Characterization of focal liver lesions using a rule-based decision support system: initial results

Poster No.: C-1123
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Abdomen, Liver, Computer applications, CT, MR, Ultrasound, CAD, Computer Applications-Detection, diagnosis, Observer performance, Education and training, Quality assurance, Tissue characterisation
DOI: 10.1594/ecr2014/C-1123

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Aims and objectives

PURPOSE

The purpose of this study was to assess the performance and subjective acceptance of a newly developed rule-based decision support (DS) system for radiologic characterization of focal liver pathology.

In order to compare with current clinical practice, observers were asked to provide a diagnosis and / or differential diagnosis (1) without any help, (2) with help of books and existing online resources, and (3) with help of the DS system.

BACKGROUND

Although rule-based DS systems have been shown to improve practitioner performance in many areas of medicine [2, 4-6], their use in diagnostic radiology is almost non-existent. Currently, making accurate diagnoses is still based on personal experience, advice of colleagues, and, if needed, search of pertinent information in Internet resources and textbooks. Each unusual or difficult case (e.g. rare diseases, or atypical presentations of common or uncommon diseases) may initiate a time-consuming search for information, with negative effect on workflow efficiency and professional satisfaction.

Based on the experience with DS systems in other areas, there seems to be no reason why they could not play a supportive role in diagnostic radiology, provided that they are designed in accordance to the specific needs of radiologists. Currently however, few such systems have been developed and tested.

In this study, a classic rule-based expert system was tested.

STRUCTURE OF A RULE-BASED EXPERT SYSTEM

A rule based expert system has 4 components: the knowledge base, the database, the interference engine, and the user interface (Fig. 1 on page 4).

The knowledge base contains the domain knowledge useful for problem solving. In a rule-based expert system, the knowledge is represented as a set of rules. Each rule specifies a relation and has an IF (condition) THEN (action) structure. An example of a rule may be:
IF

The patient has cirrhosis,

AND there is a hyperenhancing liver lesion,

AND the size of the lesion is > 2cm,

AND the lesion has a capsule,

AND there is delayed-phase washout;

THEN

The diagnosis of hepatocellular carcinoma (HCC) is almost certain.

The database includes a set of facts used to match against the IF parts of the rules stored in the knowledge base.

The interference engine carries out the reasoning whereby the expert system reaches a solution.

The user interface is the means of communication between a user seeking a solution to the problem, and the expert system.
**Fig. 1:** Basic structure of a rule-based expert system.

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Methods and materials

THE DS SYSTEM

An extensive browser-based DS system was built for the characterization of liver pathology. Starting from a patient’s radiologic studies that are available to the user, the system confronts the latter with a number of categorized questions, in an attempt to narrow down the differential diagnosis through evidence-based rules.

After logging on to the application's home page, the user is invited to check the available types of images (magnetic resonance, computed tomography, and/or ultrasound) and to provide the system with the patient's cirrhotic status (positive versus negative, or not known).

Subsequently, the user is requested to categorize the abnormality by selecting a category of disease (e.g., "cystic" or "solid"). Categories of disease are subdivided in several subcategories and second level subcategories (e.g. "complex cyst" versus "simple cyst"). Clear definitions and examples are provided for all categories and subcategories.

Once a second level subcategory has been chosen, the user receives a set of pertinent patient- and image-related questions. These questions reflect the questions an expert would ask when confronted with a similar case. Based on the answers to these questions, one of more possible diagnoses, and their relative likelihood, are proposed by the DS system.

The DS system not only proposes one or more diagnoses, but also displays the underlying rules, thus explaining why a specific diagnosis is proposed and why others are considered unlikely.

TEST CASES

Images of 50 patients with proven diagnosis were used to test the DS system.

To be included in the study, cases needed diagnostic confirmation by means of histopathology, laboratory testing, and/or repeated long-term follow-up.

Pediatric cases and extremely infrequent pathologies were excluded from the test cases.
For practical reasons, cases were bundled into a PowerPoint presentation, consisting of a few slides per case, showing key ultrasound, CT, and/or or MRI images, and relevant clinical information and/or laboratory findings.

The diagnoses included in the 50 test cases are listed up in Fig. 2 on page 7.

STUDY DESIGN

Twelve observers (4 radiologists, 4 radiology residents, 2 gastroenterologists, and 2 medical students) were asked to double-interpret 20 cases, randomly chosen from the 50 available cases: first without any help and subsequently with the help of either the rule-based DS system or existing resources. In each test, 10 cases were interpreted using the DS system and 10 cases using existing resources. Existing resources included free online resources, commercially available diagnostic support systems, and/or books, freely chosen according to the observer's preference.

Observers were asked to provide either a "likely" diagnosis (option A), or a maximum of three possible diagnoses (either with or without preference for one of these) (option B). Alternatively, option C could be chosen, meaning that the observer could not suggest a specific diagnosis.

A proposed diagnosis was considered correct if the actual diagnosis was within the top-3 of suggested diagnoses (options A or B).

The "reporting time" (time needed to suggest one or more diagnoses) was measured for each case.

Finally, subjective acceptance of the DS system versus existing resources was assessed using a five-point grading scale (1: very poor; 5: excellent).
**Fig. 2:** 50 test cases in alphabetical order. Numbers between brackets indicate that more than one case was tested for a given type of lesion, e.g., four different cases of cavernous hemangioma were included in the 50 test cases.

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Results

SUMMARY OF RESULTS

Categorized by the 4 groups of observers and by the degree / type of assistance (none, existing resources, DS system), the respective results for diagnostic accuracy are as follows: 25, 55, and 90% for medical students; 45, 55, and 90% for radiology residents; 55, 62, and 90% for gastroenterologists, and 65, 72, and 93% for radiologists (Fig. 3 on page 12).

Results obtained with the DS system were better in all groups (p<0.05).

The average time needed to solve a single test case was 2.5, 4.3, and 3.4 minutes, respectively (Fig. 4 on page 12).

The average qualitative score assigned to the help obtained from the diagnostic support was 3.4 for the existing resources versus 4.5 for the rule-based system (Fig. 5 on page 12).

CASE EXAMPLES

CASE 1 (Fig. 6 on page 13) concerned a 45-year-old woman with a history of breast cancer.

MR images showing two focal lesions in the right liver lobe.

Final diagnosis was hepatocellular adenoma.

The diagnosis was correctly proposed by the DS system, based on lesion- and patient-related characteristics, including arterial phase hyperenhancement, homogeneous aspect, fading in portal venous phase, and lack of uptake of hepatobiliary-specific contrast medium, in a female patient without cirrhosis. Without the DS system, some observers misclassified the lesions as metastasis, hepatocellular carcinoma, or focal nodular hyperplasia.

CASE 2 (Fig. 7 on page 15) was a 37-year-old woman with an incidentally discovered solitary liver lesion. She had antecedents of acute hepatitis C, but no cirrhosis.
MR showed a focal lesion in the left liver lobe with mild hyperenhancement in the arterial phase and washout in the subsequent contrast phases.

Final diagnosis was HNF-1 alpha-mutated hepatocellular adenoma.

The diagnosis was correctly proposed by the DS system, despite the presence of washout, based on lesion- and patient-related characteristics, including signal loss of the entire lesion on gradient-echo T1-weighted images in opposed-phase. Without the DS system, the lesion tended to be misclassified as hepatocellular carcinoma.

**CASE 3** (Fig. 8 on page 16) concerned a 47-year-old woman with progressive weight loss and abdominal discomfort. There were no relevant medical antecedents. Tumor markers were within normal limits.

CT and MR images showing several focal lesions with predominant subcapsular location.

Final diagnosis was epithelioid hemangioendothelioma.

The diagnosis was correctly proposed by the DS system based on lesion- and patient-related characteristics, including multiple heterogeneous hypoenhancing lesions, hyperintense on T2-weighted images, predominantly peripheral location, capsular retraction, and normal tumor marker levels. Without the DS system, the lesion tended to be misclassified as metastases or multifocal cholangiocarcinoma.

**CASE 4** (Fig. 9 on page 16) was a 65-year-old woman with nausea and history of colon cancer.

CT showed a single heterogeneously enhancing lesion in segment 8 of the liver.

Final diagnosis was intrahepatic cholangiocarcinoma.

The diagnosis was correctly proposed by the DS system based on lesion- and patient-related characteristics, including heterogeneous hyperenhancement, and progressive delayed enhancement during portal venous and equilibrium phase. Without the DS system, some observers misclassified the lesion as metastasis or cavernous hemangioma.

**RESULTS INTERPRETATION**

The DS system proved to be a helpful tool for radiological characterization of focal liver lesions. As could be expected, the use of both the DS system and existing resources increased diagnostic accuracy.
Surprisingly, the results obtained with the DS system were far superior to those obtained with help of existing online or offline resources. Several factors may contribute to these results.

First, conventional search-based methods rely on what is searched for by the observer. If, for instance, an observer searches online encyclopedic resources for examples of intrahepatic cholangiocarcinoma, it is unsure whether or not he/she will find information pointing to the diagnosis of epithelioid hemangioendothelioma (Fig. 8 on page 16). As such, rare diseases tend to be overlooked.

Second, in current CT and MR imaging, many different types of images are available, including non-enhanced images, contrast-enhanced images obtained in the arterial phase, portal venous phase, equilibrium phase, and hepatobiliary phase, DWI images, T1-weighted images in and out-of-phase, and T2-weighted images. With the exception of subspecialty experts, observers (both radiologists and non-radiologists) may have difficulty in interpreting specific findings, particularly in cases were different features may have an apparently conflicting significance. As an example, the presence of several hyperenhancing liver lesions not showing uptake of liver-specific contrast medium may be considered suggestive of metastatic cancer in a patient with history of breast carcinoma, while isointensity at T1 may argue against this diagnosis (Fig. 6 on page 13). Observers may be confused about the relative "weight" of the different arguments in favor or against a particular diagnosis. In a rule-based DS system, the significance of such combinations of findings can be expressed as a set of rules. Once the rules have been entered into the system, and assuming that they are correctly formulated, suggesting a diagnosis becomes easy, even for a non-expert confronted with an atypical or rare case.

The difference in subjective acceptance of the DS system versus existing online resources was inversely related to the expertise of the observers. While radiologists are used to search the Internet to find diagnostic support, medical students indicated a marked preference for using the DS system. One of the reasons is that the rationale for proposing a specific diagnosis is explained in the DS system by displaying the underlying rule (e.g. "cirrhosis" + "hyperenhancing" + "size > 2cm" + "capsule" + "washout" = HCC likely). This feature was found to be of excellent didactic value by all observers.

Previously, the clinical introduction of DS systems and other systems for structured reporting has been slow, partially because of suboptimal acceptance by users. One of the critical elements in this respect is the time needed to propose a specific diagnosis or differential diagnosis. The results obtained with the DS system tested in this study were encouraging in this respect: use of the DS system did not have a significant negative impact on reporting time.

LIMITATIONS
This study does not answer the question whether or not rule-based DS systems will be useful in daily radiological practice. One of the challenges in the development of rule-bases DS systems is to make the systems work for new cases with unknown diagnosis. In our study, the DS system was tested with cases that had already been used as input to the system (in order to optimize the rules). While the results of the study show that DS systems show promise in terms of diagnostic accuracy, reporting time and user acceptance, further studies are required to test their robustness in clinical practice with a large number of observers and new patient material.
Fig. 3: Results for diagnostic accuracy. Results obtained with the DS system were better in all groups (p<0.05).

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Fig. 4: Average time needed per case. On average, use of the DS system was less time-consuming than use of existing online resources and/or books.

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Fig. 5: Subjective scores. The DS system was preferred over existing resources, particularly by less-experienced observers.

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Fig. 6: 45-year-old woman with a history of breast cancer. MR images showing two focal lesions in the right liver lobe. Final diagnosis was hepatocellular adenoma. The diagnosis was correctly proposed by the DS system, based on lesion- and patient-related characteristics, including arterial phase hyperenhancement, homogeneous aspect, fading in portal venous phase, and lack of uptake of hepatobiliary-specific contrast medium, in a female patient without cirrhosis. Without the DS system, some observers misclassified the lesions as metastasis, hepatocellular carcinoma, or focal nodular hyperplasia. A. T2-weighted image showing two lesions, one mildly hyperintense, another nearly isointense (arrows). B. Contrast-enhanced arterial phase fat-suppressed T1-weighted image, showing two mildly hyperenhancing lesions with homogeneous aspect (arrows). C. Portal venous fat-suppressed T1-weighted image showing "fading" (the lesions become almost isointense to normal parenchyma) (arrows). D. Fat-suppressed T1-weighted image obtained in the hepatobiliary phase after Gd-EOB-DTPA administration. Only one of the lesions is seen in this image (arrow), but neither lesion showed uptake.
**Fig. 7:** 37-year-old woman with an incidentally discovered solitary liver lesion. She had antecedents of acute hepatitis C, but no cirrhosis. MR showed a focal lesion in the left liver lobe with mild hyperenhancement in the arterial phase and washout in the subsequent contrast phases. Final diagnosis was HNF-1 alpha-mutated hepatocellular adenoma. The diagnosis was correctly proposed by the DS system, despite the presence of washout, based on lesion- and patient-related characteristics, including signal loss of the entire lesion on gradient-echo T1-weighted images in opposed-phase. Without the DS system, the lesion tended to be misclassified as hepatocellular carcinoma. A. T2-weighted image showing a hyperintense lesion (arrow). B. Contrast-enhanced arterial phase (left) and portal venous phase (right) fat-suppressed T1-weighted images, showing a mildly hyperenhancing lesion with subtle washout (arrows). C, D. Gradient-echo T1-weighted images in-phase (C) and out-of-phase (D), showing signal drop of the entire lesion in the out-of-phase image (arrows).
**Fig. 8:** 47-year-old woman with progressive weight loss and abdominal discomfort. There were no relevant medical antecedents. Tumor markers were within normal limits. CT and MR images showing several focal lesions with predominant subcapsular location. Final diagnosis was epithelioid hemangioendothelioma. The diagnosis was correctly proposed by the DS system based on lesion- and patient-related characteristics, including multiple heterogeneous hypoenhancing lesions, hyperintense on T2-weighted images, predominantly peripheral location, capsular retraction, and normal tumor marker levels. Without the DS system, the lesion tended to be misclassified as metastases or multifocal cholangiocarcinoma. A. Contrast-enhanced CT image obtained in the portal venous phase shows four large hypoenhancing lesions, some with capsular retraction (arrows). B, C. The lesions are moderately hyperintense on T2-weighted images and homogeneously hypointense on fat-suppressed T1-weighted images (arrows). D. Contrast-enhanced portal venous phase fat-suppressed T1-weighted image shows heterogeneous enhancement (arrows).

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Fig. 9: 65-year-old woman with nausea and history of colon cancer. CT showed a single heterogeneously enhancing lesion in segment 8 of the liver. Final diagnosis was intrahepatic cholangiocarcinoma. The diagnosis was correctly proposed by the DS system based on lesion- and patient-related characteristics, including heterogeneous hyperenhancement, and progressive delayed enhancement during portal venous and equilibrium phase. Without the DS system, some observers misclassified the lesion as metastasis or cavernous hemangioma. A, B. Contrast-enhanced CT images obtained in portal venous and equilibrium phases, respectively. Note a lesion with heterogeneous hyperenhancement and progressive "hemangioma-like" fill-in (arrows). C. CT image 2 years later, showing marked increase in size (arrow). Note: only images A and B were shown to the observers.

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Conclusion

DISCUSSION

As early as 1959, Ledley and Lusted suggested that computers could help doctors in the diagnostic process [1].

Coined as electronic systems designed to aid directly in clinical decision-making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration [2], clinical decision support systems or so-called expert systems [3] remain a major topic of artificial intelligence in medicine, with 300 to 500 PubMed citations in the last 5 years alone.

Systematic reviews have shown that clinical DS systems can significantly improve practitioner performance and patient outcome [2, 4-6]. Moreover, recent studies demonstrated a significant beneficial effect on the quality of medicine residents' differential diagnoses and management plans, along with huge potential cost-saving effects for teaching hospitals [3, 7, 8].

Features associated with success include the following [2]: the system is integrated into the clinical workflow rather than available as a separate log-in or screen; the system is electronic rather than paper-based; the system provides decision support at the time and location of care; and the system provides recommendations for care, not just assessments.

The profoundly complex nature of biological systems and the need for continuous integration of new data from clinical research are some other challenges for DS systems [9].

DS systems can be classified as knowledge-based or non-knowledge-based.

Anything from alerts, reminders, order sets, drug-dose calculations, care summary dashboards, information retrieval tools, to more encyclopedia-like knowledge resources, can be considered as knowledge-based decision support systems [6]. In more elaborate systems, the knowledge base contains rules and associations of compiled data, which often take the form of if-then rules; e.g., in a system for determining drug interactions, a rule might be that if drug X is taken together with drug Y, then the user should be alerted [9].

A Bayesian network is a knowledge-based graphical representation that shows a set of variables and their probabilistic relationships between diseases and symptoms. They are
based on conditional probabilities, the probability of an event given the occurrence of another event, such as the interpretation of diagnostic tests [9-11].

DS systems that do not use a knowledge base use a form of artificial intelligence called machine learning, which allows computers to learn from past experiences and/or find patterns in data [9].

Diagnostic DS systems are a subset of clinical DS systems, proposing a set of appropriate diagnoses from the patient's data [9]; they are designed to be interactive and aid in decision-making, rather than to provide the "right" answer to a particular problem [12].

The DS system tested in this study is a diagnostic knowledge-based DS system where simple if-then rules are combined with a limited number of more complex Bayes' rules, specifically developed for the characterization of liver pathology. Starting from a patient's radiologic studies, a series of well directed questions conduct the user to a concise, evidence-based differential diagnosis, sometimes even to a single preferential diagnosis.

In our study, 4 groups of observers, comprising radiologists, radiology residents, gastroenterologists, and medical students, were asked to interpret a total of 50 cases of liver disease independently, with the assistance of an established knowledge resources, and with the newly developed rule-based DS system.

For all 4 groups, diagnostic performance significantly improved with use of the rule-based DS system.

We assume that the approach with dedicated questions, inherent to the rule-based system, is at least partly responsible for these results, because it reminds the observers of important clues and features that might otherwise have been missed and/or neglected.

Although the small amount of data analyzed in this study is a critical weakness, we feel encouraged by our own promising results, as well as the favorable results from other studies related to DS systems in general.

In the current environment of the Internet and widespread availability of personal computers, tablets, and smartphones, the potential for routine use of decision-support systems to assist health professionals in the diagnostic process has become reality, especially when these systems succeed in overcoming certain clinical and technical challenges, as mentioned above.

FINAL CONCLUSION
In this study, use of a rule-based diagnostic support system significantly improved the radiological characterization of focal liver lesions. In addition, it proved a helpful didactic tool, also for non-radiologists, residents and medical students. These results are encouraging and suggest the need for further research on the potential future role of rule-based DS systems in radiology.
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