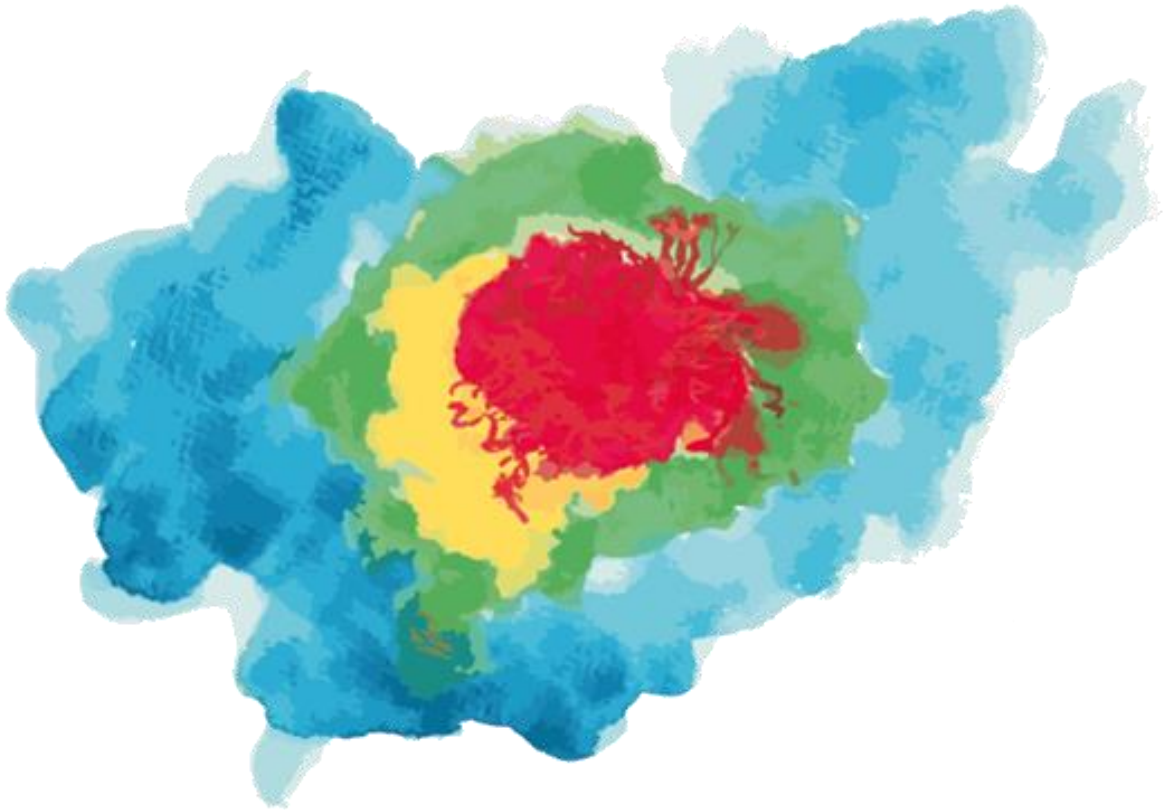
INSTRUCTIONS FOR USE OF THE ONCOhabitats MEDICAL DEVICE



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Biomedical Data Science Lab

Institute ITACA
Information and Communication Technologies

UNIVERSITAT POLITÈCNICA DE VALÈNCIA

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0 INTRODUCTION AND BACKGROUND INFORMATION

This document shows the instructions for using the ONCOhabitats software (patent number ES201431289A in Spain, EP3190542A1 in Europe, and US20170287133A1 in the USA). The product has been developed by the Biomedical Data Laboratory (BDSLab) of the Universitat Politécnica de València (UPV), Camino de Vera s/n 46022 València - Spain.

ONCOhabitats is a software for evaluating the heterogeneity of high-grade gliomas (IDH-wild Glioblastoma and IDH-mutant Astrocytoma) using MRI data. The system offers two services: 1) segmentation of high-grade gliomas and 2) delineation of vascular heterogeneity of high-grade gliomas using the HTS method. From the input data of the case to be studied, provided by the user on the web page (https://www.oncohabitats.upv.es/), the system produces as output a report with the results obtained that is sent to the user by e-mail, in addition to displaying them on the web page. This information can be used to assist in understanding the physiology and anatomy of the tumor and thus to support physicians in planning surgeries within the framework of clinical research with medical devices. Current security standards will store all data (user-entered data and results generated by the software). As for end users, the software is open source but is intended for use by clinicians and researchers who wish to obtain and analyze information on high-grade gliomas.

The software was published on the website https://www.oncohabitats.upv.es/ for academic purposes on May 3, 2021. The current version of ONCOhabitats has been carried out within the ALBATROSS (PID2019-104978RB-I00) and SINUE (INNEST/2022/87) projects. It has been retrospectively evaluated in hospitals in Spain, Italy, Belgium, and Norway in Clinical Study NCT03439332 (Del Mar Álvarez-Torres et al., 2020). Currently, ONCOhabitats is being validated by the clinical study "Evaluation of the feasibility of ONCOhabitats to assist surgery and treatment planning in patients with Glioblastoma, IDH-wild type (INNEST/2022/87)". This clinical validation is being funded by the ALBATROSS project (PID2019-104978RB-100 - Agencia Estatal de Investigación) and the SINUÉ project (INNEST/2022/87 - Agencia Valenciana de la Innovación).

As a risk prevention action for a product under clinical validation, a training course will be conducted before recruiting the first patient, and multimedia information from the course will be available on the ONCOhabitats website to ensure adequate training of professionals on the use, interpretation, and limitations of the software concerning healthcare aspects.

Given the current innovative nature of AI-based technology, all AI-based software designed and developed for healthcare use should be considered by users as an aid in their analysis of patients and never to guide diagnoses or treatments on their own. However, it is globally acknowledged that specific risks are associated with data science and AI-based technology developments. Therefore, we must identify and assess the specific risks associated with our research projects, including potential vulnerabilities in data security and ethical or privacy issues.

The Biomedical Data Laboratory (BDSLab) of the Universitat Politécnica de València (UPV) should be notified in case of detecting any failure or malfunction of the product causing a severe incident. The contact methods are available in the "contact" section of the group's website: https://www.bdslab.upv.es/#contact-page. BDSLab, as a research group of the Universitat

Politècnica de València, promoter of the study, will notify the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) through the following e-mail: psinvclinic@aemps.es.

ONCOhabitats is hosted on a secure server at the UPV, under secure protocols and following the premises of the data protection delegate of the University itself. As for the necessary hardware, it is physically located in a server room with an electronic lock that can only be accessed by authorized personnel. Likewise, the data entered by the user and generated by the software are stored following the security standards in force.

1 REGISTRATION IN THE SYSTEM

1.1. Accessing the website: www.oncohabitats.upv.es

1.2. Access the "REGISTER" section.

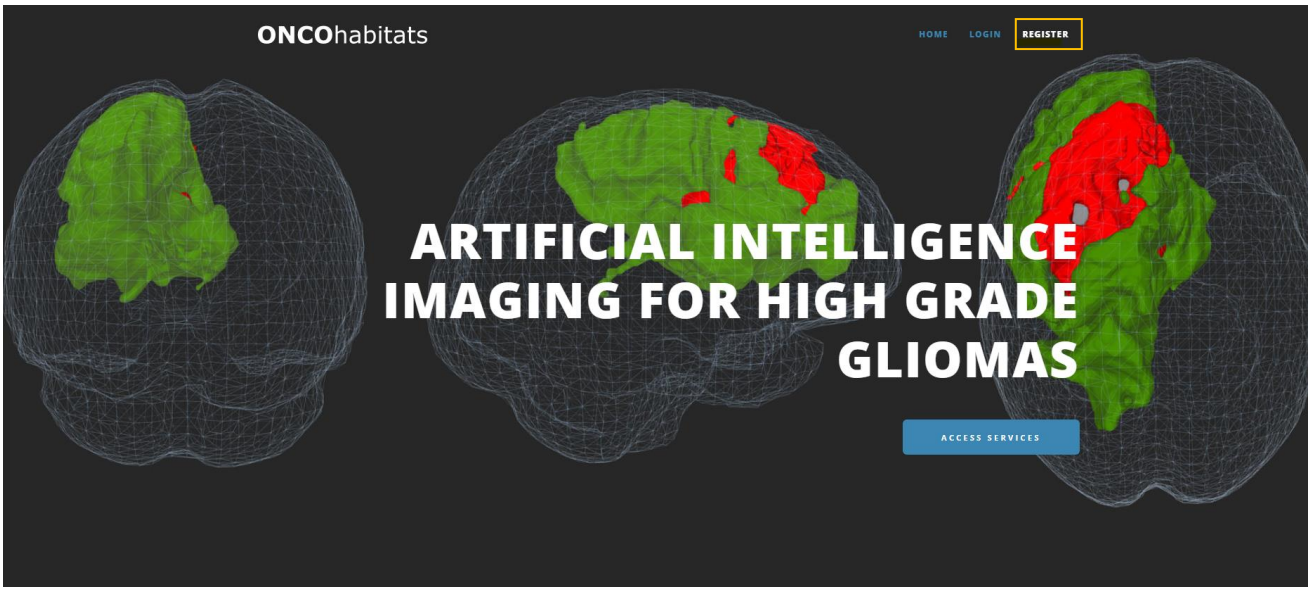


Figure 1. ONCOhabitats website.

1.3. Fill in the required data and click on the "captcha" as a test to check that the user is a person.

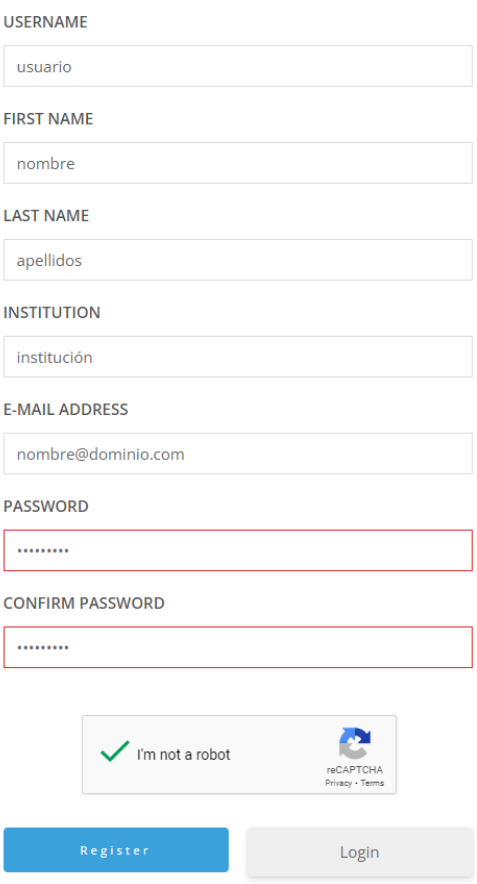


Figure 2. Registration form.

After clicking on "Register" you will receive an email in the account indicated when registering, welcoming you. Your ONCOhabitats account will now be created.

2 LOGGING ON TO THE SYSTEM

2.1. Access the website: www.oncohabitats.upv.es

2.2. Access to the "LOGIN" section

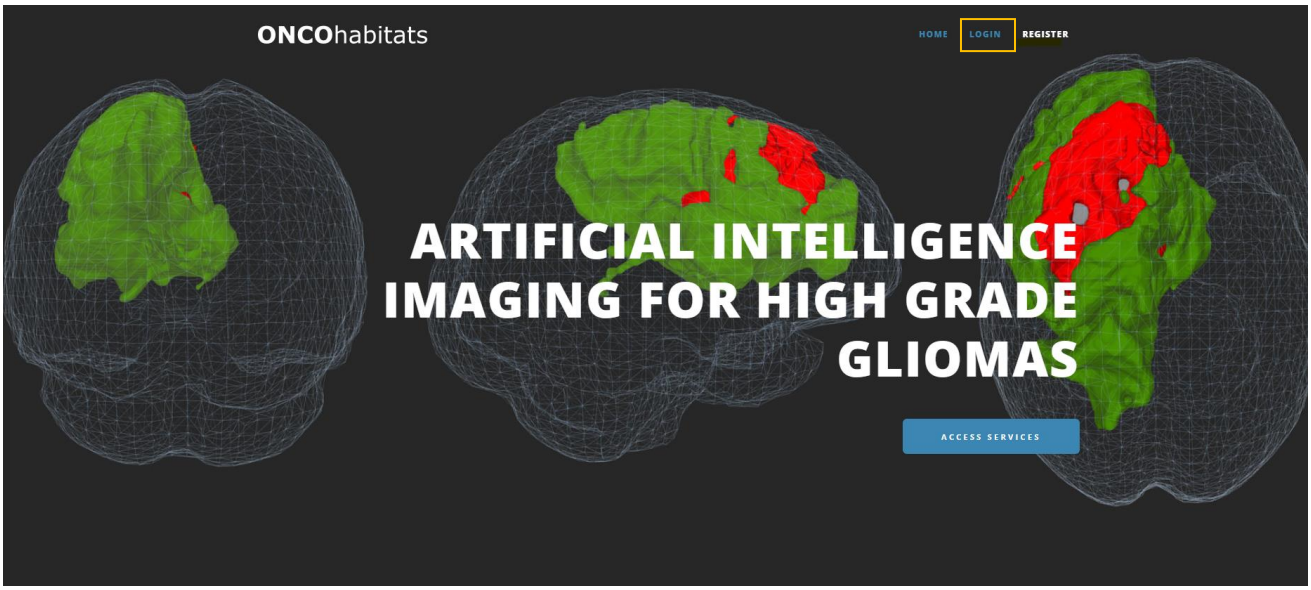


Figure 3. ONCOhabitats website.

2.3. Enter your username or email account and password. Then click on "I'm not a robot" and, after confirming the CAPTCHA, click on the "Login" button.

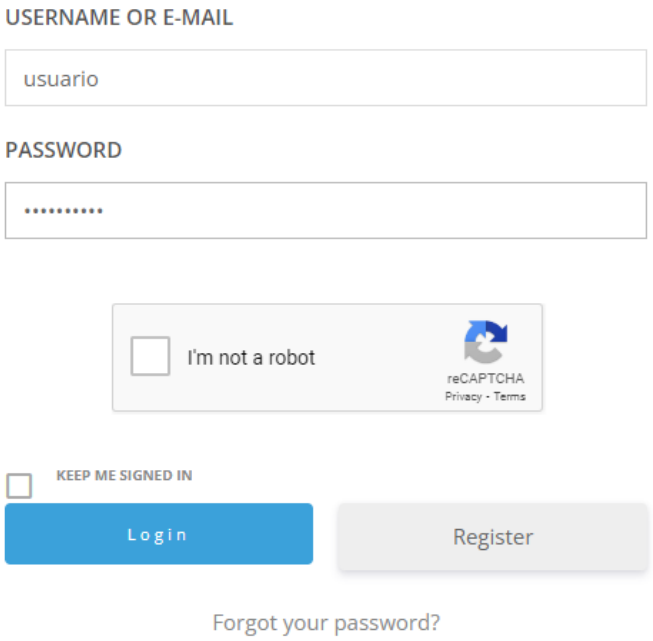


Figure 4. Login screen.

3 PERFORMING MORPHOLOGICAL SEGMENTATION

3.1. Accessing the website: www.oncohabitats.upv.es

3.2. Go to the section "SERVICES > SEGMENTATION SERVICE".

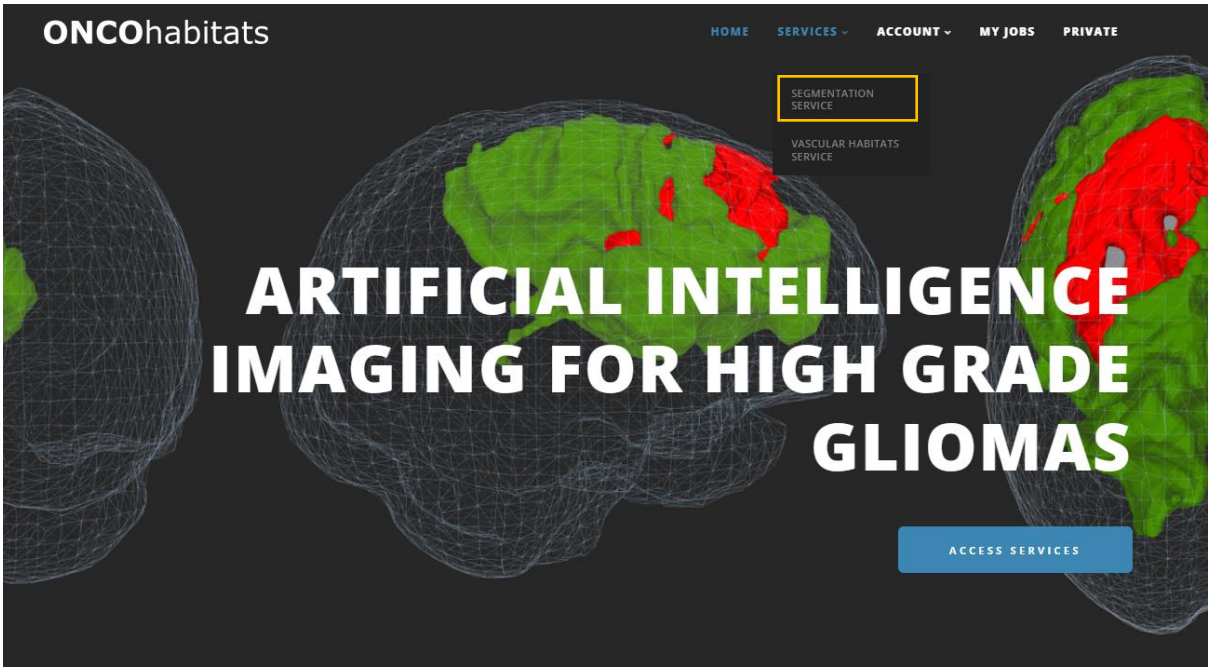


Figure 5. Selection of morphological segmentation service.

3.3. Access the "MR IMAGING" section. In the four boxes we introduce the MR image (T1, T1c, T2 and FLAIR) indicated in each one, either by dragging it from the folder where they are located, or by clicking on "BROWSE", looking for the folder where the image is located in the window that appears and, once located, click on Open.

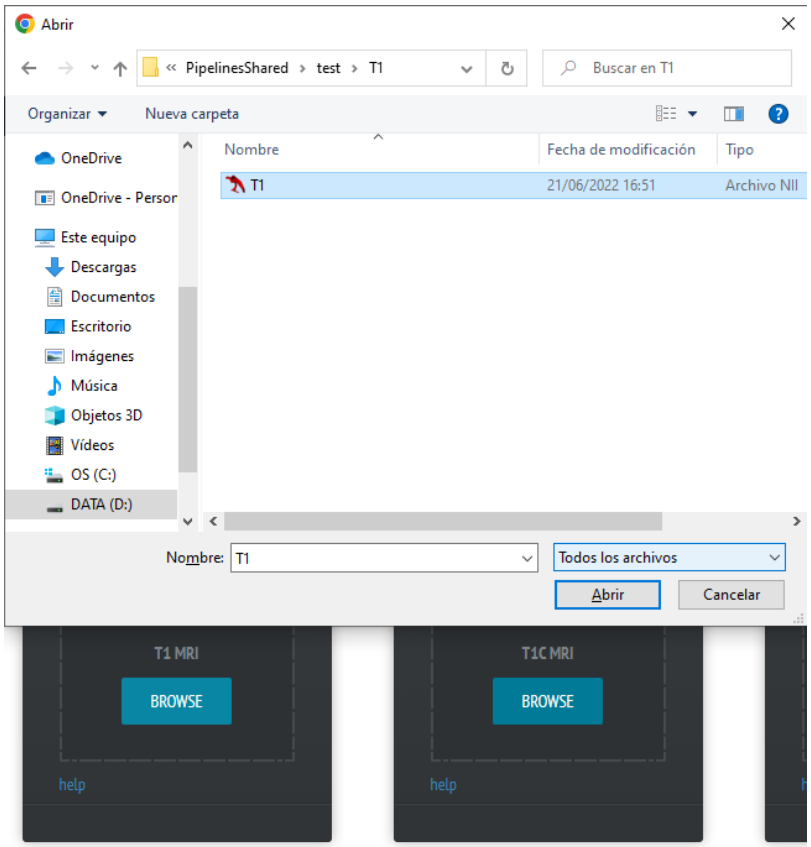


Figure 6. Select MR image.

3.4. Fill in the fields in the "CLINICAL INFORMATION" section. The field "MRI storage consent:" indicates whether the user gives permission for the case entered into the platform to be stored on the platform. If permission is not given, the case in question will be deleted from the system some time after its execution. In a clinical trial, the images will not be saved on the platform's storage server, so this box should not be ticked.

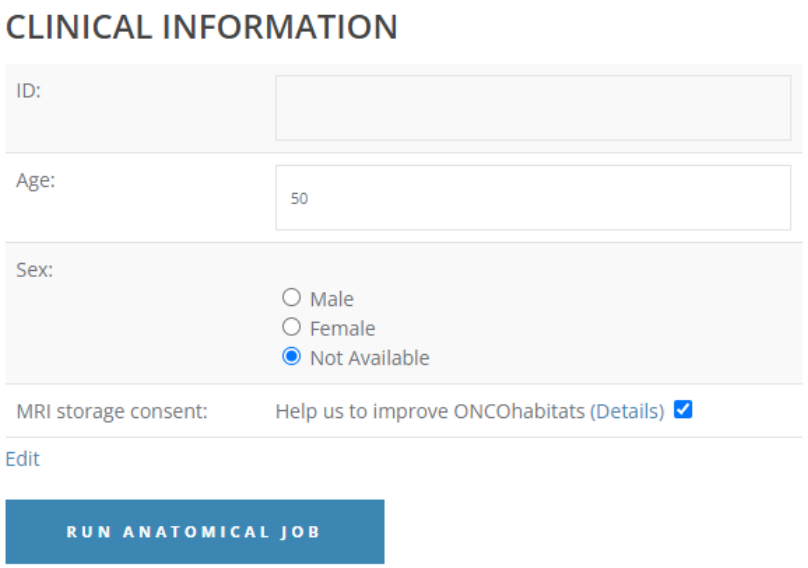


Figure 7. Clinical data entry.

3.5. Click on the "RUN ANATOMICAL JOB" button, which can be seen in the previous illustration. After this, you will see a screen indicating that the service has been successfully launched.

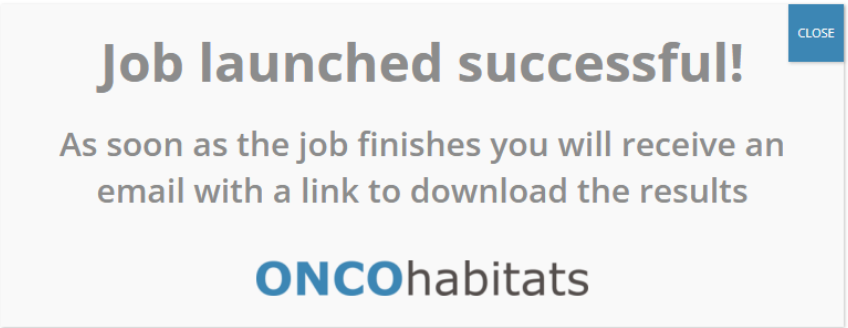


Figure 8. Screen indicating the successful launch of the service.

After this, the system will start executing the case. Once finished, the system will send an email to the user with the results: on the one hand, a report in pdf format, and, on the other hand, a folder with the images generated during the execution.

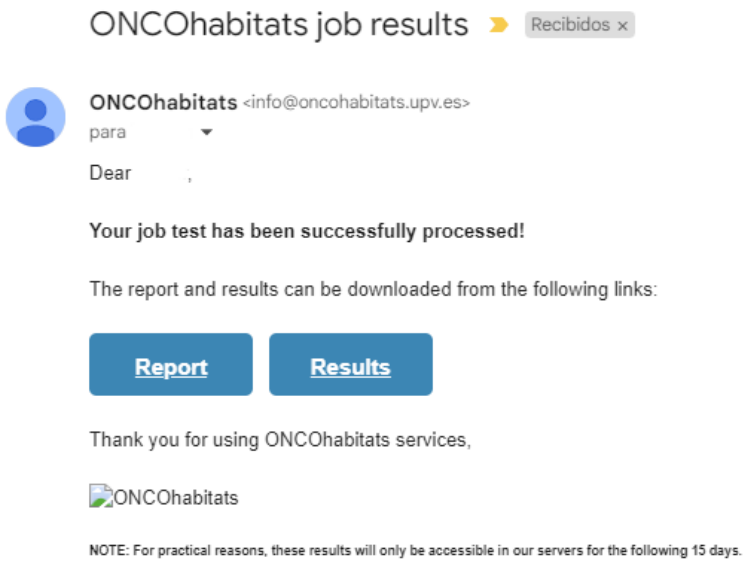


Figure 9. Mail received with the results.

You can also view the results by accessing the "MY JOBS" section of the website.

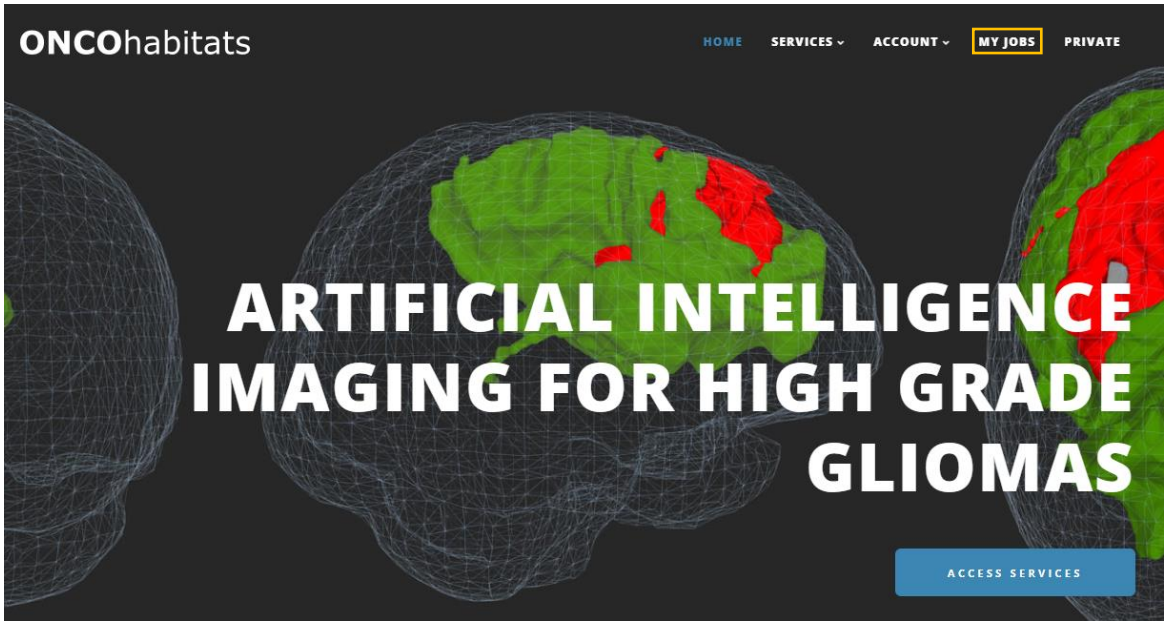


Figure 10. ONCOhabitats website.

Here you can view the data of the executed case and download the full report and results.

	2342	Anatomical segmentation	Finished	2023-01-02 11:58:38	2023-01-02 11:58:49	2023-01-02 12:37:33

patient:	test
gender:	other
age:	50
report:	download
results:	download

Figure 11. Window with the results of the job, shown in the "My Jobs" section.

The report generated and sent to the user follows the following structure:

-A cover page, with the study information data (report ID, report date, user name and institution and patient ID, gender and age), as shown in Figure 12.

A section with the calculated volumetry data for the morphological segmentation of high-grade gliomas (in cm^3), the intracranial cavity mask (in axial, sagittal and coronal planes) and the tumor segmentation map (in axial, sagittal and coronal planes) generated during the execution of the service, as shown in Figure 12.

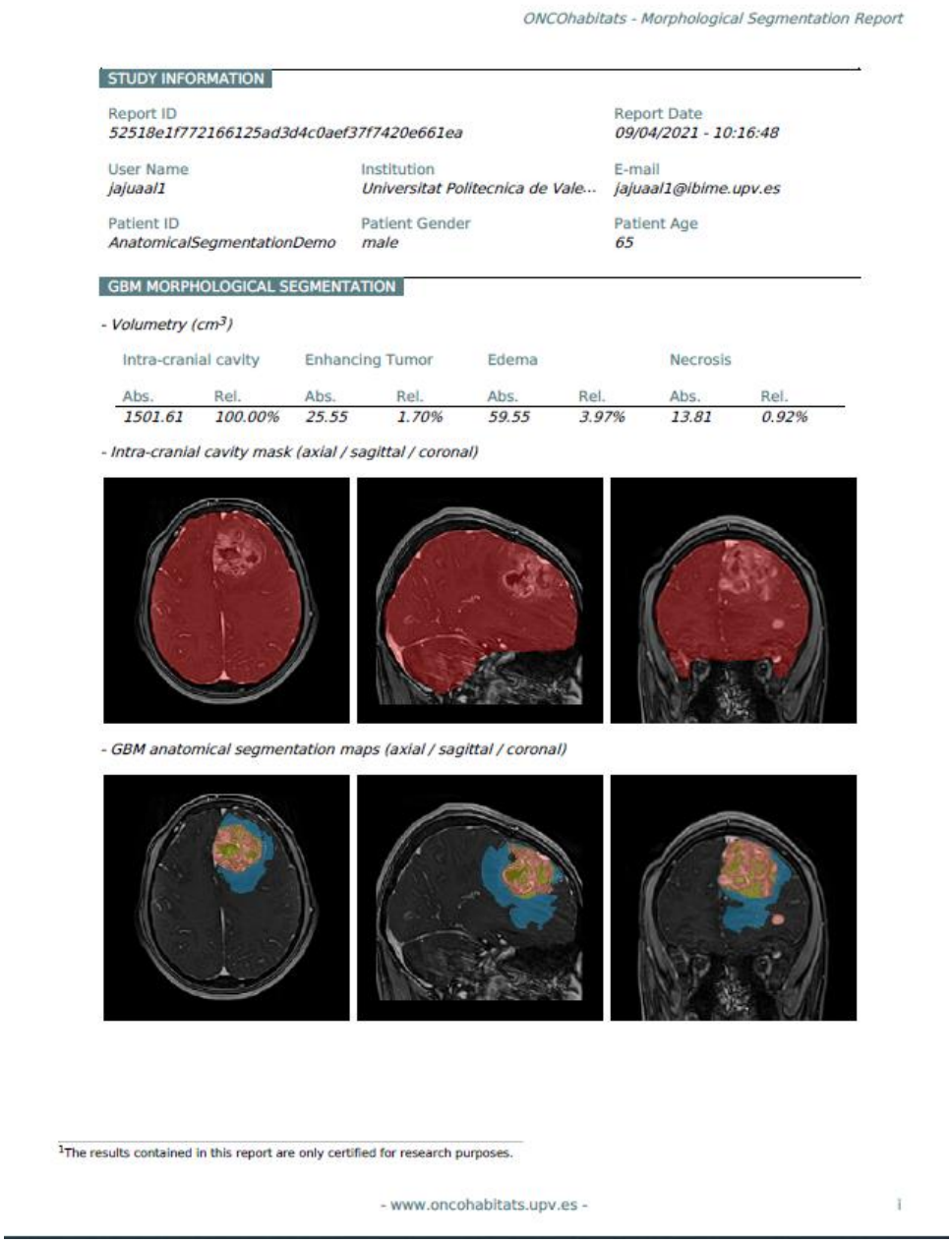
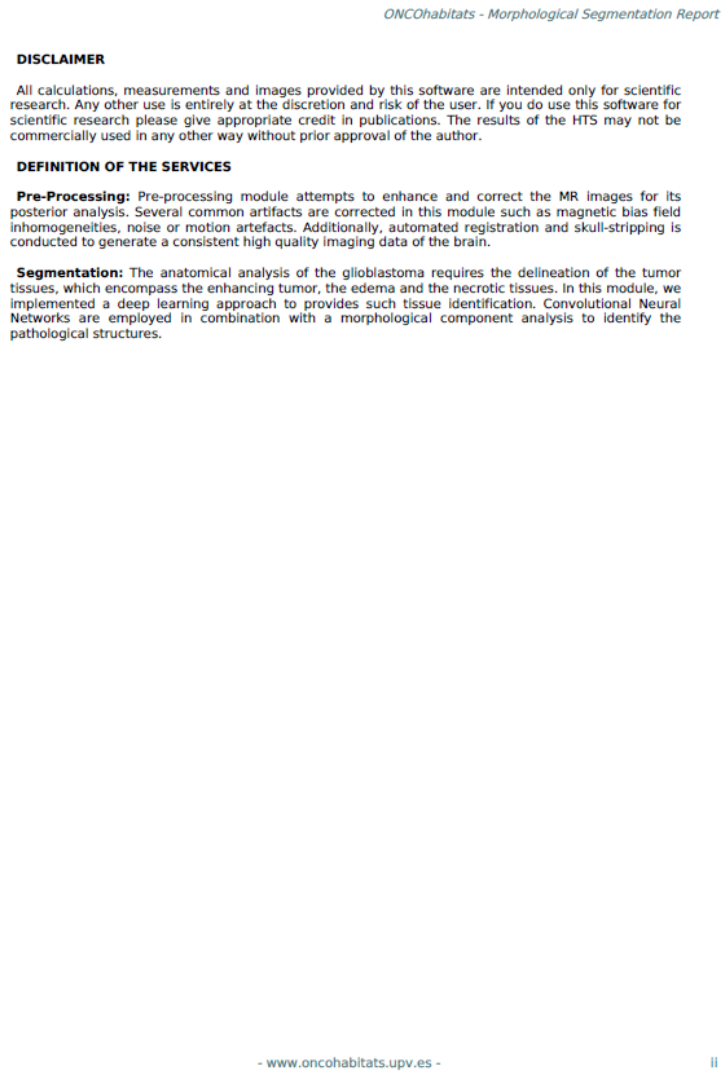


Figure 12. Page 1 of the report generated by the morphological segmentation service.

A back cover showing disclaimer information, a definition of the processes carried out in the service (pre-processing of MR images and segmentation of gliomas of some grade) and a list of the acronyms used in the report, as seen in Figure 13.



DISCLAIMER

All calculations, measurements and images provided by this software are intended only for scientific research. Any other use is entirely at the discretion and risk of the user. If you do use this software for scientific research please give appropriate credit in publications. The results of the HTS may not be commercially used in any other way without prior approval of the author.

DEFINITION OF THE SERVICES

Pre-Processing: Pre-processing module attempts to enhance and correct the MR images for its posterior analysis. Several common artifacts are corrected in this module such as magnetic bias field inhomogeneities, noise or motion artefacts. Additionally, automated registration and skull-stripping is conducted to generate a consistent high quality imaging data of the brain.

Segmentation: The anatomical analysis of the glioblastoma requires the delineation of the tumor tissues, which encompass the enhancing tumor, the edema and the necrotic tissues. In this module, we implemented a deep learning approach to provides such tissue identification. Convolutional Neural Networks are employed in combination with a morphological component analysis to identify the pathological structures.

Figure 13. Back cover of the report generated by the morphological segmentation service.

4 RUNNING A SEGMENTATION OF HABITATS VASCULAR

4.1. Accessing the website: www.oncohabitats.upv.es

4.2. Go to "SERVICES > VASCULAR HABITATS SERVICE".

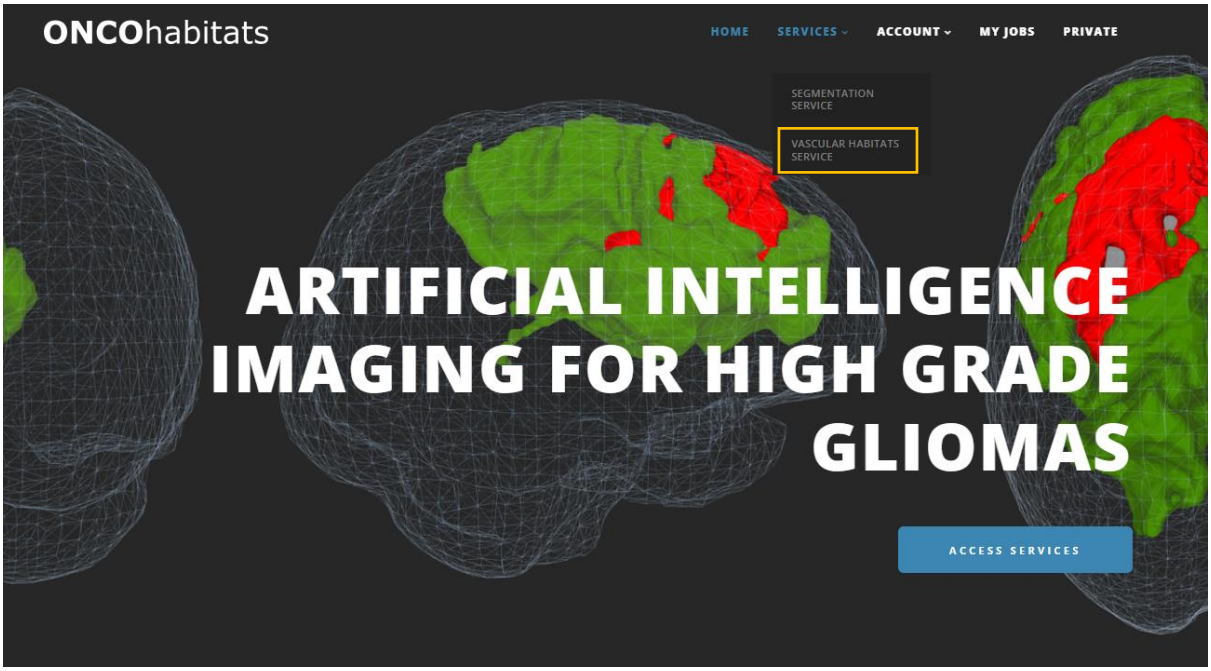


Figure 14. Selection of vascular habitat segmentation service.

4.3. Access the "MR IMAGING" section. In the five boxes we introduce the MR image (T1, T1c, T2, FLAIR and DSC), indicated in each one either by dragging it from the folder where it is located, or by clicking on "BROWSE", looking for the folder where the image is located in the window that appears and, once located, click on Open.

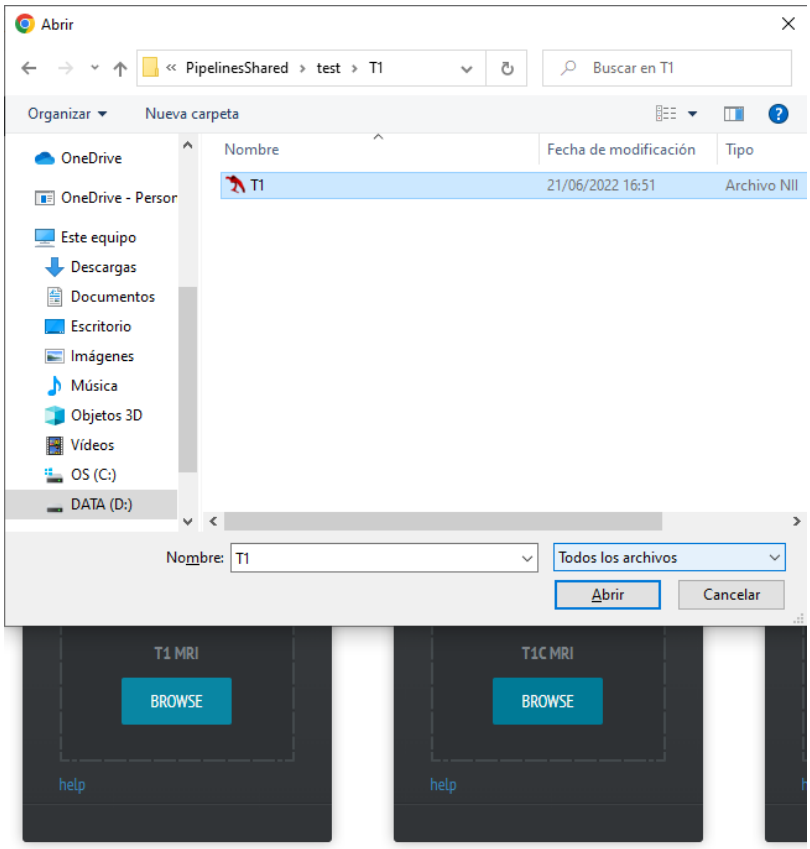


Figure 15. Select MR image

In addition, the user will have to enter the TE (Echo Time) and TR (Repetition Time) fields.

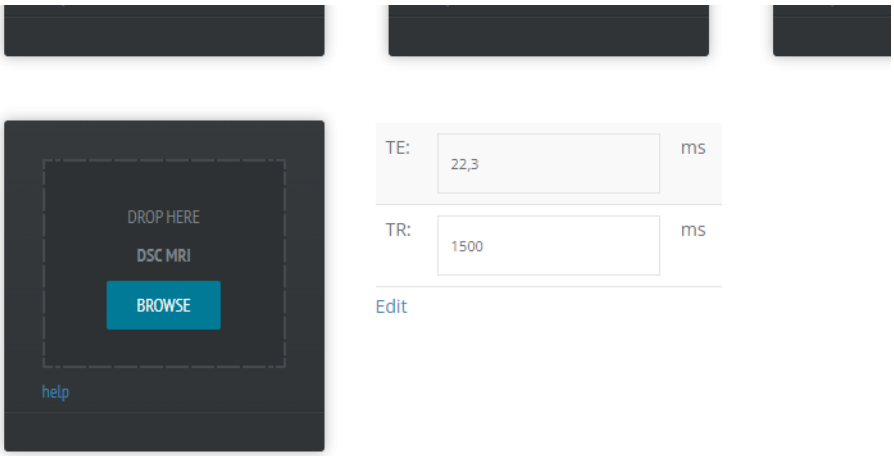


Figure 16. Fields to enter TE and TR.

4.4. Fill in the fields in the "CLINICAL INFORMATION" section. The field "MRI storage consent:" indicates whether the user gives permission for the case entered into the platform to be stored on the platform. If permission is not given, the case in question will be deleted from the system some time after its execution. In the case of a clinical trial, the images will not be saved on the platform's storage server, so this box should not be ticked.

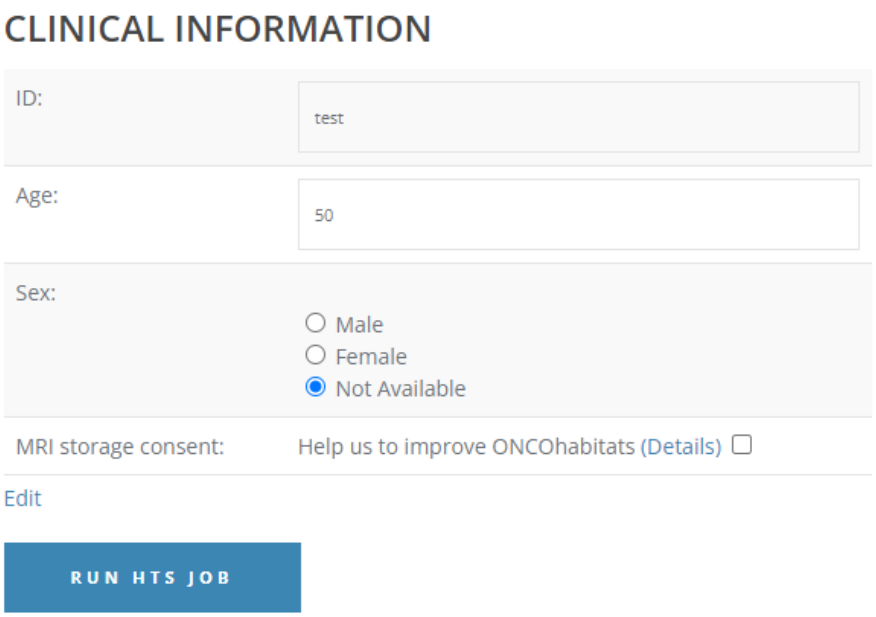


Figure 17. Clinical data entry.

4.5. Click on the "RUN HTS JOB" button, which can be seen in the previous illustration. After this, you will see a screen indicating that the service has been successfully launched.

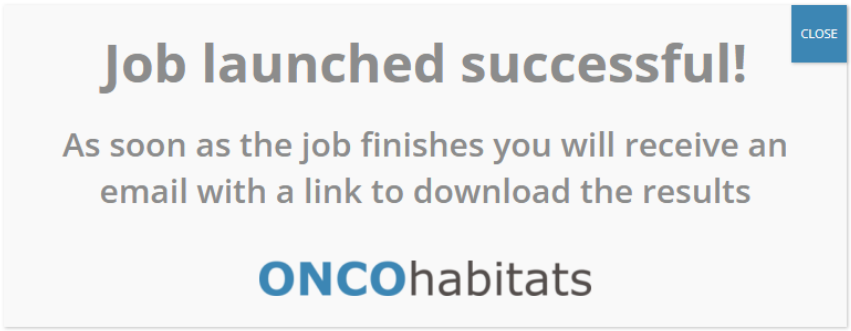


Figure 18. Screen indicating the successful launch of the service.

After this, the system will start running the case. Once finished, the system will send an email to the user with the results attached: on the one hand, a report in pdf format, and, on the other hand, a folder with the images generated during the execution.

Figure 19. Mail received with the results.

You can also view the results by accessing the "MY JOBS" section of the website, as shown in Figure 20. Here you can see the data of the executed case and download the report and the complete results.

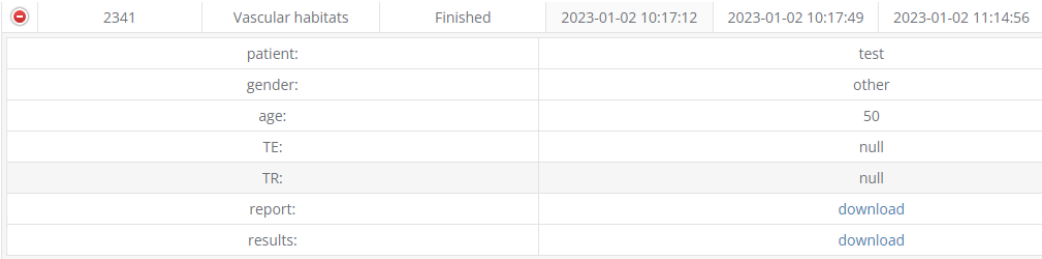
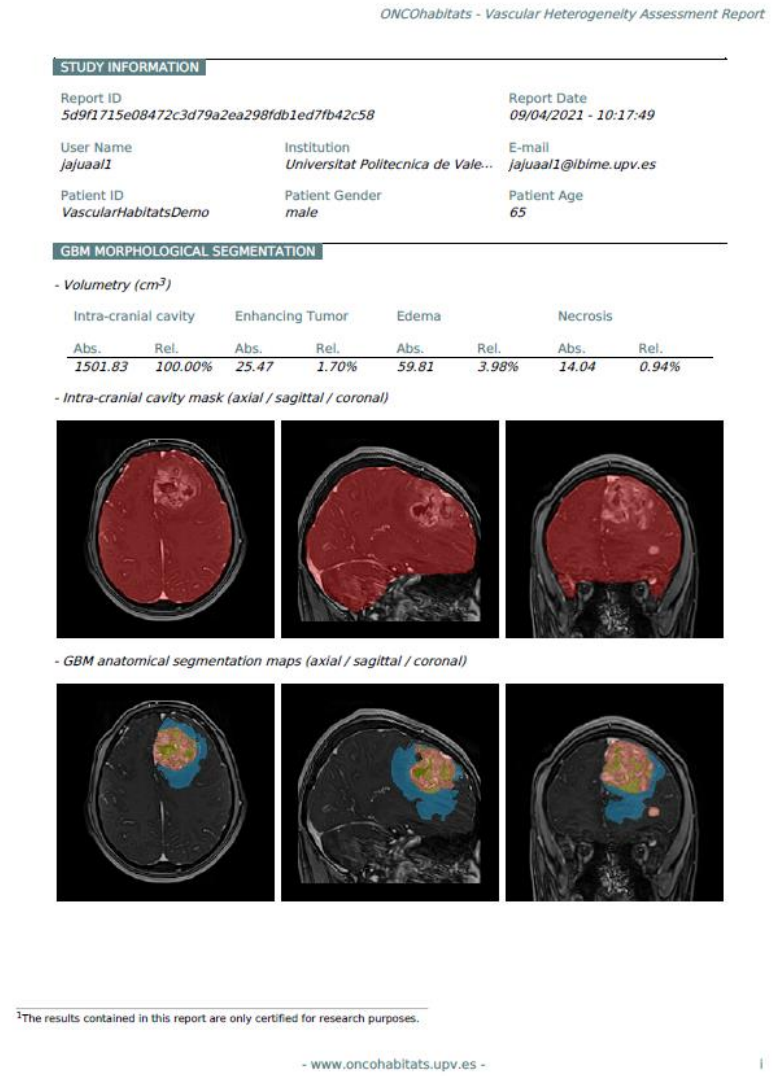


Figure 20. Window with the results of the job, shown in the "My Jobs" section.

The report generated and sent to the user follows the following structure:

-A cover page, with the study information data (report ID, report date, user name and institution and patient ID, gender and age), as shown in Figure 21.

A section with the calculated volumetry data for the morphological segmentation of high-grade gliomas (in cm^3), the intracranial cavity mask (in axial, sagittal and coronal planes) and the tumor segmentation map (in axial, sagittal and coronal planes) generated during the execution of the service, as shown in Figure 21.



ONCOhabitats - Vascular Heterogeneity Assessment Report

STUDY INFORMATION

Report ID: 5d9f1715e08472c3d79a2ea298fdb1ed7fb42c58
Report Date: 09/04/2021 - 10:17:49
User Name: jajuaal1
Institution: Universitat Politecnica de Vale...
E-mail: jajuaal1@ibime.upv.es
Patient ID: VascularHabitatsDemo
Patient Gender: male
Patient Age: 65

GBM MORPHOLOGICAL SEGMENTATION

- Volumetry (cm^3)

Intra-cranial cavity		Enhancing Tumor		Edema		Necrosis	
Abs.	Rel.	Abs.	Rel.	Abs.	Rel.	Abs.	Rel.
1501.83	100.00%	25.47	1.70%	59.81	3.98%	14.04	0.94%

- Intra-cranial cavity mask (axial / sagittal / coronal)

- GBM anatomical segmentation maps (axial / sagittal / coronal)

[1]The results contained in this report are only certified for research purposes.

- www.oncohabitats.upv.es -

Figure 21. Page 1 of the report generated by the vascular habitats service.

-A section with the generated DSC quantification information, such as the median and mean absolute deviation of the DSC biomarkers per tissue (active tumor and edema), the biomarker maps (rCBV map, rCBF map and MTT map, in the axial plane) and the K2 leakage correction map, also in the axial plane, as seen in Figure 22.

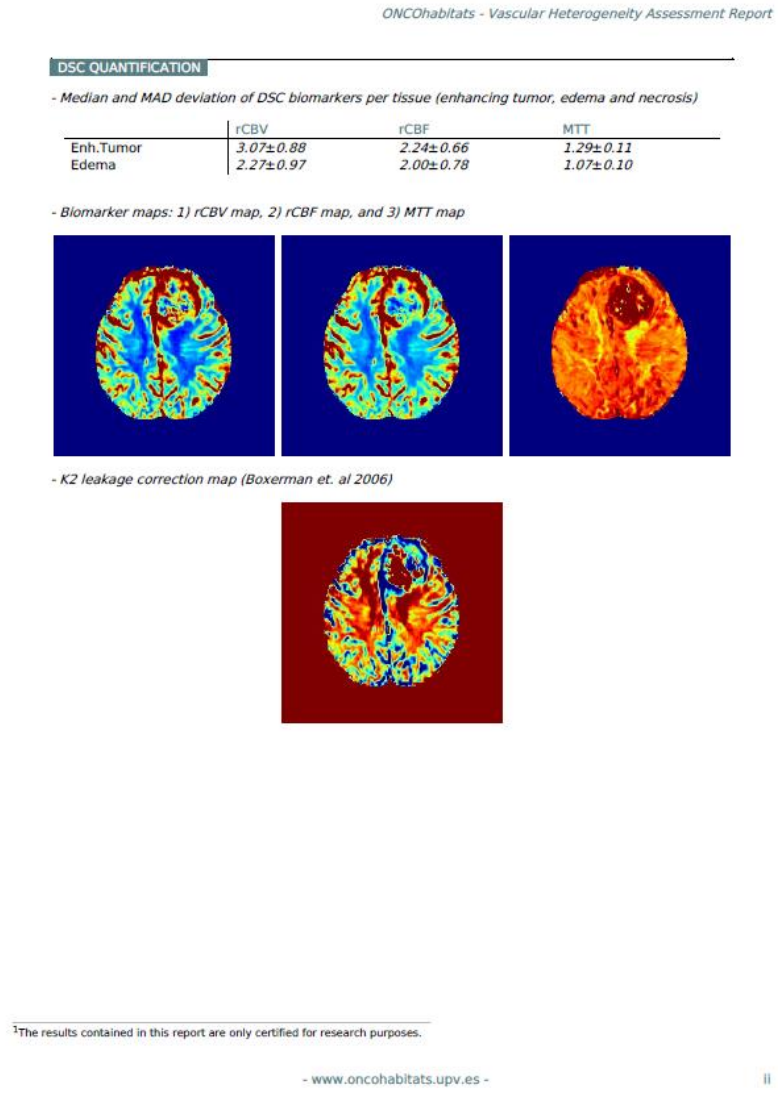


Figure 22. Page 2 of the report generated by the vascular habitats service.

A section with the generated Hemodynamic Tissue Signature DSC perfusion maps and the metrics calculated in the service, such as volumetry per vascular habitat (in cm^3), median and mean absolute deviation of DSC biomarkers per vascular habitat, the Hemodynamic DSC Tissue Signature nosology map (in axial, sagittal and coronal planes), the DSC Hemodynamic tissue signature chart and the prototype concentration-time perfusion curves, as shown in Figure 23.

The DSC Hemodynamic tissue signature chart shows how each DSC biomarker (CBV, CBF, MTT and K2) calculated in the DSC quantification process relates to each habitat (HAT, LAT, IPE and VPE), and the prototype concentration-time perfusion curves show the evolution of the intensity of the bolus of contrast injected into the patient in each habitat over time.

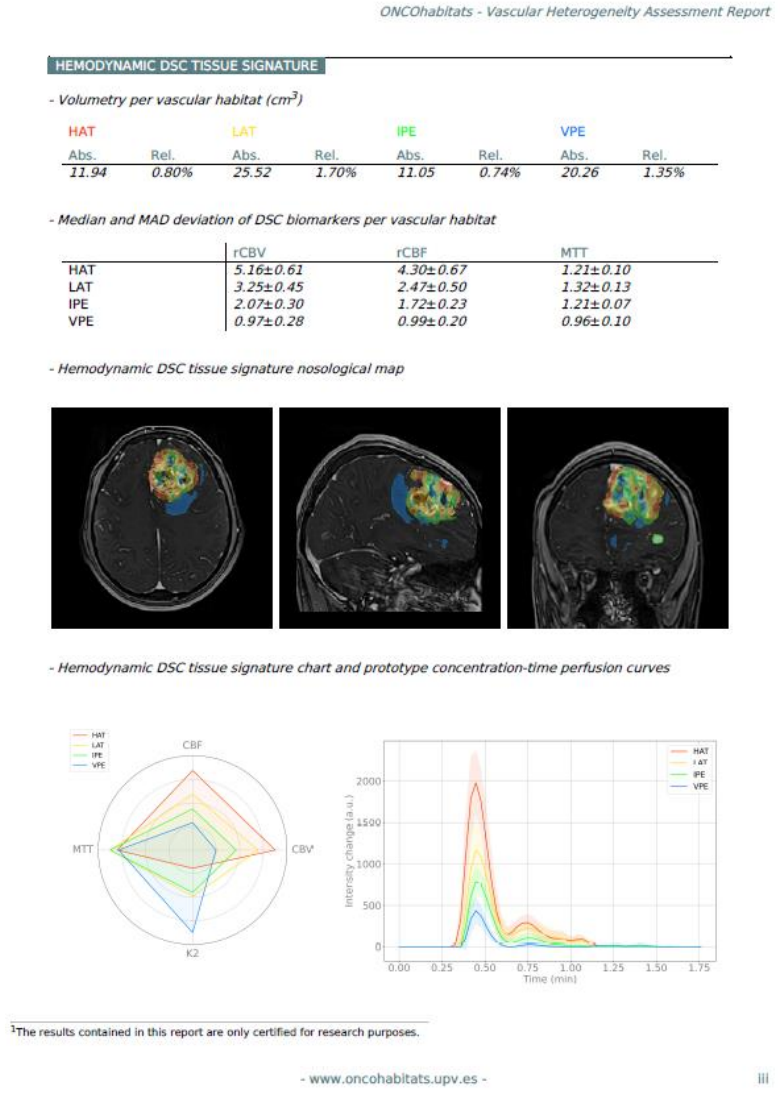


Figure 23. Page 3 of the report generated by the vascular habitats service.

A back cover showing disclaimer information, a definition of the processes carried out in the service (pre-processing of MR images and segmentation of gliomas of some grade) and a list of the acronyms used in the report, as seen in Figure 24.

DISCLAIMER

All calculations, measurements and images provided by this software are intended only for scientific research. Any other use is entirely at the discretion and risk of the user. If you do use this software for scientific research please give appropriate credit in publications. The results of the HTS may not be commercially used in any other way without prior approval of the author.

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DSC perfusion quantification: DSC quantification involves the computation of the hemodynamic indices obtained from a kinetic analysis of the first pass of a intravenously injected paramagnetic contrast agent. T1 and T2 leakge effects are also corrected to not miss-estimate the hemodynamic biomarkers. The quantified maps computed by this module are: relative Cerebral Blood Volume (rCBV), relative Cerebral Blood Flow (rCBF), Mean Transit Time (MTT) and K2 maps.

Hemodynamic Tissue Signature (HTS): HTS consist on an automated unsupervised method able to describe the vascular heterogeneity of the enhancing tumor and edema tissues in terms of the angiogenic process located at these regions. The HTS provides a characterization of the GBM, whose output is a nosologic map of the tumoral tissues grouped in different vascular sub-comparmtents with their associated MRI fingerprint. We consider 4 vascular sub-compartments for the GBM: the high angiogenic enhancing tumor region (HAT), the low angiogenic enhancing tumor region (LAT), the potentially tumor infilatrated peripheral edema (IPE) and the pure vasogenic edema (VPE). The HTS is able to capture the local heterogeneity of the tumor, hence providing relevant information about its behaviour.

rCBV relative Cerebral Blood Volume

rCBF relative Cerebral Blood Flow

MTT Mean Transit Time

DSC Dynamic Susceptibility Contrast

HTS Hemodynamic Tissue Signature

Figure 24. Back cover of the report generated by the vascular habitats service.

5 BIBLIOGRAPHY

Del Mar Álvarez-Torres, M. *et al.* (2020) 'Robust association between vascular habitats and patient prognosis in glioblastoma: An international multicenter study', *Journal of magnetic resonance imaging: JMRI*, 51(5), pp. 1478–1486. Available at: https://doi.org/10.1002/jmri.26958.