensus statements [29–35] were included. Sixteen of these documents were retrieved through searching medical databases [3,16–19,21–31], the others through the search of guideline databases and professional society websites [20,32–35].

Supplementary Table S1 summarizes general characteristics of included clinical practice guidelines and consensus statements. Fifteen national organizations [17–19,21,22,31–35] and 6 international groups [3,16,20,23,29,30] published these guidelines between 2003 and 2013. Two guidelines specifically covered TACE alone [22,23], while 19 covered HCC management more broadly. Thirteen guidelines applied an internationally recognized evidence scoring system [3,16,17,19–21,24,27,28,30,32,36] and 6 graded the strength of the guidance recommendations themselves [3,16,17,19,32,34] (Supplementary Table S1).