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Designing an on-line database for morphological studies of three-dimensional liver tumors

COSTIN TEODOR STREBA[1)], MIRCEA-SEBASTIAN ŞERBĂNESCU[2)], SORIN POPESCU[3)], ROXANA CRUCE[1)], DAN IONUŢ GHEONEA[4)], IOANA ANDREEA GHEONEA[5)]

[1)]Department of Research Methodology, University of Medicine and Pharmacy of Craiova, Romania

[2)]Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova, Romania

[3)]PhD Student, Doctoral School, University of Medicine and Pharmacy of Craiova, Romania

[4)]Department of Gastroenterology, University of Medicine and Pharmacy of Craiova, Romania

[5)]Department of Radiology and Medical Imaging, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Introduction: Primary liver and pancreatic malignancies still make up for an increasing number of deaths worldwide. Diagnostic procedures are constantly evolving, with variable availability depending on referral center. Integrating and transmitting relevant medical data is becoming more necessary, for both medical learning and patient management. *Patients, Materials and Methods*: We selected a sample cohort from our larger study involving patients with liver and pancreatic primary malignancies. All patients provided informed consent and procedures were performed in accordance with usual regulations. Clinical and laboratory data of the selected patients were used to populate a database that also contained multimedia files presenting an interactive three-dimensional (3D) model of liver or pancreatic tumors. *Results*: The on-line interface developed to access the database had two levels of access. The public webpage only allowed interaction with the reconstructed model. The secured module allowed viewing of medical data, interaction with the complete tumor model as well as the ability to download the anonymized digital file containing the tumor reconstruction. This allowed fast printing, with a standard 3D printer, of the complete model with different levels of stiffness, for complete interaction for both teaching purposes and pre-operatory planning. *Conclusion*: This is the first attempt to implement a full-scale on-line solution for 3D tumor representation and manipulation, corroborated with clinical and laboratory data. This technology may bring important additional information for pre-operatory evaluation, treatment planning or medical training.

Keywords: hepatocellular carcinoma, telemedicine, 3D organ printing, medical database.

Introduction

Both liver and pancreatic cancers have a constant place in cancer statistics worldwide [1–3]. Various types of predisposing conditions counterbalance many important breakthroughs in the field of prevention [4, 5]. Superior treatment for viral hepatitis B and C decreased the incidence of these pathologies in hepatocellular carcinoma (HCC) cases, replaced in endemic areas by metabolism-related liver conditions, such as non-alcoholic fatty liver disease (NAFLD) or alcoholic liver disease (ALD) due to increased consumption [6–8]. This heterogeneity also accounts for different tumor-related features, macroscopically and microscopically, with implications for curative attempts [6, 7].

Delivering patient-related medical content to professionals as well as to in-training personnel is becoming an increasing challenge for the healthcare community [9, 10]. Various types of data make up for a complex network of information that provides diverse information in a multitude of fields, each with varying degrees of availability and understandability [9]. Moreover, patients are referred to medical centers in a somewhat de-centralized manner, sometimes being sent from one location to another in order to access the expertise of different doctors in various fields of medicine [9, 11].

Bringing together a multidisciplinary team of medical professionals is most of the times unfeasible and time-consuming, thus reducing the chances that a patient can obtain an accurate and fast diagnosis [12–14]. Therefore, a desiderate of modern medicine is remote access to patient data, including imaging content that can be delivered in a fast, reliable and easy to use manner for medical specialists in different locations [12, 15]. Imaging data of tumors can greatly improve diagnosis, as well as provide important data towards establishing surgical indications, prognosis estimations as well as availability of treatment alternatives [16, 17].

Modern learning platforms can increase the performance of medical learning in a variety of fields. Cancer-related topics and tumor descriptors are valuable for medical students, as future applicability of knowledge is highly patient-dependent [15, 18]. Bringing real-life scenarios close to medical students, as well as providing patient specific examples with as much data as possible, is likely to improve decision making in many fields of medicine. Resident doctors can be trained in various medical institutions, with varying degrees of exposure to different pathologies. Therefore, telemedicine and remote access to a large variety of cases can benefit the overall level of knowledge, especially when it involves widespread tumor locations and known pathologies [10, 12, 13].

We have previously shown how both shape and stiffness information regarding liver and pancreatic tumors can greatly improve the diagnostic yield of conventional imaging methods, by producing three-dimensional (3D) printings of actual tumors for both diagnostic and teaching purposes. Palpatory information thus obtained was sufficient to increase knowledge of tumor architecture.

Aim

We have further aimed to develop an on-line remotely accessible secure medical platform to provide clinicians, both specialists and in training, to complete datasets of tumor features in a relevant clinical context.

Patients, Materials and Methods

Patient selection and ethical aspects

For this study, we selected a cohort of patients that had complete medical records stored for the purpose of our larger study, as previously described. We presented the full description of the study procedures, data recording and methods of using and interpreting said data to the patients, who then gave their informed consent in writing. The initial ethical clearance covered the use of anonymized data for the purpose of the present study. No procedure interfered with normal diagnostic, follow-up and treatment option.

All patients had undergone diagnostic imaging, such as either computed tomography (CT), magnetic resonance imaging (MRI) or both in some cases. In addition, we had elastography and contrast-enhanced ultrasound data stored for the purpose of the study.

Inclusion criteria were age above 18, irrespective of gender, with proven liver primary malignancy (positive CT or MRI). We collected results from all blood tests relevant for our pathologies or associated conditions.

Imaging data integration and computerized tumor reconstruction

We extracted relevant imaging data following the already established protocol [14]. Briefly, the digital imaging and communications in medicine (DICOM) file format was used to store imaging data from either CT or MRI. This file format contains several annotated series of cross-sectional sections (*x–y* images arranged in *z*-series), thus allowing for 3D reconstruction of entire body sections.

We further processed these whole-body sections and extracted the entire organ, then the needed area-of-interest (AOI) in a semi-automatic manner, using existing software (InVesalius – Renato Archer Information Technology Center, Brazil). This selection was used to recreate the 3D render of the surface model that we could later export in a stereolithography (STL) digital file.

The produced STL file containing surface information was later processed in order to include the inside information of tumor stiffness, represented through different methods that we previously described [14]. We then prepared the result for inclusion in the on-line database and platform.

On-line platform development

We developed an on-line platform in order to provide secure remote access from any device connected to Internet capable to deliver the complete 3D data of tumor models as well as the possibility to print complex tumor data, complete with stiffness information for palpatory inspection.

We constructed a structured SQL database containing a unique, random code for each patient, along with fields pertaining to all clinical and laboratory relevant data. We deposited tumor imaging as multimedia content – representation of the relevant imaging aspects (anonymized) and the previously generated STL computer file containing a 3D representation of the tumor.

We further developed a website in PHP (a programming language that can be used for various applications, being particularly suited for web application) that accessed the structured query language (SQL) database and hosted it on a dedicated server, in a secure data center, with remote administration. This functionality allowed us to control all aspects of the platform remotely, without direct access to the server, thus contributing to the portability of the application.

We designed the website to offer both public and private data access, in separate user interfaces especially designed for each task. We also provided the web interface with a specially designed section where the designated clinicians could insert medical data into the database and populate its content with the medical cases, including clinical, paraclinical and imaging data.

Results

Patient demographics

We included data from 75 HCC patients (Table 1). Median age was 56 years (minimum 21, maximum 89 years old); we had three patients under 30 years (two males) and the majority above 50 years (56 cases, 74% of the study group). We recruited 46 males (61.3% of the group). Both males (28 cases) and females (17 cases) came from an urban background (45 cases, 60% respectively).

Table 1 – *Demographic data of the included HCC patients. Viral B or C refers to hepatitis viral infection; B+C patients are a separate subgroup that had both, while the cirrhosis field comprises patients from all previous fiends that had clinical or laboratory signs of cirrhosis (including any viral etiology, NAFLD or alcohol consumption)*

	Male	Female	Total
18–30 years old	2	1	3
31–40 years old	4	2	6
41–50 years old	6	4	10
51–60 years old	12	7	19
61–70 years old	12	8	20
Above 70 years old	10	7	17
Urban	28	17	45
Rural	18	12	30
Viral B	18	12	30
Viral C	12	7	19
Viral B+C	6	1	7
NAFLD	6	8	14
Alcohol	4	1	5
Cirrhosis	38	23	61

HCC: Hepatocellular carcinoma; NAFLD: Non-alcoholic fatty liver disease.

Most patients had viral etiology (56 cases, 74% of the group) and 61 of them (81.3% of the entire group) had at least two signs of liver cirrhosis present. Only alcohol consumption was a cause for HCC in five patients (four males) and we identified NAFLD as the only predisposing factor in 14 patients.

Regarding tumor morphology, all cases were solitary HCCs ranging from 1.4 to 6.6 cm in largest diameter (median 3.4 cm). We recorded 36 cases as having "round", 21 "oval" or "round-oval" and 8 as "irregular" in shape; 22 cases (14 males) had distant metastases.

We also included 21 pancreatic cancer patients that had complete medical history and either CT or MRI imaging that we could use to model the 3D tumor and interpret stiffness data. Demographic data can be found in Table 2. Median age in this group was 61 (minimum 35, maximum 84 years), 14 patients were males and 19 came from an urban background. Fifteen had reported alcohol consumption and six could only report possible dietary factors and family aggregation as possible risk factors for the malignancy. Of all, 19 were also smokers.

Database structure

The demographical data registered in the database included birth year, the year of diagnosis, gender, place of residence (urban or rural). Medical data was comprised of etiological information – viral B or C liver infection, alcohol consumption, NAFLD, with or without a diagnosis of cirrhosis.

Furthermore, we collected data pertaining to the tumor, such as main tumor site (either liver or pancreas), presence of secondary sites, and the size of the largest formation, its shape as well as stiffness data from elastography, CT or MRI, as well as information regarding vascularization – as determined on contrast-enhanced ultrasound (CEUS), CT and MRI (Figures 1 and 2).

Table 2 – ***Demographic data of the included pancreatic cancer patients. Percentages are expressed in accordance to the entire group of 21 patients***

	Male	Female	Total	Percentage
31–40 years old	1	0	1	4.8
41–50 years old	2	1	3	14.3
51–60 years old	3	2	5	23.8
61–70 years old	4	2	6	28.6
Above 70 years old	4	2	6	28.6
Urban	12	5	17	80.9
Rural	2	2	4	19.0
Smoking	13	6	19	90.5
Alcohol	12	3	15	71.4
Dietary	2	4	6	28.6

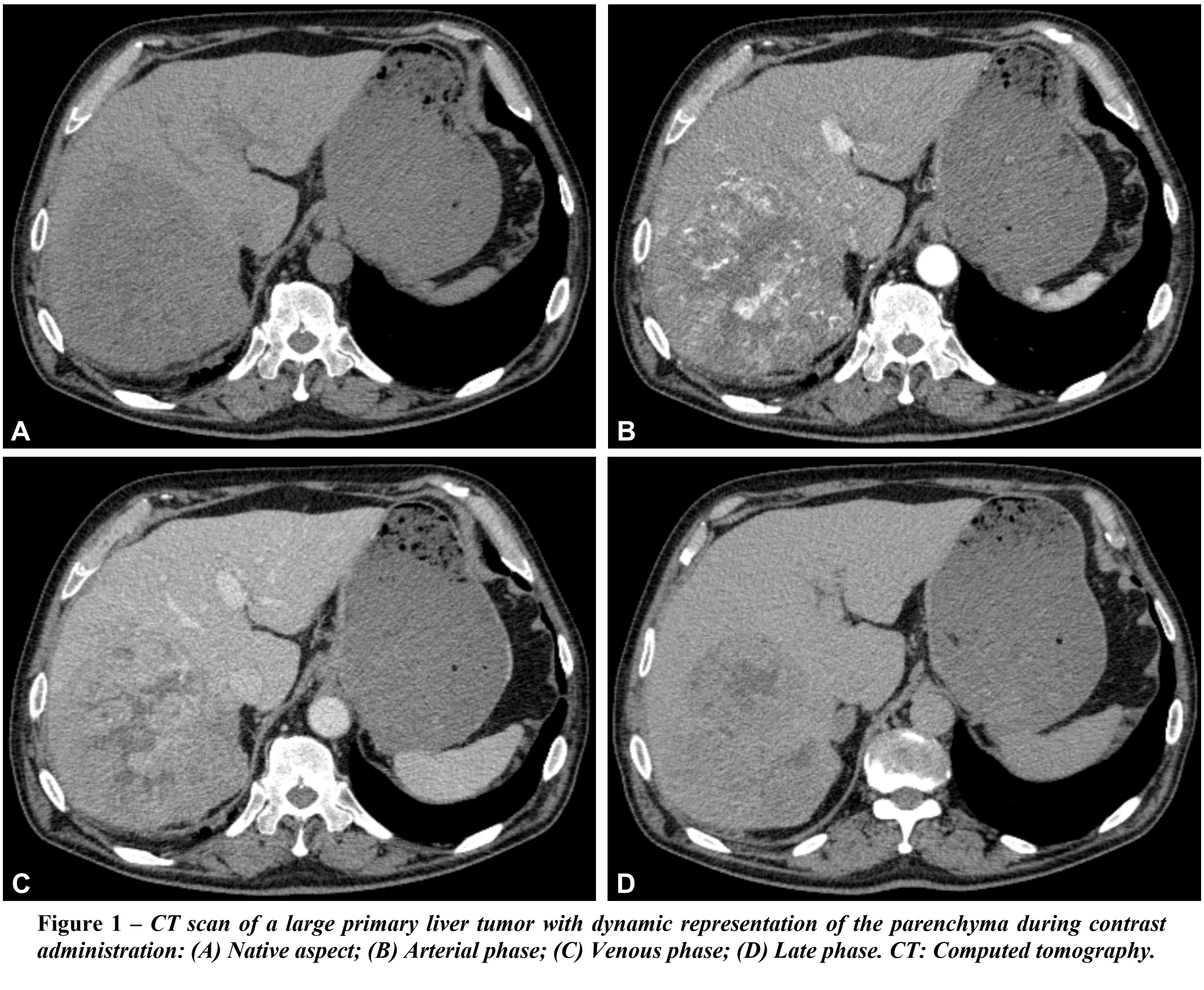

Figure 1 – ***CT scan of a large primary liver tumor with dynamic representation of the parenchyma during contrast administration: (A) Native aspect; (B) Arterial phase; (C) Venous phase; (D) Late phase. CT: Computed tomography.***

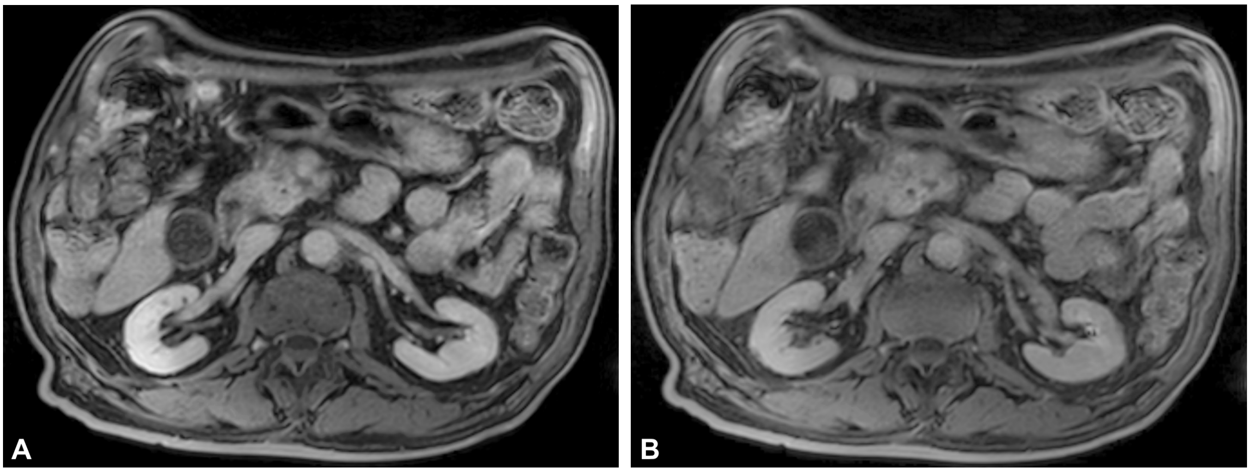

Figure 2 – ***MRI aspects of a pancreatic tumor of the head and uncinated process: (A) Arterial phase; (B) Venous phase. MRI: Magnetic resonance imaging.***

Other data pertaining to each case included co-morbidities, prognosis scores, treatment-specific data (treatments already undergoing or other possible future treatment options, etc.).

Laboratory data was restricted to relevant values, pertaining to liver or pancreatic function, as well as metabolic conditions, such as liver aspartate amino-transferase (AST) and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, bilirubin (total and direct), glucose (and hemoglobin A1c depending on case). Also, several specific tumor markers were recorded, depending on case: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), etc.

We easily populated the database through a dedicated back-end interface (Figure 3) that it was accessible only after a secure login, the account requiring validation as an administrator that can add cases further on.

Online platform and website integration

The website is available at www.tumorfeel.net, for both public and private data access (Figure 4).

The public data consisted only of the simplified version of the tumor shape. We developed it to be accessible so that the user can visualize the 3D model of the tumor (Figure 5). In order to insure the privacy of patient data, we generate randomized filenames and the model has no information about the patient (Figure 6).

We made the private section of the website accessible only after a secure login (Figure 7). The doctor-oriented part of the interface consisted of the full 3D model file of the tumor, the imaging report and relevant clinical and laboratory data. The 3D model could be downloaded at any time and from anywhere in the world, in order to be 3D-printed.

We integrated a STL file viewer that allowed the 3D reconstruction of tumors to be displayed directly in the browser window. We designed this feature to function irrespective of the device used – either fixed or mobile personal computers or mobile devices, such as personal digital assistants (PDAs), smartphones or tablets (Figure 8). We reconstructed the digital model of tumors with all relevant information regarding shape and deformability, and the users could interact with the virtual representation through gestures or various input devices (computer mouse, trackpad, joysticks, virtual reality gear, such as glasses and touch devices, etc.).

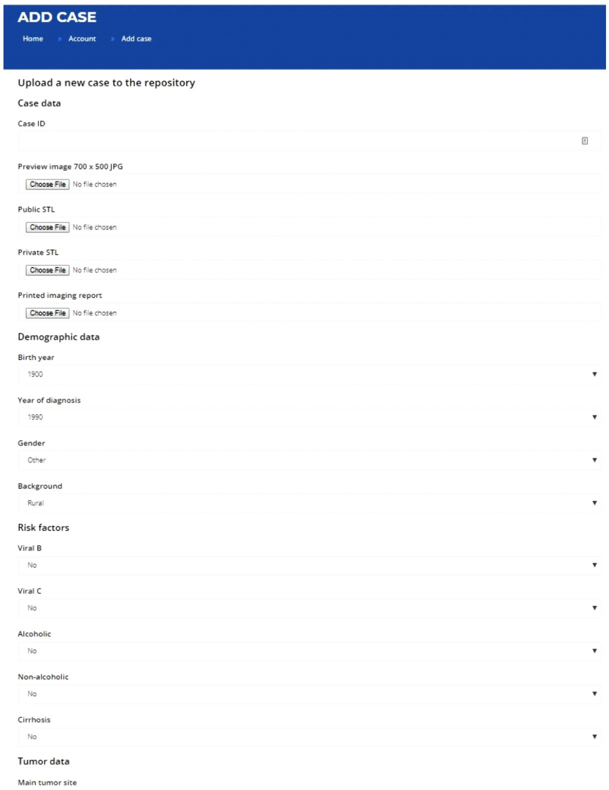

Figure 3 – ***Back-end secure interface designed to input data into the database.***

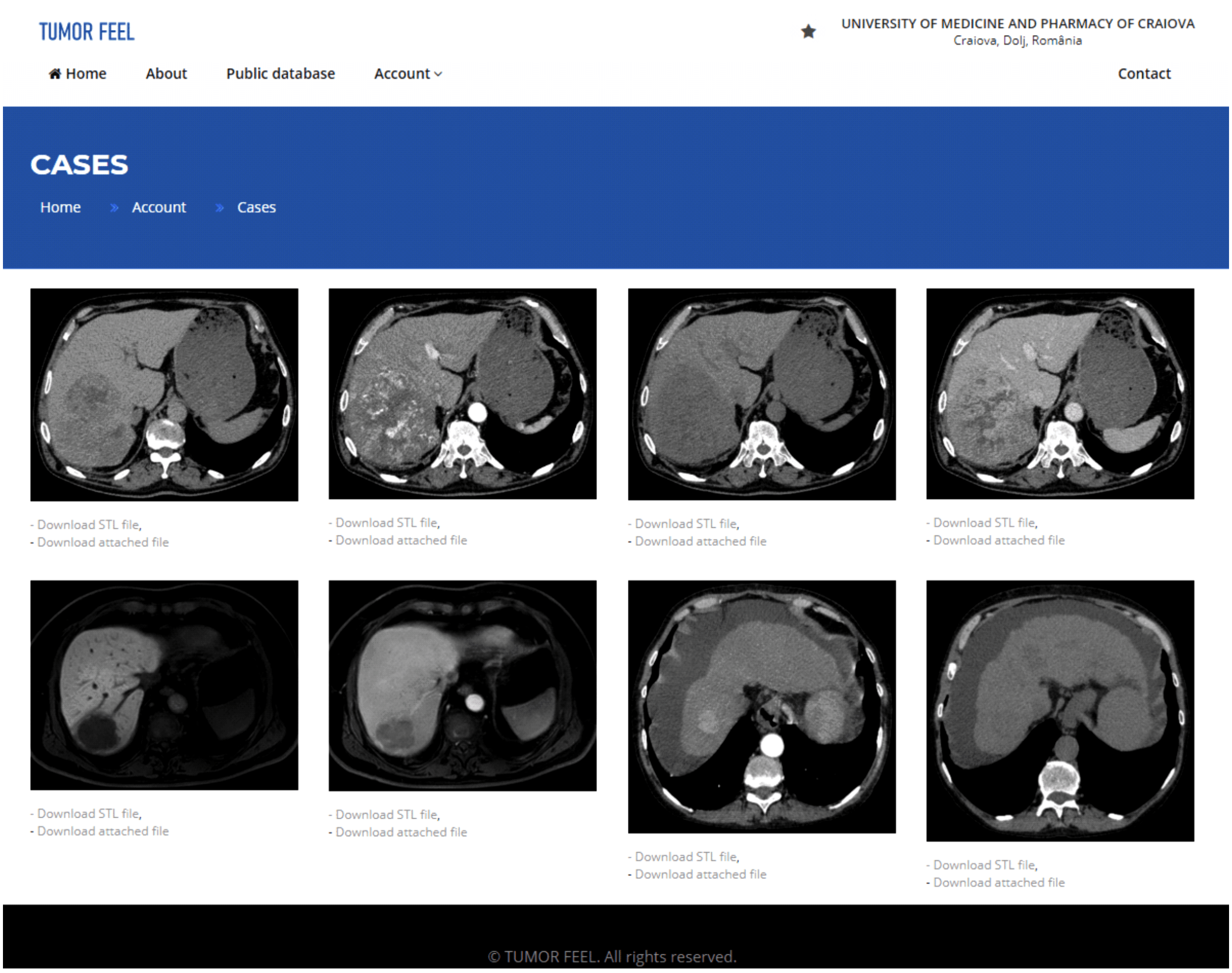

Figure 4 – *The main screen of the web interface, with CT or MRI images representative for each case. The interface can be accessed after secure login and only designated medical doctors can retrieve data. No identifiable data pertaining to specific patients is stored or displayed at any point. CT: Computed tomography; MRI: Magnetic resonance imaging.*

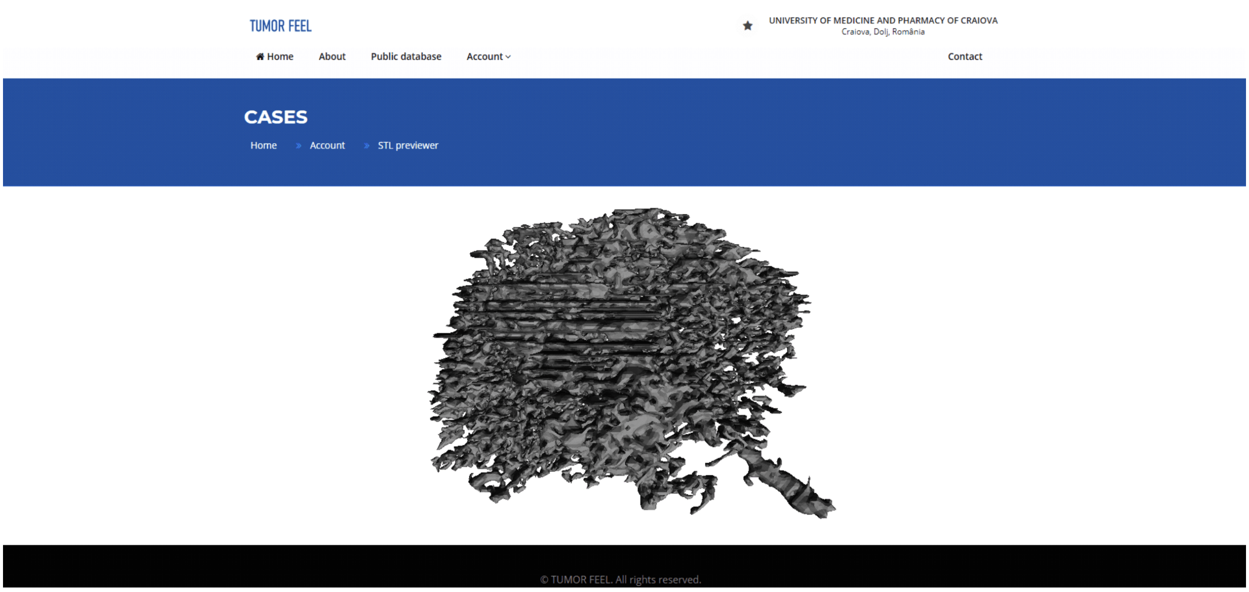

Figure 5 – *Example of a tumor reconstructed within the public part of the on-line platform. We designed this interface to only display the tumor model, without any clinical or relevant medical data, for educational purposes only.*

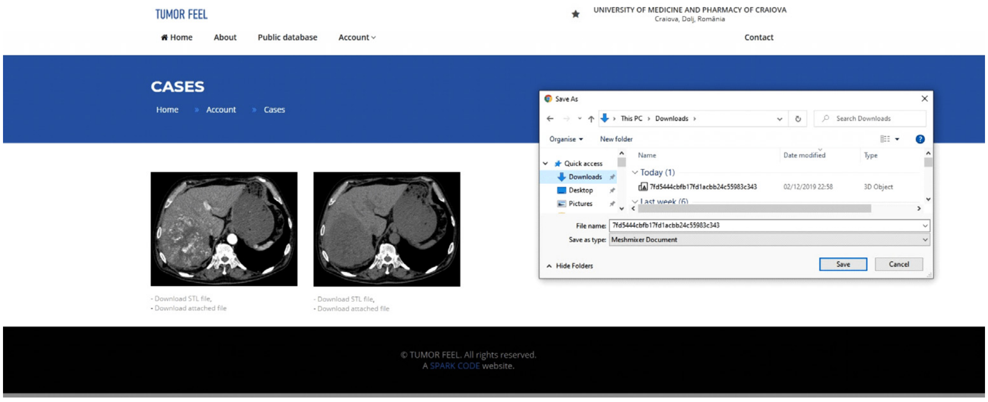

Figure 6 – ***When the STL file is generated for retrieval a random string of characters is used as default naming in order to ensure the confidentiality. STL: Stereolithography.***

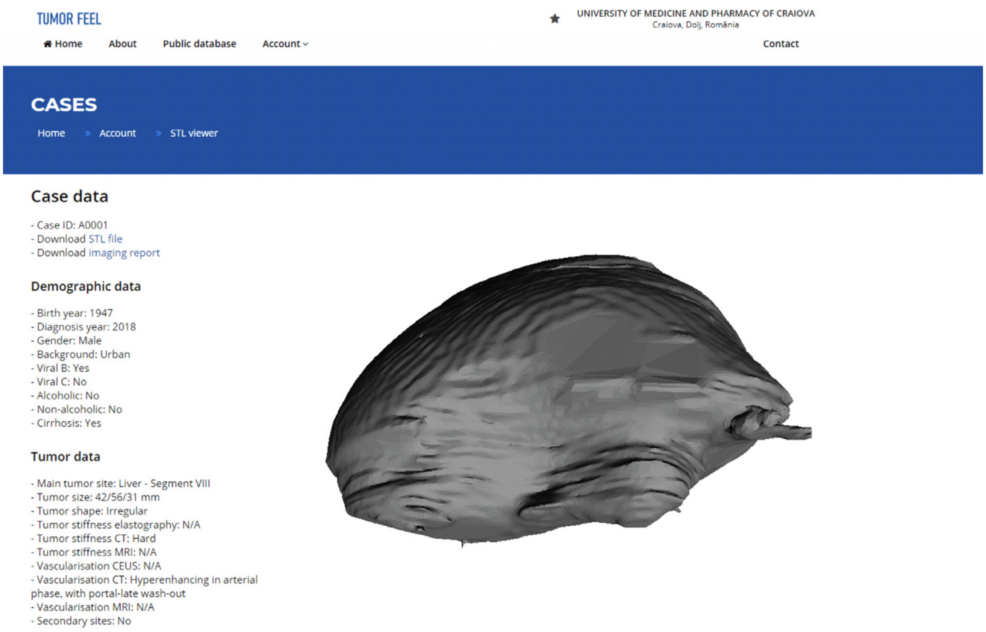

Figure 7 – ***Interface designed to show clinical data and the fully interactive tumor model. The STL file, along with a file containing all imaging data, can be downloaded remotely and processed locally at any other referral center. STL: Stereolithography.***

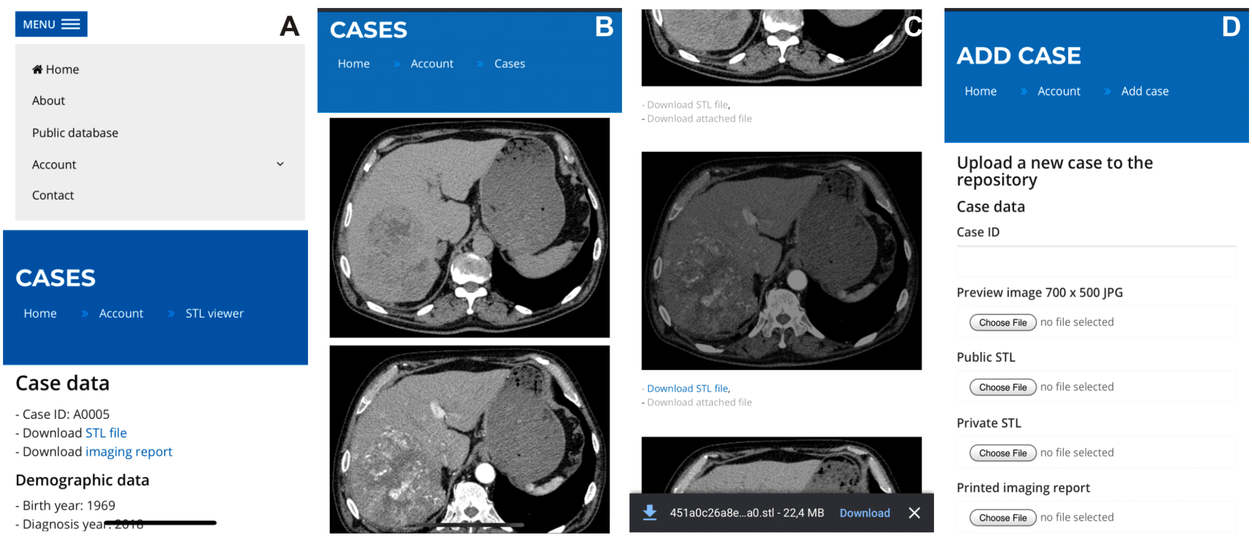

Figure 8 – ***Aspects of the interface on a standard smartphone capable of Internet access. The web interface is fully scalable (A), irrespective of the resolution of the device. Both the public database and the private, complete, interface are accessible (B) All functionality, including the download of STL files for web printing, can be accessed (C). Also, it is possible to use the interface to input new cases or modify existing data from mobile device, making the solution exceptionally portable (D). STL: Stereolithography.***

Discussions

The need to provide relevant medical content in a multitude of environments is increasing worldwide [15–18]. Novel imaging methods provide a plethora of data for the clinician, which can help guide decisions before taking therapeutic steps or when determining a diagnosis [19]. Tumor morphology plays a key role, thus determining the exact location, shape and inherent properties of the tissue involved is paramount. Large-scale cross-sectional imaging (such as CT or MRI) is at present indispensable tools when diagnosing HCC or pancreatic carcinomas (PC) [1–3]. Data obtained from elastography may further enhance the understanding of the tumor morphology in the absence of biopsy or other pre-operatory tissue sampling [3, 6–8]. Medical personnel cannot appreciate tumor stiffness during normal palpatory maneuvers; therefore, having the tumor recreated both in a virtual environment and in real-life through 3D printing can provide important information for the multidisciplinary medical team involved in cancer management [16–18].

We have shown here how morphological data of liver and pancreatic tumors can be digitally stored along with important patient data in a secure database model for remote retrieval and interpretation. Our solution is, to the best of our knowledge, unique in its configuration and functions.

The ability to download a file with all tumor stiffness data at a remote medical location and use the computerized data to 3D print a to-scale replica of the tumor, with all morphological data intact as well as with deformability close to the real example is one of the key novelties and strengths of the solution [20, 21]. Its applications can be primarily exploited in a clinical setting, for pre-operatory assessment or for medical training, providing junior doctors with valuable knowledge of tumor architecture and tissue properties.

The proposed website configuration offers the advantage of fast data access from anywhere in the world *via* an Internet connection (telemedicine). A second advantage is the cost efficiency; both the PHP and SQL servers have no acquisition costs. The third advantage of the solution is the security generated by the dedicated server hosted in a secure data center with remote administration thus providing the latest security available on the internet, including future updates.

The solution is suitable for teaching, *e*-learning and patient education as the website and models could be used for frontal presentations and workshops and for *e*-learning.

Conclusions

Presenting clear medical data pertaining to tumor morphology in a secure manner to remote medical facilities may improve diagnostic and therapeutic options for cancer patients. Structuring diverse and patient-centric medical data, especially related to tissue characteristics of deep tumors that are otherwise inaccessible to direct inspection, can be valuable to both training and specialist doctors from various fields of medicine. A medical tele-platform that combines virtual representations of tumors on various devices connected to the Internet with the possibility to recreate at-scale deformable models by 3D printing of cancerous tissue is novel and with great expandability potential due to its inherent scalability and adaptability.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Costin Teodor Streba & Roxana Cruce have contributed equally to this paper and thus share main authorship.

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Corresponding author
Mircea-Sebastian Şerbănescu, Lecturer, MD, PhD, Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40745–766 610, e-mail: mircea_serbanescu@yahoo.com

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