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DEVELOPMENT OF AN INTELLIGENT SUPPORT SYSTEM FOR HEPATOCELLULAR CARCINOMA TREATMENT SELECTION

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The object of the study is the clinical decision-making process for selecting of hepatocellular carcinoma (HCC) treatment method based on the patient's medical data. The process of the HCC treatment method selection remains poorly formalized and is characterized by multi-criteria and the presence of numerous clinical situations, for each of which it is necessary to promptly identify the most accurate therapeutic solution.

This study develops an intelligent medical decision support system for HCC treatment method selection based on knowledge applicable in clinical practice.

It offers architectural and functional principles of the intelligent decision support system, classifying clinical situations by HCC treatment method, consisting of multiple possible combinations of 44 informative parameters. Based on the current values of these parameters, expert knowledge is transformed into production rules identifying HCC treatment methods.

A heuristic procedure treatment selection is developed based on production rule analysis in accordance with current parameter values, reproducing the reasoning patterns of participants in a multidisciplinary council during their consensus decision-making process regarding HCC treatment appointment. A software implementation of a decision-making model for HCC treatment selection, implemented in C# using the Visual Study 2019 platform, enabled the integration of an intelligent system with web technologies.

The intelligent medical decision support system automates the unique experience of professionals and helps physicians in a multidisciplinary consultation make prompt and informed decisions online regarding the appointment of personalized therapy. The system was piloted with expert physicians in several iterations until complete match between the consensus decision of the multidisciplinary council and the decision made by the developed system in accordance with clinical recommendations was achieved

Keywords: hepatocellular carcinoma, treatment selection, intelligent decision support system, knowledge base

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1. Introduction

Among the most widespread malignant liver tumors, HCC is one of the main causes of cancer-related death in the world [1]. HCC is rated 5–6th in terms of incidence among cancers. HCC is diagnosed in about one million people worldwide every year [2]. HCC, the most widespread among malignant liver tumors, reveals in various clinical conditions and is often mistaken for hepatitis and cirrhosis [3].

The main diagnostic sign of HCC is contrast retention in the arterial phase and contrast washout in the venous phase. It is most common in people aged 60–70 and mainly in males (2.5 times more often than in females). In some risk countries (Far East, Africa), it is more often observed in people aged 30–40.HCC is a progressive and irreversible process and, if not treated, causes complications and lethality within a few months. The following methods are used in the treatment of HCC [4, 5]:

– surgical treatments – liver resection and transplantation;

– loco-regional treatments – ablations (thermal, electro and chemical destructions), intraarterial embolization (chemoembolization, radioembolization), radiotherapy, arterial infusions;

– systemic anticancer treatments (targeted, immunotherapy, cytotoxic chemotherapy);

– symptomatic treatments.

Liver resection, transplantation and ablations of small tumors are considered radical treatments of HCC. Loco-regional and systemic methods aim to reduce tumor progression and aggressiveness. Indications for liver resection in HCC are as follows [6, 7]:

– tumor is resectable – according to its bio-behavior, it is suitable for surgery, there is no metastasis or it can be removed, the tumor can be completely removed and the blood supply of the remaining liver is preserved, there is no invasion of large vessels and surrounding organs;

– the liver is resectable – it has sufficient reserves (no or minimal parenchymal disease and dysfunction), there is no portal hypertension, the remaining liver volume is sufficient (more than 30% in normal liver, more than 50% in cirrhosis);

– the patient is operable – comorbidities and performance allow surgery.

The indications for liver transplantation in HCC are as follows:

– the tumor is transplantable – the tumor can be removed, the tumor has a favorable bio-behavior (low aggressiveness): its size is less than 5 cm, its number is less than 3, there is no invasion or metastasis to large vessels, lymph nodes, or surrounding organs, AFP (α-fetoprotein is a primary liver cancer marker) level is below 200–400;

– transplantation is possible – there is a donor organ, there are no contraindications to immunosuppression and pulmonary hypertension;

– the patient is operable – concomitant diseases and performance allow surgery and immunosuppression.

In the presence of contraindications to surgery, that is, signs of unresectable, non-transplantable, and inoperability, resection and transplantation are considered contraindicated. In general, the classical approach to the treatment of HCC takes into account the stage of the disease, the tumor's bio-behavior, the liver's condition, the patient's general status, and the effectiveness of the method [7, 8].

The first choice in treatment is radical methods (resection, transplantation), the second choice is locoregional treatments (ablation, embolization), the third choice is systemic anticancer therapies, and the last choice is symptomatic treatment.

For the general approach algorithm, international classifications (clinical, NCCN, Barcelona, Milan, Malatya, etc.) are recommended, and for the individual treatment selection, discussion in a multidisciplinary council is suggested [2].

The above shows that a large number of parameters refers to in the treatment selection of HCC, which is represented by various clinical symptoms. According to the clinical situations arising from the various combinations of values that these parameters can take, one of the above treatment methods is selected in the multidisciplinary council for stage-based treatment selection.

The large number, complexity, hierarchy, and quantitative and qualitative nature of the aforementioned parameters characterize the HCC treatment methods choosing under conditions of uncertainty. One of the most effective approaches to solve this problem is the development of intelligent systems based on the knowledge of medical specialists.

Therefore, research on the development of an intelligent system for supporting the choice of a method for treatment of hepatocellular cancer is relevant.

2. Literature review and problem statement

The study [9] examined the development of an intelligent system for diagnosing liver diseases based on the integration of principal component analysis (PCA) and k-nearest neighbors (KNN) methods. The liver disease prognosis results offered by the system based on the liver patient dataset are compared using metrics such as accuracy, sensitivity, and specificity. Although the study obtained high results according to the specified criteria, these data are aimed at demonstrating the effectiveness of the proposed approach and have no practical application. The liver patient dataset also does not identify specific liver diseases, although specific features characterize each of them.

In the study [10], a hybrid machine learning method using support vector machine (SVM) and simulated annealing (SA) algorithms for hepatitis diagnosis based on a dataset from the UCI database was proposed. Classification accuracy is achieved using 10-fold cross-validation. Similar to the results obtained in [9], the high classification accuracy demonstrates the effectiveness of the proposed hybrid approach compared to other machine learning methods described in the literature. However, the authors do not provide any practical implementation of the obtained results.

In [11], the integration of artificial neural networks and genetic algorithms is performed to detect liver diseases and stadialization liver fibrosis in chronic hepatitis C. A comparative analysis of the experimental results of the proposed tandem approach based on the analysis of a statistical dataset showed the advantage of this approach compared to the results obtained for solving similar problems using other methods. It should be noted that despite the high effectiveness of identifying stages of liver fibrosis, the study has not been implemented in clinical practice. The main reason for this is, first of all, the lack of trust among doctors in the results obtained, as well as the unresolved legal and ethical issues of introducing new artificial intelligence methods in medicine.

In [12], a model for segmentation of liver tumors based on computer tomography (CT) images is proposed. The probability distribution of liver tumors is estimated using fuzzy clustering to improve object identification. Although the model proposed by the authors allows for more accurate identification of liver tumors, the issues of further use of the obtained results in making diagnostic or treatment decisions remain unaddressed.

In the study [13] towards the development of next-generation medical decision support systems that provide higher accuracy in diagnosis and prognosis, the authors proposed an approach for liver failure based on a combination of principal component analysis (PCA) and a multilayer perceptron (MLP) neural network. The performance of the proposed system was evaluated on two validated datasets, compared with reference methods and showed improvement in key metrics such as accuracy, sensitivity and specificity. However, it should be noted that an important drawback of the study is that the experiments conducted were limited to only two standard data sets, which leaves the possibility of generalizing the results to different clinical populations unproven.

Artificial neural networks are used for different tasks, for example, there are interesting their applications to diagnose acute lymphoblastic leukemia [14–16].

Analysis of white blood cells from blood can help to detect Acute Lymphoblastic Leukemia, a potentially fatal blood cancer if left untreated. An expert typically performs the morphological analysis of blood cells images manually; however, this method has numerous drawbacks, including slow analysis, low precision, and the results depend on the operator's skill. An automated method for the identification and classification of white blood cells using microscopic images of peripheral blood smears was developed. The authors propose describing every image using brightness, contrast, and micro-contour orientation histograms. These parameters are the inputs for the neural classifiers, the Random Threshold Classifier (RTC) [14, 15] or Limited Receptive Area (LIRA) neural classifier [16]. The classifier's output is the recognized class, which is either a healthy cell or an Acute Lymphoblastic Leukemia-affected cell. The proposed RTC achieved a recognition rate of 98.3% when the data has partitioned on 80% training set and 20% testing set [14, 15]. LIRA neural classifier achieved a rate of 96.56% [16]. The both systems based on RTC and LIRA were evaluated using the public dataset of peripheral blood samples from Acute Lymphoblastic Leukemia Image Database. These approaches can be useful for medical diagnosticians and are a good tool that will help speed up the diagnostic process. The disadvantage of these works is the limited size of the real database used to conduct the experiments. It is important to mention that these systems can serve as a computational tool for detection of other diseases, where blood cells undergo alterations, such as Covid-19 or liver diseases as HCC.

An analysis of the problems identified in related works allows to draw the following conclusion: the majority of research is devoted to the development of hybrid intelligent systems for supporting medical decision-making based on machine learning methods, artificial neural networks, genetic algorithms, etc. Common drawbacks of these studies are the difficulty in interpreting the results obtained due to the latter functioning on the "black box" principle. These studies are aimed at developing and demonstrating the effectiveness of the proposed approaches and methods for solving diagnostic and prognostic problems. The testing of developed approaches is carried out mainly at the experimental level, primarily on a limited data set, and does not reach the point of implementation in clinical practice. However, these studies may form the basis for next-generation decision support systems if the problems that currently hinder their implementation in clinical practice are resolved in the future.

In [17], the authors suggest that the use of contextual factors in clinical decision support systems can improve personalized medicine and optimize clinical outcomes. However, while focusing on generalizing and categorizing contextual factors in the clinical decision-making process, the authors themselves note that they do not aim to evaluate specific implementation strategies or the applicability of contextual factors in real-world settings.

The [18] presents the functioning principles of a medical decision support system for the diagnosis of liver diseases in a local environment. The system includes a knowledge base consisting of 28 rules generated based on the expert physician's knowledge in the diagnosis of liver diseases, a conclusion block, and an interface block. Although the automation of the diagnostic decision-making process related to liver disease is solved in this system, the system doesn't support the decision-making process related to specific diseases such as hepatitis, obesity, cirrhosis, and HCC. A limitation of this study is the lack of information regarding the practical implementation of a medical decision support system for diagnosing liver diseases. The study also does not address the treatment selection process after diagnosis.

In [19, 20], it is substantiated that the parameters used for the diagnosis of HCC are multifactorial, manifest themselves with weak and atypical symptoms, information is incomplete and inaccurate, and the decision-making process takes place in terms of uncertainty. In [19], a conceptual model of a system based on fuzzy rules and a decision tree for the diagnosis of HCC is presented. The paper demonstrates the mechanisms for converting knowledge obtained from medical experts into rules based on a production model for determining the stages of HCC. The logical continuation of these studies is the development of the functioning principles of an expert system for the diagnosis of HCC [20]. These studies were based on the principles of evidence-based medicine, and the research results have been implemented in clinical practice.

Therefore, these studies have left unresolved issues related to the implementation of such an important step as the prescription of individualized therapy after a physician makes a definitive diagnosis.

All this allows to state that it is advisable to conduct a study devoted to the development of an intelligent decision support system for HCC treatment method selection HCC based on knowledge applicable in clinical practice.

3. The aim and objectives of the study

The aim of the study is to develop an intelligent decision support system that supports the process of choosing a treatment method for HCC based on the knowledge and experience of experts, and implement it as a web application. This will allow physicians quickly identify HCC therapy by classifying all possible clinical situations according to treatment methods in an online environment.

To achieve this aim, the following objectives were accomplished:

– to develop of the architecture of an intelligent decision support system for HCC treatment method selection;

– to formulate the rules based on the physician's knowledge regarding for HCC treatment selection;

– to develop the heuristic procedure for decision making regarding for HCC treatment selection and system implementation.

4. Materials and methods

The object of the study is the clinical decision-making process for the HCC treatment method selection based on the patient's medical data.

The main hypothesis of the study is that an intelligent decision support system on the HCC treatment method selection, based on the expert-doctors knowledge and patient clinical data will improve the accuracy of therapeutic decisions in accordance with the current clinical situation, reduce the risk of medical errors, and increase the efficiency of treatment.

Assumptions made in the study are the possibility of modeling expert heuristic knowledge and reasoning regarding the HCC treatment method selection; the possibility of developing software for a clinical decision-making support system regarding on the HCC treatment method selection, which would allow the system to be integrated with web technologies and provide access to it in an online environment; the need to coordinate the recommendations of the intelligent system with clinical guidelines and the opinions of the participants of the multidisciplinary council.

Simplifications adopted in the study are availability of heuristic knowledge and reasoning of physicians participating in the multidisciplinary council; a pre-determined number of clinical and laboratory parameters characterizing HCC.

The choice of treatment method for HCC is one of the poorly formalized tasks. Thus, HCC is characterized by a variety of examination data and their clinical signs, the degree of expression of which varies in each specific case of the disease. The patient's clinical condition is determined by the combination of initial clinical sign values. Various combinations of clinical sign values form a variety of possible patient-centered situations, the "severity" of which determines the criticality and stage of HCC for each patient. In this context, various combinations of clinical features form possible clinical situations of HCC. According to medical protocols, one of the above treatment methods may be prescribed for each situation. According to medical protocols, depending on the patient-centered clinical situation, a multidisciplinary council makes a coordinated decision regarding the choice of one of the following treatment methods:

– resection;
– transplantation;
– ablation;
– embolization;
– systemic anticancer therapies;
– symptomatic treatment.

Rapid identification of the most appropriate treatment method for HCC in a given situation requires significant effort, time, and attention from physicians, and sometimes leads to medical errors. Addressing these issues, including reducing the burden on physicians and increasing the accuracy and efficiency of medical decisions, highlights the need to develop systems to support medical decision-making for selecting a treatment method for HCC, based on artificial intelligence technology.

In this study, intelligent systems based on the knowledge of experienced medical experts were selected as one of the effective tools for supporting the adoption of treatment and diagnostic decisions.

Modeling of the decision-making process for choosing a treatment method for HCC in such systems is implemented in the following stages:

– obtaining knowledge from physician-experts, determining the system of informative parameters and their values characterizing the HCC;

– formalization of expert knowledge for the selection of a treatment method based on a production model based on rules of the "IF-THEN" type interpreted as a set of heuristic inference rules: "If condition, THEN action". Here, a condition is understood as a certain sample sentence (fact), and an action is a set of actions performed upon a successful search outcome. The rules created by the expert reflect the process of choosing the correct response to a variety of possible clinical situations. This choice, based on a simplification mechanism, eliminates facts and rules that are not directly related to the problem at hand;

– software implementation of an intelligent decision support system for HCC treatment method selection;

– integration of the developed system with web technologies.

To model the decision-making process for HCC treatment method selection, it is necessary, first of all, to form a group of experts and collect information on the informative parameters characterizing HCC.

The knowledge of the medical specialists of the Surgical Diseases Clinic of the Azerbaijan Medical University and the classical approach to decision-making are used as a source of knowledge for building an intelligent support system for the selection of HCC treatment.

In the treatment selection of HCC, 44 parameters are referred to, the names of some of which, the values they can take and the conventional designations are presented in Table 1.

Table 1

Examination data, the values they can receive and their conditional marking

No.	Examination data	Marking	Possible values examination data may receive	Marking the examination data values
1	Size of tumor	x_1	Pcs	number
2	Number of tumors	x_2	Pcs	number
3	Location of tumor	x_3	In one lobe/ in two lobes/ Central bile duct neighboring, Exophyte grown subcapsular derivative	y_{31} / y_{32} / y_{33}
4	Segmental portal vein invasion	x_4	Yes/No	y_{41} / y_{42}
5	Portal vein invasion of one lobe	x_5	Yes/No	y_{51} / y_{52}
6	Portal vein invasion of both lobes	x_6	Yes/No	y_{61} / y_{62}
7	Main portal vein invasion	x_7	Yes/No	y_{71} / y_{72}
8	Right hepatic vein invasion	x_8	Yes/No	y_{81} / y_{82}
9	Left hepatic vein invasion	x_9	Yes/No	y_{91} / y_{92}
10	Middle hepatic vein invasion	x_{10}	Yes/ No	y_{101} / y_{102}
11	Two hepatic veins invasion	x_{11}	Yes/No	y_{111} / y_{112}
...	...	...	...	...
35	Residual volume after resection-normal Qc	x_{35}	Pcs	Number
36	Residual volume after resection-cirrhotic Qc	x_{36}	Pcs	Number
37	Residual volume after resection-fatty Qc	x_{37}	Pcs	Number
38	Donor	x_{38}	Yes/No	y_{381} / y_{382}
39	Contraindications to immunosuppression	x_{39}	Yes/No	y_{391} / y_{32}
40	Active infections	x_{40}	Yes/No	y_{401} / y_{402}
41	Active malignancies	x_{41}	Yes/No	y_{411} / y_{412}
42	Extrahepatic organ failure (uncorrectable)	x_{42}	Yes/No	y_{421} / y_{422}
43	Performance	x_{43}	Pcs	Number
44	Weakness (minute walk distance – m)	x_{44}	Pcs	Number

5. Results of research on the development an intelligent system to support treatment selection

5. 1. Development of the architecture of an intelligent decision support system for selection the HCC treatment method

In this study, using the classical methodology for designing intelligent knowledge-based decision support systems, system architecture is proposed consisting of the following interconnected and interdependent functional components [20]: database, knowledge base, inference engine, interface block.

Fig. 1 shows the architecture of the intelligent decision support system for selecting the HCC treatment method and its functioning scheme.

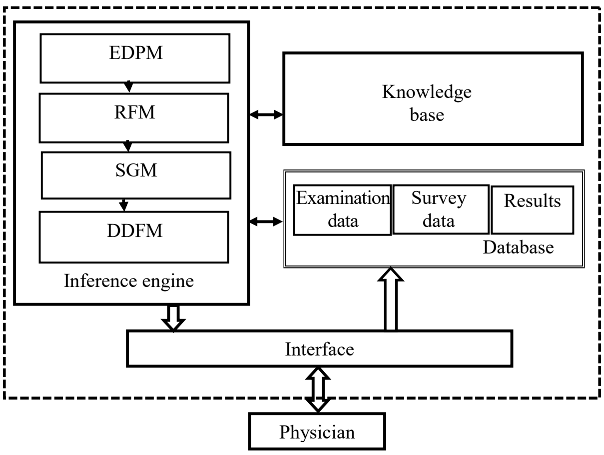

Fig. 1. Architecture of the intelligent support system for selection the HCC treatment method and its functioning scheme

To create a real intelligent decision support system for choosing the HCC treatment method, the following architectural components were developed:

– a database of the system based on the range of changes in the values of informative parameters characterizing the HCC;

– a knowledge base based on rules generated by experts;

– a logical inference engine block that activates a rule from the knowledge base that corresponds to the current situation and transmits it to the interface block;

– an interface block for entering the patient's current values and providing the result (treatment method) to the user.

The logical inference engine block of the system consists of following 4 submodules:

– examination data processing module (EDPM);

– result formation module (RFM);

– scheme generating module (SGM) of selected the HCC treatment method;

– input data tabular display formation module (DDFM) according to the selected treatment method.

Based on the current input data a new fact is formed in EDPM. After checking the fact for compliance with the conditional part of the rules in the knowledge base and confirming compliance, the rule in RFM is activated. Obtaining the scheme corresponding to the activated rule and transferring the result part of the rule to the interface block is performed by SGM. Transferring the values obtained by the examination data entered into the system to the interface block in the form of a table is performed by DDFM.

The interface block is intended to ensure communication between the user-physician and the expert system. This block performs the functions of controlling the screen, organizing a dialogue with the system, entering initial data (examination data values) into the system and delivering the results to the user.

5. 2. Formulation of the rules based on the physician's knowledge regarding for HCC treatment selection

The core of the intelligent support system for the selection of treatment methods in HCC is the knowledge base. To create this block, it is necessary to transform expert knowledge, reasoning and facts in accordance with clinical protocols into heuristic rules formalized based on a production model of knowledge representation.

The knowledge, reasoning, and conclusions of medical specialists and the authors' approach to choosing a solution were adopted as a source of knowledge for the formation of rules for identifying a method of treating HCC in each specific case.

Below, using a specific example of choosing the treatment method for HCC – "Resection", is a description of the rule based on the following 25 facts:

Fact 1. Location of tumor is central bile duct neighboring.

Fact 2. Exophyte grown subcapsular derivative, Portal vein invasion of both lobes is no.

Fact 3. Main portal vein invasion is no.

....

Fact 25. Performance is 1.

The heuristic rule for choosing a treatment method for HCC – "Resection", which integrates the expert's reasoning regarding all the above-described facts into the production model, has the following form:

If *(location of tumor – central bile duct neighboring, Exophyte grown subcapsular derivative, Portal vein invasion of both lobes – no, Main portal vein invasion – no, …, Residual volume after resection-normal Qc – is large and equal 30, Residual volume after resection-cirrhotic – is large and equal 40, Residual volume after resection-fatty Qc – is large and equal 35, Active infections – no, Active malignancies – no, Extrahepatic organ failure (uncorrectable) – no, Performance – (0 or 1 or 2))* Then *(HCC treatment – Resection).*

Based on the possible values of 44 examination data, shown in Table 1, the knowledge (judgments) obtained from expert physicians regarding the selection of HCC treatment is transformed into rules, which are shown below:

Rule 1. IF [$(x_3 = y_{31})$ & $(x_6 = y_{62})$ & $(x_7 = y_{72})$ & $(x_{12} = y_{122})$ & $(x_{13} = y_{132})$ & $(x_{16} = y_{162})$ & $(x_{17} = y_{172})$ & $(x_{21} = y_{212})$ & $(x_{22} = y_{222})$ & $(x_{23} < 3)$ & $(x_{24} < 1,7)$ & $(x_{27} = y_{272})$ & $(x_{28} = y_{282})$ & $(x_{29} = y_{292})$ & $(x_{30} = y_{302})$ & $(x_{31} < 35)$ & $(x_{33} = (A \vee B))$ & $(x_{34} < 9)$ & $((x_{35} \geq 30)$ ˅ $(x_{36} \geq 40) \vee (x_{37} \geq 35))$ & $(x_{40} = y_{402})$ & $(x_{41} = y_{412})$ & $(x_{42} = y_{422})$ & $(x_{43} = (0 \vee 1 \vee 2))$] **Then "Resection is permissible"**.

Rules for other HCC treatment methods are generated in a similar manner. It should be noted that the number of facts and their semantics vary for each treatment method:

Rule 2. IF [$(x_1 \leq 5)$ & $(x_2 \leq 3)$ & $(x_3 = (y_{31}$˅$y_{32}))$ & $(x_4 = y_{42})$ & $(x_5 = y_{52})$ & $(x_6 = y_{62})$ & $(x_7 = y_{72})$ & $(x_8 = y_{82})$ & $(x_9 = y_{92})$ & $(x_{10} = y_{102})$ & $(x_{11} = y_{112})$ & $(x_{12} = y_{122})$ & $(x_{13} = y_{132})$ & $(x_{14} = y_{142})$ 1& $(x_{15} = y_{152})$ & $(x_{16} = y_{162})$ & $(x_{17} = y_{172})$ & $(x_{19} \leq 200)$ & $(x_{26} \leq 100)$ & $(x_{31} < 35)$ & $(x_{38} = y_{381})$ & $(x_{39} = y_{392})$ & $(x_{40} = y_{402})$ & $(x_{41} = y_{412})$ & $(x_{42} = y_{422})$ & $(x_{43} = (0 \vee 1 \vee 2))$] **Then "Transplantation is permissible"**.

Rule 3. IF $[(x_1 \leq 3)$ & $(x_2 \leq 3)$ & $(x_3 = (y_{31} \vee y_{32}))$ & $(x_4 = y_{42})$ & $(x_5 = y_{52})$ & $(x_6 = y_{62})$ & $(x_7 = y_{72})$ & $(x_8 = y_{82})$ & $(x_9 = y_{92})$ & $(x_{10} = y_{102})$ & $(x_{11} = y_{112})$ & $(x_{12} = y_{122})$ & $(x_{13} = y_{132})$ & $(x_{21} = y_{212})$ & $(x_{22} = y_{222})$ & $(x_{24} \leq 1.7)$ & $(x_{28} = y_{282})$ & $(x_{29} = y_{292})$ & $(x_{33} = (A \vee B))$ & $(x_{40} = y_{402})$ & $(x_{41} = y_{412})$ & $(x_{43} = (0 \vee 1 \vee 2))]$ **Then "Ablation".**

Rule 4. IF $[(x_6 = y_{62})$ & $(x_7 = y_{72})$ & $(x_{21} = y_{212})$ & $(x_{22} = y_{222})$ & $(x_{23} < 3)$ & $(x_{24} \leq 1.7)$ & $(x_{28} = y_{282})$ & $(x_{29} = y_{292})$ & $(x_{30} = y_{302})$ & $((x_{33} = (A \vee B))$ & $(x_{40} = y_{402})$ & $(x_{41} = y_{412})$ & $(x_{42} = y_{422})$ & $(x_{43} = (0 \vee 1 \vee 2))]$ **Then "Embolization".**

Rule 5. IF $[(x_{21} = y_{212})$ & $(x_{22} = y_{222})$ & $(x_{23} > 3)$ & $(x_{24} < 1.7)$ & $(x_{27} = y_{272})$ & $(x_{28} = y_{282})$ & $(x_{29} = y_{292})$ & $(x_{30} = y_{302})$ & $(x_{33} = A)$ & $(x_{40} = y_{402})$ & $(x_{42} = y_{422})$ & $(x_{43} = (0 \vee 1 \vee 2))]$ **Then "Systemic treatment".**

These rules form the knowledge base of the intelligent system.

5. 3. Development of the procedure for making decisions regarding the selection of HCC treatment and system implementation

Implementation of the system requires:

– to develop of a decision-making heuristic procedure for choosing the HCC treatment method in accordance with a step-by-step classical approach;

– to develop of software that allows to integrate the system with web technologies.

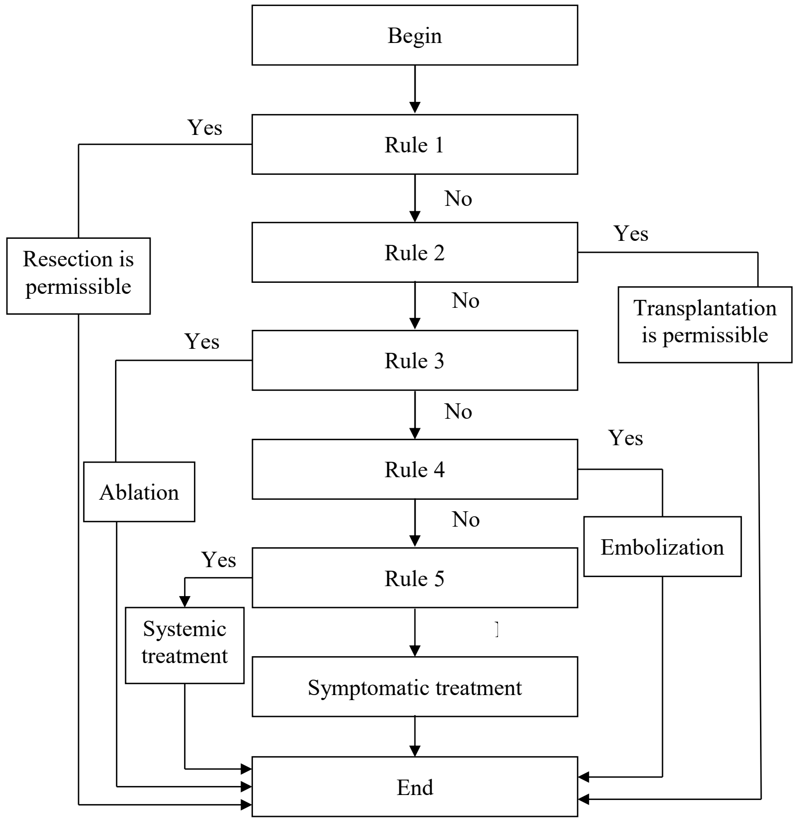

Fig. 2. The heuristic procedure for selecting by a multidisciplinary council of the hepatocellular carcinoma treatment method based on a step-by-step classical approach

Fig. 2 shows the heuristic procedure for selecting by a multidisciplinary council for HCC treatment method based on a step-by-step classical approach.

The intelligent system for the HCC treatment selection is developed in the object-oriented programming language C#.

C# is used to develop a wide range of applications, including desktop and web applications, mobile applications, Unity-based games, cloud applications on Microsoft Azure, and database applications.

After logging into the system, the window illustrated in Fig. 3 opens in front of the user-physician. This interface window consists of a large number of sub-windows, each of which corresponds to the examination data of HCC and the values they can receive.

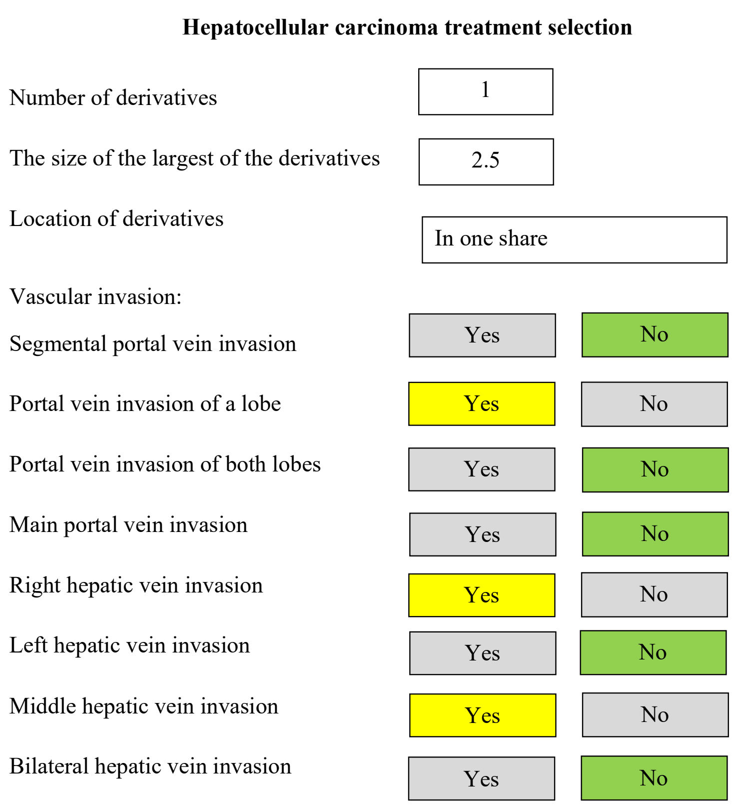

Fig. 3. Entering the examination data values for the hepatocellular carcinoma treatment selection into the system from the opened interface window

Each of these windows is active and enables the user-physician to enter the current examination data. The current values of the examination data are entered into the system from the opened interface window and the "Initial result" button is pressed. The current values of the examination data entered into the system are recorded in the database. These data also form the EDPM in the inference engine. The latter is compared with the condition part of the rules in the knowledge base, and when an overlap occurs, the result (HCC treatment method) part of that rule is recorded in the inference engine of the RFM.

Based on the rule corresponding to the formed result, the selected treatment method of HCC in the ERM (for example, “Resection is permittable”) is transferred to the interface window via the SFM. Then, the table formed in the DDFM based on the entered data and their values is transferred to the interface. The results of the selected HCC treatment method registered in the ERM, the entered data, and their values are presented to the user through the interface block (Fig. 4).

HCC treatment selection

RESECTION

Number of derivatives	1	INR	16
The size of the largest of the derivatives	2.5	Platelet	55
Location of derivatives	In on share	QQT	75
Segmental portal vein invasion	No	Ascites	No
Portal vein invasion of a lobe	Yes	Varicose bleeding	No
Portal vein invasion of both lobes	No	Encephalopathy	No
Main portal vein invasion	No	Decompensation	No
Right hepatic vein invasion	Yes	Pulmonary hypertension	32
Left hepatic vein invasion	No	OHS (15 minutes)	11.6
Middle hepatic vein invasion	Yes	Child	B
Bilateral hepatic vein invasion	No	MELD	8.4
Invasion of three hepatic veins	No	Residual volume after resection-normal Qc	32.8
Invasion of ABV	No	Residual volume after resection-cirrhotic G_C	15
Spread to lymph nodes	No	Residual volume after resection – fatty Qc	31.8
Metastasis – can occur alone	Yes	Donor	No
Metastasis – cannot go away on its own	No	Contraindication to immunosuppression	No
Metastasis multiple	No	Active infections	No
Degree	Low	Active other malignant diseases	No
AFP	77	Extrahepatic organ failure (uncorrectable)	No
Cirrhosis	No	Performance (ECOG)	2

Fig. 4. Interface window for delivering the result to the user in the intelligent system for the HCC treatment selection

The choice of the treatment method appropriate to the situation shown in Fig. 3 corresponds to the decision option “Resection”. This decision is made as a result of the activation of Rule 1 in the knowledge base of the intelligent support system for the HCC treatment selection.

6. Discussion of the results of hepatocellular carcinoma treatment selection support system implementation

As is generally recognized, two different approaches are currently used to select a treatment method for hepatocellular carcinoma using artificial intelligence (AI) technologies. These approaches differ in criteria such as methodology, knowledge source, decision transparency, and explainability of the latter.

The methodological basis of intelligent decision support systems is a deductive approach (from rules to facts), while the source of knowledge includes rules created by expert physicians based on facts, clinical guidelines, and protocols. This clearly describes cause-and-effect relationships, ensuring the transparency and explainability of decisions and, consequently, physician trust in them [18–20].

Machine learning (ML) and deep learning (DL) are based on an inductive approach (from multiple examples to rules), and their source of knowledge is primarily Big Data. ML and DL are trained on data, automatically identifying patterns and dependencies from medical records, images, tests, etc. Since decisions generated by ML and DL systems are implemented using a “black box” principle, they are non-transparent to physicians and often raise doubts about the outcome [9–16].

The proposed methodology for developing an intelligent system for primary treatment selection for hepatocellular carcinoma is based on a deductive approach, which ensures the critical explainability of clinical decisions for physicians.

The knowledge of the medical specialists of the Surgical Diseases Clinic of the Azerbaijan Medical University a used as a source of knowledge for building an intelligent support system for the selection of HCC treatment.

In the treatment selection of HCC, 44 parameters are referred to, the names of some of which, the values they can take and the conventional designations are presented in Table 1.

The architecture of an intelligent decision support system was developed for selecting a treatment method for HCC (Fig. 1). It consists of the following components: a database, a knowledge base, a logical inference block, and an interface block. The proposed architectural solution explicitly represents the interrelationships and interdependencies of the system’s structural components.

Based on the possible values of 44 informative parameters examination data the knowledge obtained from expert physicians regarding the selection of HCC treatment is transformed into rules (task 5.2, Rules 1–5). Solving this problem allows to create a knowledge base that forms the core of an intelligent system for selecting a treatment method for HCC.

As a result of completing task 5.3, a decision-making procedure were developed that reflects the step-by-step classical approach to selecting a treatment method for HCC (Fig. 2) and a system for selecting a treatment method for HCC in the object-oriented programming language C# (Fig. 3, 4).

The implementation of the support system for HCC treatment selection on the Visual Study 2019 platform in the C# programming language enabled its integration with web technologies. This solution of the problem facilitates a multidisciplinary council in an online environment. For this purpose, a link to the system was collocated on the Surgical Diseases Clinic of the Azerbaijan Medical University website (http://cerrahiplatforma-001-site2.atempurl.com/WebForm1.aspx).

Experimental testing of the system was implemented with the participation of medical experts in this field. The primary criterion for assessing the system's quality and suitability for clinical use was a complete match between the consensus decision of the multidisciplinary council and the decision made by the developed system. To achieve this goal, the experiments were carried out in several iterations, after each of which, taking into account the comments and feedback of doctors, changes were made to the database, knowledge base and software.

The developed intelligent system for selecting a treatment method for HCC has the following advantages:

– prompt response to the situation, accuracy and reliability of the decision taken;

– access to the system via the Internet without restrictions on time, space and number of users.

The disadvantages of the proposed system are following:

– the difficulty of obtaining knowledge from experts due to their workload;

– the periodic need to monitor the adequacy of rules in the knowledge base due to the emergence of new approaches to HCC treatment, which update changes in medical recommendations;

– consensus-based decision by a multidisciplinary council on the choice of treatment for HCC is based on a verbal online discussion of each participant's opinions. A limitation of this study is that the developed system allows a multidisciplinary panel to make treatment decisions only for HCC. Research is currently ongoing to adapt the proposed approach to the treatment of liver diseases such as cirrhosis and fatty liver.

Further development of the system is planned expanding its capabilities and applicability to other diseases, taking into account their specific characteristics. Future plans include formalizing and automating the process for making a single, consensus-based group decision and developing a corresponding module.

7. Conclusions

1. Architecture for an intelligent decision support system for selecting a treatment method for HCC has been developed. The system consisted of following interconnected components a database of the system based on the range of changes in the values of informative parameters characterizing the HCC; a knowledge base based on rules generated by experts; a logical inference engine block that activates a rule from the knowledge base that corresponds to the current situation and transmits it to the interface block; an interface block for entering the patient's current values and providing the result (treatment method) to the user.

2. Expert knowledge was formalized using a production model interpreted as a set of heuristic inference rules, "If condition, THEN action," allowing for the classification of a set of possible combinations of 44 informative parameters across six HCC treatment methods.

3. A heuristic procedure treatment selection is developed based on production rule analysis in accordance with current parameter values, reproducing the reasoning patterns of participants in a multidisciplinary council during their consensus decision-making process regarding HCC treatment appointment. A software implementation of a decision-making model for HCC treatment selection, implemented in C# using the Visual Study 2019 platform, enabled the integration of an intelligent system with web technologies. The quality of the system and its suitability for clinical use were assessed by the criterion of complete match between the consensus decision of the multidisciplinary council and the decision made by the developed system in accordance with clinical guidelines. The system testing process was carried out with the participation of expert doctors in several iterations until the accepted quality criterion was met.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this study, whether financial, personal, authorship or otherwise, that could affect the study and its results presented in this paper.

Financing

The study was performed without financial support.

Data availability

Manuscript has no associated data (in article we present the link).

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

CRediT

Masuma Mammadova: Conceptualization, Methodology, Writing (original draft), **Nuru Bayramov:** Formal analysis. Validation. Writing (editing), **Zarifa Jabrayilova:** Methodology, Software, Writing (original draft); **Tetyana Baydyk**: Investigation, Supervision, Writing (review & editing); **Mehriban Huseynova**: Data curation, Validation, Visualization.

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