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# Picture: A web application for decision support in glioma surgery

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ABSTRACT

*Background and Objective:* Patients with glioma, the most common primary malignant brain tumor, often undergo surgery, aiming to remove as much tumor as possible while maintaining functional integrity. However, there is large variation in surgical decisions. This study aims to provide a data-driven approach to surgery planning and evaluation, estimating personalized potential extent of resection, based on a large multicenter MRI database.
*Methods:* We developed an interactive web-application (PICTURE tool), that uses segmented MRI scans from prior surgeries to create resection probability maps. The maps depict the chance of tumor tissue resection based on decisions in prior surgeries.
*Results:* The PICTURE tool enables uploading scans of a new patient and comparing these with the resection probability map of previous patients. This map can then be filtered for clinical characteristics to compare with similar patients and can be interactively explored to determine which parts of the tumor are more or less likely to be resected in a particular patient. Additionally, tumor characteristics and expected extent of resection are reported.
*Conclusions:* The PICTURE tool can enable data-driven glioma surgery planning through interactive generation of resection probability maps.

## 1. Introduction

Gliomas are the most common primary malignant brain tumors. Life expectancy can range from 13 months for patients with glioblastoma (GBM) WHO grade 4 up to 17 years for oligodendroglioma WHO grade 2 [1]. Patients with glioma can suffer from a wide range of neurological and cognitive symptoms [2]. Patients are often treated with resective surgery followed by radiotherapy and chemotherapy. Surgery aims for maximum tumor removal while preserving healthy functional brain tissue [3]. However, there are no current guidelines or standards to achieve this goal and surgeons need to decide themselves how much tumor can be removed and which techniques to use. Hence a wide variety of surgical methods are practiced, and decisions on extent of resection are often based on the neurosurgical team's expertise.

Patients with glioma usually undergo MRI scans before surgery, after surgery and during follow-up. This data can be leveraged to map surgical decisions for patient populations by means of resection probability maps (RPMs) [4–8]. RPMs can group data from multiple surgical teams and indicate the likelihood of tumor being resected considering brain location. The expected extent of resection can be estimated from these likelihoods for a given new patient [9]. However, challenges remain in applying this generalized data to surgical planning of individual patients.

Decision support systems for brain tumor patients are scarce and generally focus on tumor diagnosis and prognosis [10,11]. One FDA approved clinical decision support system extracts tumor features and longitudinally arranges individual patient data to track tumor changes over time [12]. Additionally, clinical decision support systems for other surgical and treatment fields have been developed such as preventing surgical thromboembolism, infection site prediction, incisional hernia prediction, surgical team selection, and treating traumatic brain injury [13–17]. However, data-driven clinical decision support systems for brain tumor surgeries have not been developed to our knowledge.

To address this gap, we developed the PICTURE tool; a web-based

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open-source decision support system to plan and contextualize glioma surgery (tool.pictureproject.nl). The tool aims to provide data-driven insights based on a large glioma dataset to support informed surgical decision making and patient counseling. In this paper we describe the tool and its architecture.

## 2. Specifications

### 2.1. Scope

Within the PICTURE tool it is possible to evaluate resection probability of a new glioma patient based on prior extent of resection in a reference database of over 1400 glioma surgeries worldwide. To define the scope and requirements of the tool, multiple iterations and co-creation meetings between neuroradiologists, neurosurgeons, researchers, software engineers, data scientists and designers were conducted. From these sessions, the scope of the tool was defined as glioma data aggregation to better inform resection decisions. The design is based on the hypothesis that individualized RPMs may predict the expected extent of resection for the patient. The following functional requirements were included; (a) present data in a 3-dimensional format with an intuitive interface for easy interpretability familiar to clinicians and researchers to minimize learning curves, (b) upload, process, register and segment prospective scans in DICOM format, (c) allow to filter the reference database depending on patient characteristics and thus generate a patient-specific resection probability map, (d) extract and display tumor features from MRI data, (e) view population-based resection probability maps for reference.

### 2.2. Dataset

Data of adult patients with glioma was collected from 15 hospitals worldwide (Table 1) as part of the PICTURE project dataset [18]. This retrospective study was exempt from IRB approval by the Medical Ethical Committee of Amsterdam UMC (reference number 2014.336, date 23th July 2014), and informed consent from patients was obtained according to local regulations.

Patients were included if they received a first-time resection or biopsy, without prior treatment, for a histopathologically confirmed glioma between 2008 and 2016. Patient age, sex, and preoperative Karnofsky Performance Scale (KPS) were collected. Additionally, we collected preoperative MRI scans including T1 weighted series without

**Table 1**
Dataset characteristics.

| | Predominantly Non-enhancing glioma (grade 2 and 3) | Enhancing glioma (grade 4) | Total |
|---|---|---|---|
| **No. Patients** | 387 | 1047 | 1435 |
| **Age** (years; median [IQR]) | 39 [18] | 64 [16] | 58 [22] |
| Unknown | 5 | 58 | 63 |
| **KPS** | | | |
| 90–100 | 18 | 429 | 447 |
| 70–80 | 3 | 402 | 405 |
| <70 | 0 | 152 | 152 |
| Unknown | 366 | 64 | 431 |
| **Surgery type** | | | |
| Resection | 387 | 764 | 1152 |
| Biopsy | 0 | 282 | 282 |
| Unknown | 0 | 1 | 1 |
| **Preoperative tumor volume** (ml; median [IQR]) | 49.6 [66.5] | 28.9 [40.9] | 32.4 [47.1] |
| **Extent of Resection*** (%; median [IQR]) | 84.4 [33.1] | 94.6 [16.5] | 92.0 [24.1] |

IQR = inter quartile range; KPS = Karnofsky Performance Scale; *only calculated when surgery type is resection.

(T1w) and with (T1c) gadolinium contrast enhancement, T2 weighted (T2w), and fluid attenuated inversion recovery (FLAIR) series as available. In total, we included data from 1435 patients of whom 388 had predominantly non-enhancing glioma (lower-grade glioma, WHO grade 2 and 3) and 1047 had predominantly enhancing glioma (glioblastoma, WHO grade 4). Grades were defined according to WHO criteria at the time, i.e. WHO 2007.

Preoperative and postoperative tumor volumes, and resection cavities were manually segmented using Brainlab's smartbrush tool [19]. Lower-grade gliomas (grade 2 and 3) were defined by combining non-enhancing hyperintense signal on T2w or FLAIR scans with possible enhancing signal on T1c scans. For glioblastomas (grade 4), tumors were defined by the tumor core consisting of the enhancing signal and necrosis on T1c scans. Scans were then skull-stripped using the HD-BET MRI brain extraction tool and registered to Montreal Neurological Institute (MNI) 152 standard space using ANTS diffeomorphic SyN transformations after which these transformations were applied to the segmentations [20,21]. All registrations were visually verified.

The full dataset is available in the online version of the tool for visualization and analysis. We provide a mock dataset for the local version of the tool, however, this test-set was fully anonymized and randomized. Thus, it cannot be used to draw conclusions.

## 3. User interface and tool architecture

Here we will describe the user flow of the tool. In each section we will first explain the user interface (a full walkthrough can be seen in the digital Video) followed by a detailed elaboration of the technical implementation. The first section starts with a general overview of the tool's functionalities and architecture, followed by patient upload, scan processing and analysis, the patient viewer, and additional functionalities.

### 3.1. General

The PICTURE tool is a web-based application (tool.pictureproject.nl). To access the tool's full functionality, an account must be created. After authentication, the user is directed to the Brain Map Manager, displaying the user's previously uploaded patients. From here, users can decide to upload and start analysis on a new patient (Fig. 1A) or view one of their previously uploaded patients (Fig. 1B), as detailed below.

The tool consists of three main components: the front-end web application for visualization, the application programming interface (API) with pipelines for filtering, and the backend including a database for storage. This organizational strategy enhances back-end data processing capabilities while allowing the frontend to concentrate on user interactions and effective presentation of data. This configuration ensures that the processing of complex, personalized analyses is both efficient and manageable.

The tool's front-end architecture uses web technologies to provide an intuitive user interface (Fig. 1C). The front-end technology stack consists of Nuxt.js with Vue.js to build universal web applications, enabling faster and optimized web performance through client- and server-side rendering. BrainBrowser is used for interactive brain imaging visualization [22].

The back-end architecture (Fig. 2) leverages Docker to manage services, which ensures scalability, reproducibility, and reliability [23]. The technology stack includes the API built with Laravel to manage back-end operations and provide endpoints for image filtering and data retrieval [24]; a MySQL database for storing structured data [25]; Flask and Celery for task management and creating microservices [26]; Redis for performance enhancement and caching [27]; and Nginx as a reverse proxy [28].

The registration service first applies an affine registration to atlas space utilizing the ANTsPy library. The segmentation service then applies nnU-net based automatic segmentation, which was trained

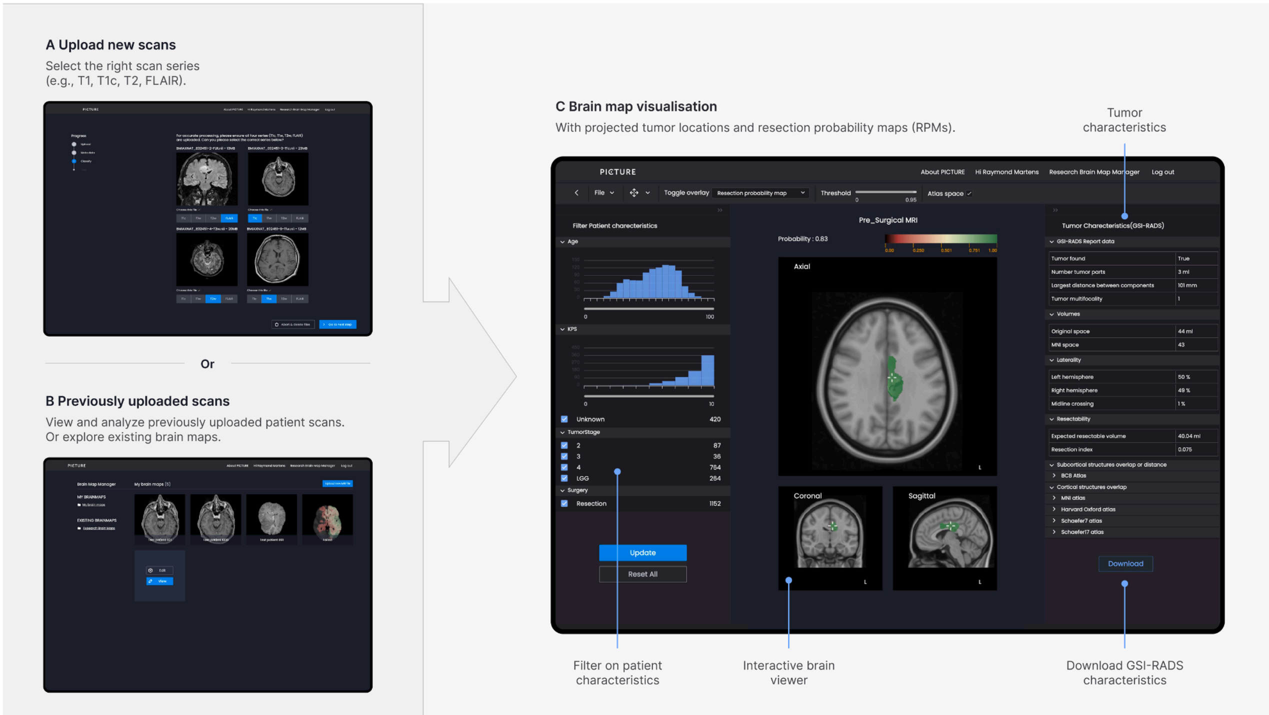


**Fig. 1. The PICTURE tool user interface.** A) Upload new scans: select the right scan series (e.g., T1, T1c, T2, FLAIR) or B) analyze previously uploaded patient scans; C) Brain map visualization: projected tumor locations and resection probability maps (RPMs).

including the reference database. Next, the registration service applies a deformable (SyN) registration using Mutual Information cost function and the tumor segmentation as cost function mask [20,29,30]. Filtering processes are managed through pipelines, facilitating data processing.

The tool is hosted on the SURF HPC Cloud, featuring an Intel(R) Xeon (R) Gold 6342 CPU @ 2.80 GHz with 22 cores and 176 GB RAM, along with two NVIDIA A10 GPUs, each offering 24 GB VRAM. The application can be locally installed on Linux (Ubuntu 20.04 LTS), macOS (Sonoma 14.6), and Windows Subsystem for Linux (WSL). The minimum hardware requirements include a system with at least 16 GB of RAM, though 32 GB is recommended for optimal performance. Utilizing a GPU with CUDA significantly speeds up the analysis process, making the tool more efficient for large datasets. From upload to first results takes 3 to 5 min for the online tool with GPU. On local machines with CPU, this process takes about 30 to 45 min.

### 3.2. Patient scan upload

When a user decides to upload a new patient's scan, they are directed to the imaging upload and processing interface (Fig. 1A). Here, the user first uploads a zip file containing preoperative structural MRI images in DICOM or NIfTI format. Before uploading, the user is asked to accept the tool's data policy where it is advised to only upload anonymized data to comply with privacy regulations. Four pulse-sequences need to be uploaded and selected: T1w, T1c, T2w, and FLAIR series. Scans should not be skull-stripped. After uploading the scans, the user can enter patient characteristics and is then prompted to classify or verify detected scan series after which images are processed and analyzed by the tool.

In the backend, all files are scanned for viruses using ClamAV. DICOM files are temporarily stored and converted to NIfTI format, using dcm2niix, to streamline handling and enhance analysis efficiency. This step, also removes identifiable information that may have remained in the DICOM headers as an additional attempt to anonymize the data. Processed data and derived outputs, are securely stored on general data protection regulation (GDPR) compliant servers with advanced encryption and access controls to ensure data security. Secure storage and processing of data are maintained through AES-256 encryption, transport layer security (TLS) and secure sockets labels (SSL), aiming to comply with healthcare data standards such as GDPR and health insurance portability and accountability act.

### 3.3. Scan processing and analysis

Once the upload is complete, the analysis pipeline starts (Fig. 3). Scans are registered to the Montreal Neurological Institute (MNI) 152 1 mm brain space and tumors are segmented. These steps happen without additional user input and can be viewed by the user in the patient viewer once complete.

The registration process is managed by a dedicated registration service running in a Docker container. The core registration script uses the ANTsPy library, primarily utilizing CPU resources as ANTsPy does not natively support GPU acceleration. Scans are co-registered to T1c space and normalized by subtracting the minimum voxel intensity value. Images are then skull stripped using HD-BET, which can leverage GPU acceleration if available, followed by affine registration. A Flask application handles API requests for uploading images, initiating registration tasks, and retrieving results.

Subsequently, the segmentation server is initiated. The tool employs a previously developed nnU-net segmentation algorithm [30]. Before entering the model, images are preprocessed and normalized to reduce variations in intensity scaling. Images undergo N4 bias field correction to reduce artifacts and improve scaling. Segmentation processes are GPU-based, although they can also run on CPU. Afterwards, these segmentations serve as cost-function masks for deformable registration of scans to MNI space using the ANTsPy SyNOnly algorithm, with mutual information.

The segmentation volume is converted to a base64-encoded Metalmage (MHA) volume, a format commonly used for storing medical imaging data. Base64 encoding transforms binary data into a text string, allowing the volume to be efficiently transmitted as a string within HTTP POST requests in JSON format. Once received, the base64 string is decoded back into an MHA volume for further processing. This process

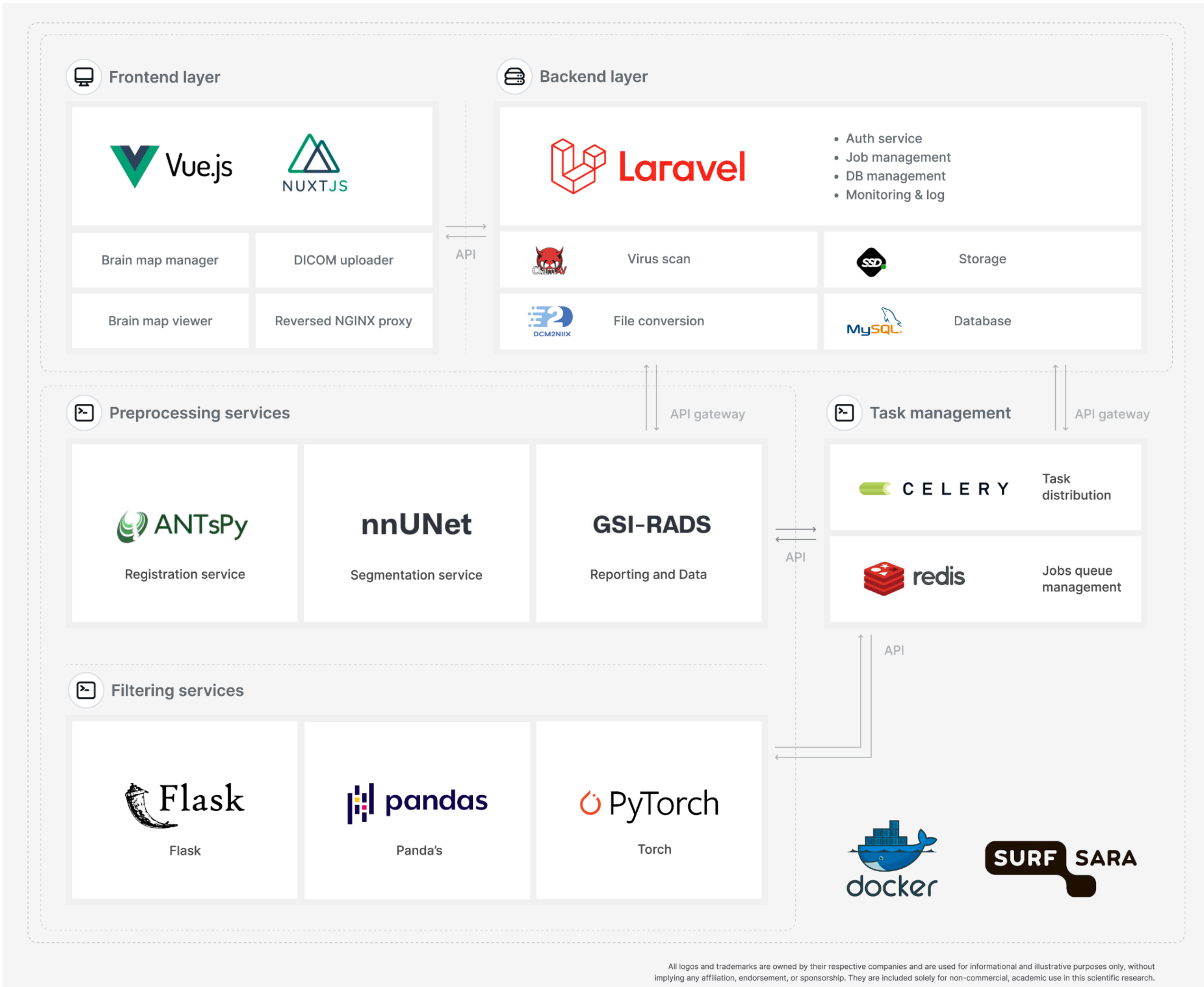


**Fig. 2. Software architecture component diagram.** The PICTURE tool's architecture includes a frontend using Nuxt.js, Vue.js, and BrainBrowser for interaction and visualization. The backend, built with Laravel, handles operations and data retrieval, incorporating DCM2NIIX for file conversion. Docker containers manage services with Flask, Redis, and MySQL. Preprocessing and filtering use ANTsPy, nnU-net, PyTorch, and Pandas, managed via Celery and Redis. The tool operates on SURF HPC Cloud with Intel Xeon CPUs and NVIDIA GPUs.

ensures data integrity and compatibility with web-based applications

In local versions of the tool, users can alter the upload process by adding custom models to the registration and segmentation services, updating the Docker configuration to include necessary libraries, and extending the API to support new processing tasks. Leveraging existing libraries like SimpleITK and TensorFlow, users can integrate various segmentation models and customize preprocessing steps.

### 3.4. Patient viewer

After image processing is finished, the user is directed to the patient viewer (Fig. 1C) which displays patient-specific results. By default, the central view displays a patient's segmented tumor volume on the MNI atlas in radiological convention. Users can toggle between atlas or registered patient T1c images as underlay. The tumor is overlaid on a resection probability map of previously resected patient. The map is built by comparing the sum of residual tumor segmentations with the sum of preoperative tumor segmentations across patients as detailed in [4,5]. Users can visually inspect resection probability to discern patterns that might inform surgical decision making. The color scale ranges from low resection probability (0, red) to high resection probability (1, green). The exact voxel-wise resection probability is displayed by clicking on the map.

In the top bar, users can download or share files. The downloaded zip file includes scans and segmentation in atlas space including applied transforms. Alternatively, a pdf of the MRI slices containing the largest cross-section of tumor can be downloaded to simply view the segmentation. Users can also toggle between resection probability map and tumor incidence map. The incidence map depicts the amount of patients the resection probability map is built from showing the number of preoperative tumors per voxel. Additionally, users can set thresholds for the estimated resection probability to only display voxels meeting the specified resection probability.

The left panel displays patient characteristics from the entire dataset, including clinical variables such as age, KPS, surgery type, and tumor grade. Using dynamic navigation, the resection probability map can be filtered to match the uploaded patient's profile to specified clinical variables which may further support surgical decision making (Fig. 1C, Fig. 4). The right panel displays tumor characteristics as defined by GSI-RADS, such as tumor volume and overlap with different brain regions [31]. Notably, the expected resectable volume and expected resectability index of the entire tumor are displayed, which may assist in the decision to perform a resection or biopsy. With the bottom button all GSI-RADS characteristics can be downloaded to a csv file.

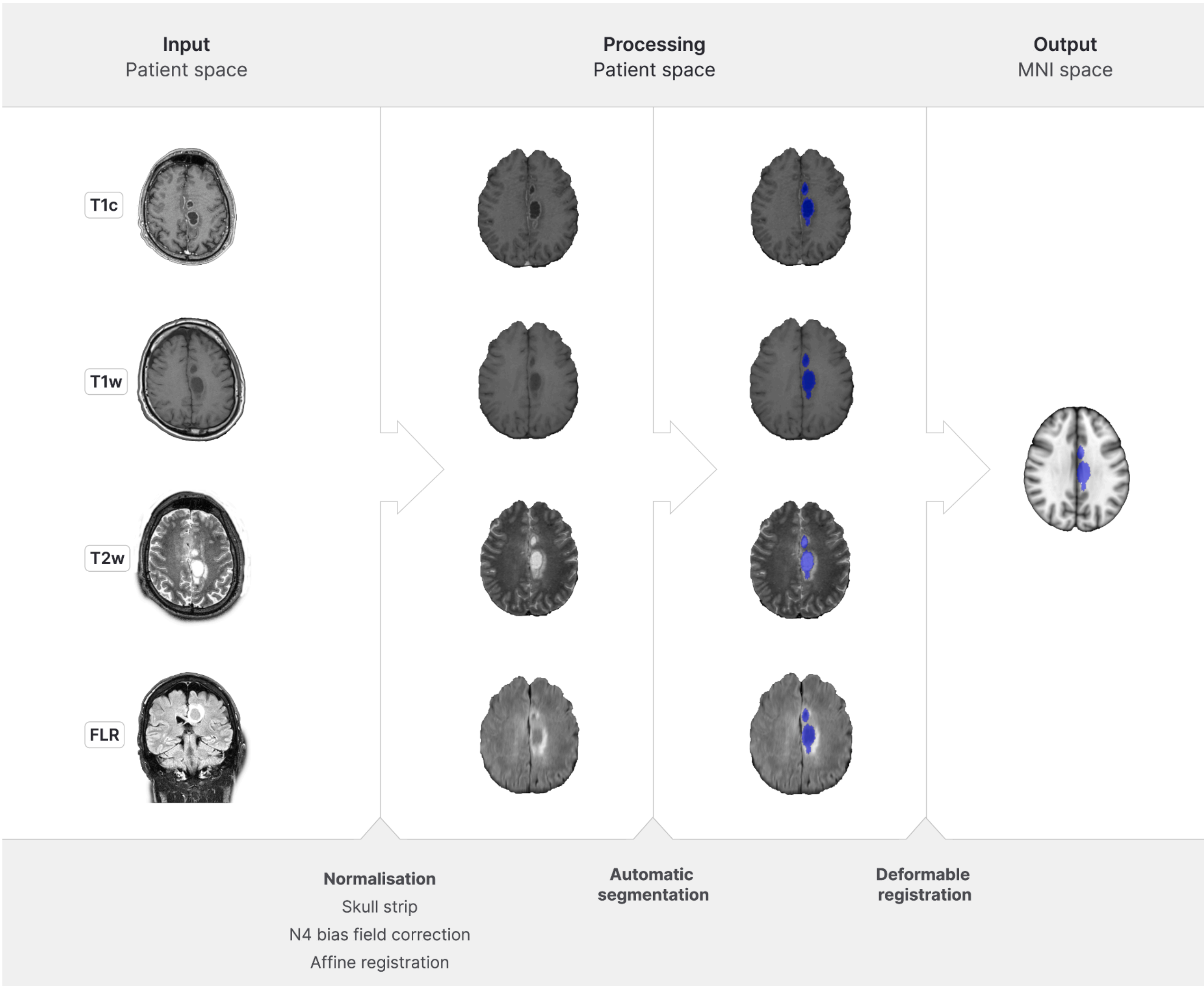


**Fig. 3. MRI scan processing.** User inputs a new patients' scans which get skull stripped using HD-BET followed by affine registration to MNI 152 space using ANTSpy within the registration service. In the segmentation service, scans then get normalized, N4 bias field correction gets applied, and an automatic segmentation nnU-net algorithm gets deployed. As a final step, scans and segmentation undergo deformable registration to MNI 152 space within the registration service. T1c – T1 weighted series with gadolinium contrast; T1w – T1 weighted series without contrast; T2w – T2 weighted series; FLR – Fluid attenuated inversion recovery series.

Filter criteria are processed asynchronously through API endpoints in the background using the filter microservice. This microservice generates filtered RPM and tumor incidence maps, based on the criteria provided. The selected criteria are sent to the filter service, which selects a subgroup of patients matching the specified criteria to create a new RPM using only these similar patients. By keeping the binary segmentations of all patients in VRAM, a new RPM can be generated within approximately 3 seconds. These RPMs are calculated by determining voxel resection probability. The resulting RPMs are displayed, enabling users to visually assess the expected resection outcome. Fig. 4 shows that not all tumor parts are equally likely to be resected after filtering for a matching patient cohort, which can be taken into account when drafting a surgical plan.

GSI-RADS characteristics are calculated in the background through API endpoints using a pre-configured Docker container. The analysis pipeline, consisting of the GSI-RADS package, is executed, and analyzed data is stored and made available via API endpoints for further interpretation [32].

### 3.5. Additional functionalities

For reference, resection probability maps from previously published studies can also be viewed under research brain maps (Fig. 5) [4,9,33]. This functionality is accessible both with and without a user account. The maps are displayed on a canvas, like the patient viewer but without additional functionalities such as filtering and tumor characteristics, which are specific to individual patient data.

## 4. Discussion and future work

We present the PICTURE tool which contextualizes prospective patient's tumor outlines against past surgical decisions through RPMs, facilitating informed surgical decision making for new glioma patients. Additionally, we disseminate our design and code (https://github.com/PICTURE-project-nl) for others to build upon, including a mock dataset. Using a microservice architecture and docker containers, the tool separates frontend and backend to allow for flexibility, scalability and efficiency.

### 4.1. Strengths

The tool provides a novel approach to leverage the vast amounts of information from routine clinical data of glioma surgeries. We have shown the feasibility of generating interactive, individualized RPMs

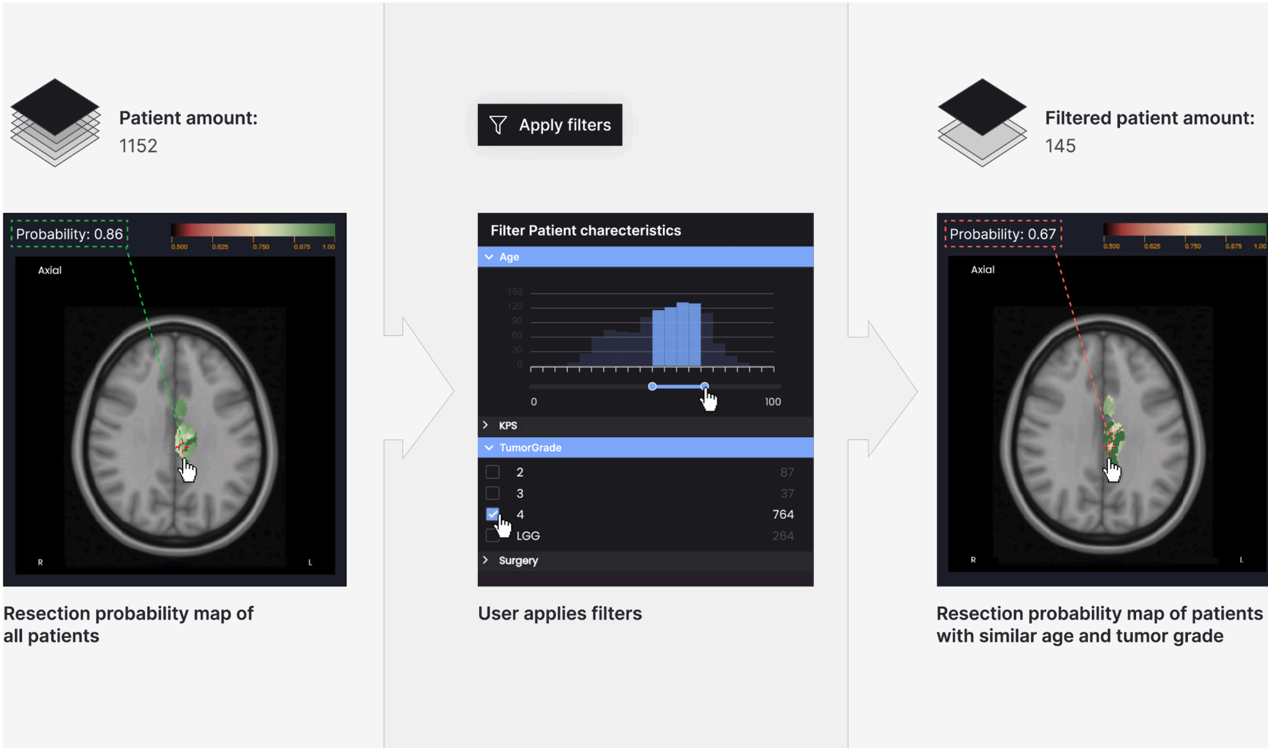


**Fig. 4. Filtering process.** Left: resection probability for a specific patient based on the map of all patients. Right: resection probability filtered for patients with similar tumor grade and age. Through filtering it becomes apparent that not all tumor parts are equally likely to be resected for the specific patient.

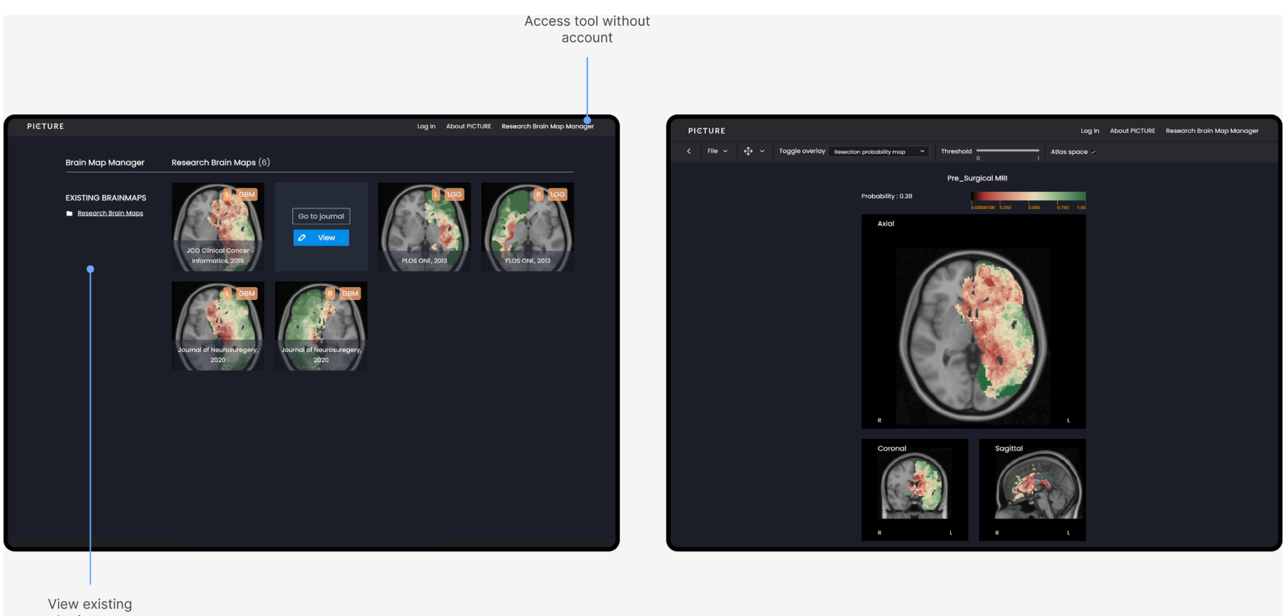


**Fig. 5. Research brain map user interface.** Left: research brain map manager for previously published resection probability maps. Right: resection probability map viewer. The interface is similar to the patient viewer, however, not filterable.

tailored towards the patient profile in a limited timeframe. Additionally, the tool provides means to apply RPMs without prior user knowledge through background provision of complex technical aspects such as automatic segmentations and registrations. The choice of making a web-based tool allows for easy accessibility and uniformity. However, a web-based tool may be more easily targeted by hackers and less accessible in areas without internet connection. To mitigate the latter, we provide open-source packages which can be run locally.

### 4.2. Future work

Through developing this tool, we have shown the feasibility of generating interactive, individualized RPMs. Future iterations of the tool could include more variables, and further research could assess the added benefit of filtering on each variable and providing guidelines on the ranges to use to filter RPMs. For example, preoperative mapping, preoperative tumor volume, and mapping during surgery may all influence resection boundaries and thus the RPM.

Including patient outcomes after surgery such as survival, oncological outcome, functional outcome and adverse events, may further improve the tool. With these outcomes, prediction models for new patients could be derived, which could further inform surgical decision-making and patient counseling. However, to achieve this functionality, patient outcomes should be collected systematically, which is not always common in current clinical practice.

The hypothesis that individualized RPMs aid surgical planning has not yet been (prospectively) verified. Future work could, therefore, focus on validating the PICTURE tool in practice. For clinical validation, a randomized control study should be conducted [34]. To measure the value of the tool, discussions about the neurosurgical plan could be evaluated in experienced neurosurgical teams with and without use of the tool. Especially in difficult surgical cases an optimization of the surgical plan would be expected with as much tumor removal as possible without loss of function. Expected versus realized extent of resection could be considered as well to measure prediction accuracy. Furthermore, reduced discussion times would be expected as decisions would be better informed with less speculation [9]. These factors combined should reduce practice variation. Additionally, usability, adoption and implementation questionnaires should be filled out. This approach would adopt an effectiveness-implementation hybrid design [35].

### 4.3. Implications

Although thorough validation is still necessary, the tool could be adopted as an integral part of the clinical workflow through supporting multidisciplinary meetings. We do not foresee its use to guide decisions during surgery, in particular we do not advocate its use to replace functional mapping. Decisions on extent of resection should be defined by patient-specific function. For integration, trained personnel could upload relevant or especially difficult cases to the tool and extract resection probability maps and tumor characteristics. These results could then be discussed to support the decision to resect and further optimize surgical plans. To ease this implementation the tool could be integrated with Electronic Patient Record (EPR) and Picture Archiving and Communication System (PACS) systems by setting up a local instance of the application. By using reproducible build techniques like containers and infrastructure through code principles, we enable relatively easy local installation and integration with limited effort. However, compliance with all applicable security protocols should still be abided.

Adopting the PICTURE tool as clinical decision support system may encounter several challenges. Implementation could disrupt the established clinical workflow of clinicians, requiring clinicians to invest time in adapting to the new system [36]. As time is often critical in the clinical workflow, willingness and acceptance of change may be limited. Therefore, seamless integration and trust in the system is thus paramount. Ethical considerations should be addressed throughout the implementation process, ensuring the user remains responsible for final decisions.

The PICTURE tool was specifically designed for analyzing glioma surgeries, but its architecture allows for potential application to other types of surgeries, such as brain metastasis and meningioma. The modular nature of the system, built using containerized microservices with Docker, enables easy modification of the image processing and analysis modules. By adapting these modules to accommodate different imaging modalities and clinical endpoints, the tool could be repurposed to work within various 2D or 3D standardized spatial frameworks where data are represented in a binary fashion. For example, altering the segmentation algorithms or updating the filtering criteria can tailor the tool to specific medical scenarios such as other solid tumors like liver, lung and pancreas surgeries. While such adaptations would require targeted development efforts, the flexible microservice-based architecture supports these potential extensions, indicating the system's broader applicability beyond glioma surgeries.

### 4.4. Limitations

The tool's inbuild segmentation algorithm has demonstrated performance within or above human inter-variability range [30], however, there is still a chance of misrepresenting the tumor as automatic segmentation accuracy is never perfect for all patients. The registration and image processing steps may introduce further misalignments as well. These discrepancies can be detected visually within the tool and the clinician's judgement remains final. In the current version of the tool there is no alternative segmentation algorithm if the segmentation is deemed unfit. Additionally, gliomas are often associated with tissue distortion on MRI and the maps are thus inherently biased to some extent [37]. Finally, RPMs are a representation of the underlying dataset. For the PICTURE dataset, the RPMs should be considered common practice based on previous surgeries, and not necessarily best practice. Datasets curated for excellent functional and oncological outcome may enable better surgical decisions.

The current PICTURE tool is limited to proof of concept. This tool has not been evaluated or approved by any regulatory authority (such as the FDA, EMA, or equivalent bodies). It does not qualify as a medical device and should not be treated as such. Further development requires regulatory approval processes and compliance with relevant healthcare standards and regulations. However, further development and validation are both labor and cost intensive and is in the current funding landscape only feasible if a clear business case exists. We strongly believe in the tool's potential and the significant impact it could have on individual patients' lives. Nevertheless, considering glioma is a rare disease [1] and survival will likely remain poor, difficulties remain to develop a profitable business case.

## 5. Conclusion

In conclusion, the PICTURE tool enables users to create and explore individualized RPMs, leveraging past surgical experiences for current treatment decisions. Additionally, we disseminate the tool as an open-source package.

## Ethics statement

All procedures in this study were performed in compliance with relevant laws and institutional guidelines. This retrospective study was exempt from IRB approval by the Medical Ethical Committee of Amsterdam UMC (reference number 2014.336, date 23th July 2014), and informed consent from patients was obtained according to local regulations.

The work described has not been published previously and is not under consideration for publication elsewhere. The article's publication is approved by all authors.

## Availability

The PICTURE tool is available online at https://tool.pictureproject.nl. The code can be accessed on GitHub at https://github.com/PICTURE-project-nl. The open-source package can be downloaded and run locally on any modern machine, though analyzing speed may be compromised without GPUs. An anonymized random example dataset to build RPMs is included with the code. explore the tool's functionality without owning data, a glioblastoma patient dataset can be found at https://doi.org/10.17026/dans-zg9-nhrj. More technical and content details are available in the repository's README.

## CRediT authorship contribution statement

**Maisa N.G. van Genderen:** Writing – review & editing, Visualization, Software, Investigation, Writing – original draft, Validation, Methodology, Formal analysis, Funding acquisition, Conceptualization, Project administration, Data curation. **Raymond M. Martens:** Validation, Resources, Methodology, Formal analysis, Writing – original draft, Conceptualization, Writing – review & editing, Visualization, Software, Funding acquisition, Data curation, Project administration, Investigation. **Frederik Barkhof:** Supervision, Writing – review & editing, Project administration, Methodology, Conceptualization, Funding acquisition. **Philip C. de Witt Hamer:** Methodology, Funding acquisition, Writing – review & editing, Investigation, Conceptualization, Supervision, Project administration. **Roelant S. Eijgelaar:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization, Visualization, Supervision, Resources, Methodology, Data curation, Software, Project administration, Funding acquisition, Validation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpbup.2025.100199.

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