REVIEW

Delta-radiomics Entropy Based on Tumor Heterogeneity Concept – Response Predictor to Irradiation for Unresectable/recurrent Glioblastoma

Camil Ciprian MIRESTEAN[1,2], Roxana Irina IANCU[3,4], Dragos Teodor IANCU[3,5]

Abstract

Although adjuvant radiotherapy in combination with Temozolomide administration has clearly demonstrated the benefit in improving the prognosis of patients with multiforme glioblastoma, radiotherapy as only treatment or in combination with systemic treatment is one of the best supportive in unresectable cases. For recurrent cases, the salvage radiotherapy option (re-irradiation) can be chosen in carefully selected cases so that the benefit is greater than the toxicities. Radiomics, a new subdomain of artificial intelligence (AI), relies on advanced analysis in high-resolution medical imaging to establish diagnostic, prognostic and predictive models for clinical medicine. The variation of the delta-radiomics parameters analyzed within a tumor volume may be via tumor heterogeneity indirectly correlated with the response to treatment. The aim of the study is to propose a delta-radiomic based on entropy algorithm to allow the non-invasive pre-therapeutic identification of patients with unresectable or recurrent multiform glioblastoma who will benefit from irradiation and/or salvage re-irradiation.

Keywords: radiotherapy, temozolomide, multiforme glioblastoma, radiomics

Rezumat

Radioterapia adjuvantă, asociată cu Temozolomidă (ca agent alchilant), si-a demonstrat în mod clar beneficiul de îmbunătățire a prognosticului la pacienții cu glioblastom multiform. Deasemeni, radioterapia ca tratament individual sau în combinație cu tratamentul sistemic, rămâne una dintre cele mai bune optiuni si în cazurile nerezecabile. Pentru cazurile de glioblastom recurent, opțiunea radioterapiei de salvare (re-iradiere) poate fi aleasă în cazuri atent selectate, astfel încât beneficiul să fie mai mare decât toxicitățile induse de tratament. Radiomica, un nou subdomeniu al inteligenței artificiale (AI), se bazează pe analiza avansată a imaginilor medicale de înaltă rezoluție în scopul conceperii unor modele diagnostice, prognostice și predictibile aplicabile în medicina clinică. Variația parametrilor delta-radiomici analizați în cadrul unui volum tumoral poate fi corelată, indirect prin datele referitoare la heterogenitatea tumorii, cu răspunsul la tratament. Scopul studiului este de a propune un model delta-radiomic bazat pe parametrul entropie care să permită identificarea pre-terapeutică, neinvazivă, a pacienților cu glioblastom multiform nerezecabil sau recurent care pot beneficia de iradiere și/sau reiradiere de salvare.

Cuvinte cheie: radioterapie, temozolomidă, glioblastom multiform, radiomică

[1]University of Medicine and Pharmacy of Craiova, Craiova, Romania
[2]Railways Clinical Hospital, Iasi
[3]"Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[4]"St. Spiridon" Emergency Hospital, Iaşi, Romania
[5]Regional Institute of Oncology, Iasi,Romania

Corresponding author:
Roxana Irina IANCU, "Gr. T. Popa" University of Medicine and Pharmacy, Oral Pathology Department, 16th Universitatii Street, 700115, Iasi, Romania.
E-mail: roxana.iancu@umfiasi.ro

INTRODUCTION

Although the role of external beam radiotherapy as adjuvant treatment for resected glioblastoma has already been demonstrated, the addition of radiotherapy prolonging survival in patients with multiforme glioblastoma compared with patients who received only surgery alone from 3-4 months to 10-12 months. There is uncertainty about the optimal treatment of primary unresectable glioblastoma, because there are no randomized studies based on scientific evidence. Usually the choice between best supportive care, palliative radiotherapy and radiotherapy combined with treatment with Temozolomide (TMZ) is at the discretion of the clinician, the patient's performance status and life expectancy being decisive in the therapeutic option. Another challenge is to identify a possible benefit in cases of relapsed glioblastoma of rescue treatment by re-irradiation compared to salvage surgery, TMZ alone or combined-modality therapy. Median survival for radiotherapy cases varies between 6-7 months and updated data including the use of irradiation-associated chemotherapy report median survivals ranging from 5 to 13 months. However, in patients treated with radiotherapy, a 2-year survival was <10%. Controversies over the cases in which a more aggressive approach combining radiotherapy and chemotherapy bring a benefit to the best supportive that make it necessary to identify predictive biomarkers of response to therapy in order to provide the best option for each case. If general factors such as favorable performance status (KPS ≥70) and younger age are accepted predictors of the benefit of rescue treatment, the response to irradiation in terms of tumor radio-sensitivity is difficult to predict. The use of 3D conformal techniques, intensity-modulated radiotherapy (IMRT), brachytherapy, stereotactic radiosurgery (SRS) or stereotactic fractional radiotherapy are preferred for salvage re-irradiation, based on a precise delineation of radiosensitive organs and of the tumor target volumes within the concept of image guided radiotherapy (IGRT). The association of imaging guidance with a high-conformal irradiation technique, to provide the most accurate envelope of the target volume including "banana shape" target volumes, is essential in obtaining the maximum therapeutic benefit without compromising the function of healthy organs including healthy brain tissue[1-4].

Radiomics, a subdomain of artificial intelligence (AI) aims to extract a large amount of information and data from high-resolution medical imaging in order to build predictive and prognostic diagnostic models. The concept of generating and using in clinical practice a large volume of "Big data" information is shared by several "omics" groups, including proteomics, genomics, ie. Radiomics quantitatively approaches the field of medical imaging in order to improve the information available to clinicians, using non-intuitive mathematical methods. Oncology is one of the medical fields that enjoys the widespread application of radiomics, the method being perfected with the improvement of the quality and reproducibility of medical imaging. Data regarding the shape, interrelation and intensity of the pixel signal, spatial distribution, texture are just a few examples of characteristics extracted by radiomic analysis and impossible to evaluate by the eye of the expert imaging or clinical examiner. Radiomic analysis can be performed on basic imaging techniques such as Digital X-rays (DRX) or Ultrasonography (US) as well as high performance techniques such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and even hybrid imaging such Positrons Emission Tomography – Computerized tomography (PET-CT)[5-6].

AIM AND SCOPE

The aim of the study is to propose a radiomic algorithm to allow the non-invasive pre-therapeutic identification of patients with unresectable or recurrent multiforme glioblastoma who will benefit from irradiation and rescue re-irradiation using CT simulation imaging for radiotherapy planning.

MATERIALS AND METHODS

The proposed algorithm proposes the selection from CT imaging simulation for radiotherapy planning of a Digital Imaging and Communications in Medicine (DICOM) image without a selected contrast agent at the tumor iso-center. The volume will be delineated by a radiation oncologist with experience in radiation therapy for brain tumors. Subsequently, the DOCOM image will be analyzed using the free MaZda application, the entropy being evaluated. Choosing between 5 square flat images of 3/3mm randomly positioned at quasi-equal distances in different regions of the tumor will analyze the entropy on each case. Starting from the concept that the sum of absolute values for each delta entropy variation between the evaluated value from a

square image and the value of the entire tumor volume is correlated with heterogeneity and unfavorable response to radiotherapy treatment, we propose to evaluate the concept in correlation with patient response data to treating[7-9].

RESULTS

The value of the entropy calculated for the entire section of the tumoral volume was 2.40 and for the 5 rectangular subdivisions chosen from the tumor section: 2.08, 2.11, 1.92, 1.86, 1.88 [Image1-Image2].

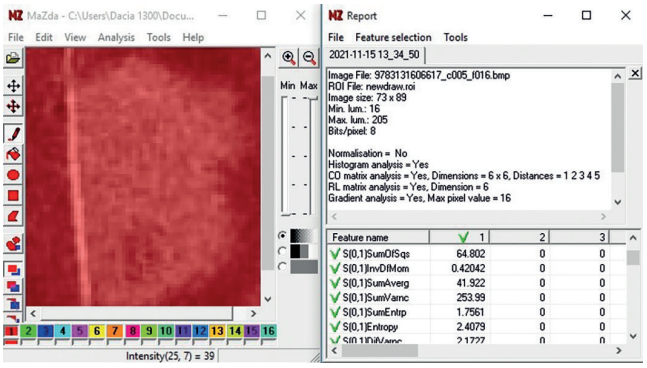

Figure 1. Radiomic analysis of the entire tumor slide (MaZda free radiomics software evaluation)

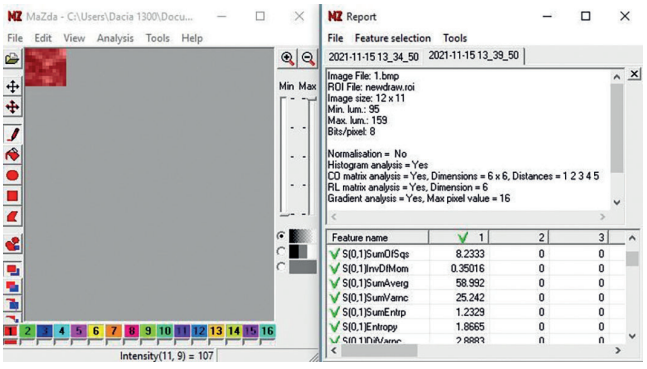

Figure 2. Radiomic analysis of the 3/3mm square image selected from tumor (MaZda free radiomics software evaluation)

DISCUSSIONS

1.Radiomics – basic concept

Radiomic analysis includes 4 essential steps. Step 1 called image segmentation consists in delimiting the region of interest (ROI). Whether it is a two-dimensional (2D) process or a three-dimensional (3D) volume of interest (VOI) delineation, it is an essential step for the accuracy of subsequent ROI analysis. Among the free software solutions that can be used for image segmentation and radiomics analysis we mention LifeX, IbeX, ImageJ. The automatic segmentation has the advantage of being able to eliminate the subjectivity of the human expert. Step 2 called image processing has the role of standardizing VOIs from which data will be subsequently extracted without altering pixel spacing, gray-level intensities, bins of the gray-level histogram. Applying filters is part of the image processing algorithm. The calculation of features that will be extracted is recommended to be done in accordance with the Image Biomarker Standardization Initiative (IBSI) to ensure the reproducibility of radiomic studies. If radiomic features already identified in other studies as having predictive or prognostic value will not be used as reference for a new research, the feature selection step is essential to choose a finite number of radiomic features that may have a medical imaging based biomarker value. Intensity or histogram based, shape, texture features, transform-based, and radial features are the most commonly analyzed types of radiomic features and wavelet or Gaussian filters are the most commonly applied filters. Combining features by methods as the principal component analysis (PCA) and obtaining stes of radiomic features is also a part of fetures reducing process, the 3rd step of radiomics analysis. Step 4 (the radiomic model creation), includes construction of the radiomic classifier using algorithms such as random forest or support vector machine (SVM). Model performance testing is based on training and testing/validation, using 2 different data sets. The reduction of radiomic features is a multi-level process that ultimately results in the elimination of redundant non-reproducible and non-relevant radiomic features from the dataset. Reproducibility is one of the most common problems in radiomic studies. First-order features, especially entropy is considered more reproducible than 2nd order features like shape textural features[6,10,11].

2. Entropy radiomic features in oncology

Entropy is a measure irregularity or randomness for any kind of dynamic system. Considered one of the most interesting radiomic features and one of the most frequently reported in the literature, entropy can be an imaging biomarker of the tumor phenotype being correlated not only with cancer staging, outcomes, molecular pathways, response to therapy and tumor metabolism in different malignancies (for example

lung, esophageal, colorectal, head and neck cancer). Shannon's entropy evaluated after applying Laplacian of Gaussian filters from the TexRAD package (Cambridge, United Kingdom) is perhaps the one of the most analyzed radiomic feature[6,12].

Entropy is a biomarker already tested in predicting response to therapy, gene expression, and disease prognosis. The identification of tumor features based on radiomic evaluation (a value of Shannon's entropy evaluated on the basis of Laplacian of Gaussian transformation using TexRAD software) is one of the interesting applications as a concept that demonstrates the diversity of radiomic research at present. Entropy and homogeneity, respectively decreased entropy and increased homogeneity were identified as predictive of the response to chemotherapy of liver metastases, an evolution evaluated in different types of medical imaging. A study involving Digital Breast Tomosynthesis (DBT) identified entropy as being next to energy and radiomic dissimilarity features significantly correlated with tumor size, with no prognostic value. However, entropy has been linked to estrogen receptor status. Co-occurrence of Local Anisotropic Gradient Orientations (CoLlAGe) is also a radiomic feature also based on entropy that measures local anisotropy in brain tumors. Although demonstrated to be less discriminatory than heterogeneity as a radiomic feature, entropy has been identified as predictive in discriminating low-grade gliomas (LGG) from high-grade gliomas (HGG). Without wishing to cover the full range of applications of entropy as a radiomic feature, we have presented several applications in oncology in various types of tumors and correlations with different epidemiological variables of cancer[13-18].

3.Radiomics and glioma – future diagnostic and management perspectives

Radiomics and radiogenomics open new perspectives in the diagnostic, prognostic and predictive accuracy of these primary tumors with unfavorable and unpredictable evolution. By extracting morphological, textural and functional signatures from MRI imaging, complex models with prognostic and predictive power can be created that will improve diagnosis and management. As in other fields of medicine, the lack of homogeneity between studies and standardization is the limit that has not yet allowed the translation of radiomic models into clinical practice. Given the difficulties of making a differential diagnosis between pseudo-progression, recurrence/progression and radio-necrosis, but also taking into account the importance of non-invasive assessment of the tumor molecular profile, especially for cases with absolute contraindication for any invasive maneuver including stereotactic biopsy, radiomics could be a vital partner both in research, diagnosis and clinical management of gliomas[19,20].

Radiomics has the ability to non-invasively assess the status of the MGMT (methyl-guanine-DNA methyl-transferase) promoter, and thus indirectly become a prognostic and predictive tool. MGM methylation is associated with an improved prognosis but also with a favorable response to alkylating agents. Rivera et al. demonstrated that methylation of MGMT may also be associated with an improvement in radio-sensitivity by evaluating the response to irradiation in patients with known MGMT status who did not receive Temozolomide treatment during irradiation[21].

Another application of radiomics of major interest is the noninvasive prediction of pseudo-progression using pre-treatment MRI imaging. 841 radiomic features were extracted from images obtained from 35 patients with pseudo-progression. Only two radiomic features were identified as correlated with pseudo-progression, their association having high predictive power. The addition of clinical features to the radiomic model did not improve predictive power og the proposed model. The authors hypothesize that radiomic analysis can successfully predict noninvasive pseudo-progression of gliomas, using CT images acquired prior to radiotherapy treatment[22].

Mc'Garry proposes using multi-parametric MRI radiomic profiles of de novo glioblastoma to generate predictive models for the unfavorable prognosis. The concept of using T1-weighted image, T2-weighted image, and contrast-enhanced T1-weighted image sequences is also used by Wang to create prognostic models for patients with grade II gliomas. The minimum-redundancy-maximum-relevancy as a unique method or associated with univariate logistics analysis is proposed to reduce a number of 396 radiomics feature to 9 features considered significant to build a valid model[23-24].

A radiomic study that aims to correlate clinical target volumes (CTVs) and metabolic tumor volumes (MTVs) in the case of glioblastoma multiforme compares the 2 volumes with relevance in radiotherapy. CTV for treatment planning is based on contrast-enhanced T1-weighted and T2-weighted / fluid-atten-

uated inversion recovery MRI and, for the case of metabolic imaging, tumor volume delineation for radiotherapy planning could be based on MTV generated by N-acetyl aspartate (NAA) and choline (Cho) at the tumor level. Nuclear Magnetic Resonance (NMR) spectroscopy images were also evaluated and 48 image features were extracted, of which only twenty were considered relevant. With a larger number (22 vs. 6) features including 10 semantic imaging traits (evaluated by a neuro-radiologist) and radiomic features, MTV for NAA was much closer to CTV than MTV for choline[25].

Analysis of delta variation of radiomics features extracted from dynamic contrast enhanced susceptibility (DSC) MRI between 2 opposite parts of a tumor is able to predict non-invasively tumor histological grade as demonstrated by Jeong's study which includes 25 cases of gliomas (13 HGG and 12 LGG)[26].

CONCLUSIONS

Delta radiomics based on entropy can be chosen as a biomarker of tumor heterogeneity and indirectly of the unresectable multiform glioblastoma response to radiotherapy. The identification of accessible and non-invasive imaging markers could help the escalation but also the de-escalation of the treatment for the cases that will benefit the respective one will not respond to radiotherapy or radio-chemotherapy. In the context of precision medicine, a modeling of therapy could benefit both the overall survival and the quality of life of these patients.

References

1. Koukourakis GV, Kouloulias V, Zacharias G, et al. Temozolomide with radiation therapy in high grade brain gliomas: pharmaceuticals considerations and efficacy; a review article. Molecules. 2009;14(4):1561-1577.
2. Nieder C, Grosu AL, Metha MP et al: Treatment of malignant gliomas in adults: radiotherapy, chemotherapy and integration of new targeted agents. Expert Rev Neurother 4: 691-703, 2004.
3. Nieder C, Grosu AL, Astner S, Molls M. Treatment of unresectable glioblastoma multiforme. Anticancer Res. 2005 Nov-Dec;25(6C):4605-10.
4. Mann J, Ramakrishna R, Magge R, Wernicke AG. Advances in Radiotherapy for Glioblastoma. Front Neurol. 2018;8:748. Published 2018 Jan 15.
5. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology. 2016 Feb;278(2):563-77.
6. van Timmeren JE, Cester D, Tanadini-Lang S, Alkadhi H, Baessler B. Radiomics in medical imaging-"how-to" guide and critical reflection. Insights Imaging. 2020 Aug 12;11(1):91.
7. Strzelecki M., Szczypinski P., Materka A., Klepaczko A., A software tool for automatic classification and segmentation of 2D/3D medical images, Nuclear Instruments & Methods In Physics Research A, 702, 2013, pp. 137-140
8. Szczypinski P., Strzelecki M., Materka A., Klepaczko A., MaZda-A software package for image texture analysis, Computer Methods and Programs in Biomedicine, 94(1), 2009, pp 66-76
9. Szczypinski P., Strzelecki M., Materka A., MaZda - a Software for Texture Analysis, Proc. of ISITC 2007, November 23-23, 2007, Republic of Korea, pp. 245-249
10. Traverso A, Wee L, Dekker A, Gillies R. Repeatability and Reproducibility of Radiomic Features: A Systematic Review. Int J Radiat Oncol Biol Phys. 2018 Nov 15;102(4):1143-1158. Bibault JE, Xing L, Giraud P, El Ayachy R, Giraud N, Decazes P, Burgun A, Giraud P. Radiomics: A primer for the radiation oncologist. Cancer Radiother. 2020 Aug;24(5):403-410
11. Dercle L, Ammari S, Bateson M, et al. Limits of radiomic-based entropy as a surrogate of tumor heterogeneity: ROI-area, acquisition protocol and tissue site exert substantial influence. Sci Rep. 2017;7(1):7952.
12. Zhao B, et al. Reproducibility of radiomics for deciphering tumor phenotype with imaging. Sci Rep. 2016;6:23428.
13. Lu J, Wang Z. The Systematic Bias of Entropy Calculation in the Multi-Scale Entropy Algorithm. Entropy (Basel). 2021 May 24;23(6):659. doi: 10.3390/e23060659.
14. Dercle L, Ammari S, Bateson M, et al. Limits of radiomic-based

entropy as a surrogate of tumor heterogeneity: ROI-area, acquisition protocol and tissue site exert substantial influence. Sci Rep. 2017;7(1):7952. Published 2017 Aug 11. doi:10.1038/s41598-017-08310-5
15. Fiz F, Viganò L, Gennaro N, Costa G, La Bella L, Boichuk A, Cavinato L, Sollini M, Politi LS, Chiti A, Torzilli G. Radiomics of Liver Metastases: A Systematic Review. Cancers (Basel). 2020 Oct 7;12(10):2881. doi: 10.3390/cancers12102881.
16. Tagliafico AS, Valdora F, Mariscotti G, Durando M, Nori J, La Forgia D, Rosenberg I, Caumo F, Gandolfo N, Houssami N, Calabrese M. An exploratory radiomics analysis on digital breast tomosynthesis in women with mammographically negative dense breasts. Breast. 2018 Aug;40:92-96. doi: 10.1016/j.breast.2018.04.016.
17. Beig N, Bera K, Tiwari P. Introduction to radiomics and radiogenomics in neuro-oncology: implications and challenges. Neurooncol Adv. 2021 Jan 23;2(Suppl 4):iv3-iv14. doi: 10.1093/noajnl/vdaa148.
18. Qin JB, Liu Z, Zhang H, et al. Grading of Gliomas by Using Radiomic Features on Multiple Magnetic Resonance Imaging (MRI) Sequences. Med Sci Monit. 2017;23:2168-2178. Published 2017 May 7. doi:10.12659/msm.901270
19. Singh G, Manjila S, Sakla N, True A, Wardeh AH, Beig N, Vaysberg A, Matthews J, Prasanna P, Spektor V. Radiomics and radiogenomics in gliomas: a contemporary update. Br J Cancer. 2021 Aug;125(5):641-657. doi: 10.1038/s41416-021-01387-w.
20. Bizu I, Georgescu M, Anghel R. Small cell glioblastoma: A glioblastoma subtype with an unexpected response. Medicina Moderna - Modern Medicine 26(2):93-96 DOI: 10.31689/rmm.2019.26.2.93
21. Rivera AL, Pelloski CE, Gilbert MR, et al. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma [published correction appears in Neuro Oncol. 2010 Jun;12(6):617]. Neuro Oncol. 2010;12(2):116-121. doi:10.1093/neuonc/nop020
22. Baine M, Burr J, Du Q, Zhang C, Liang X, Krajewski L, Zima L, Rux G, Zhang C, Zheng D. The Potential Use of Radiomics with Pre-Radiation Therapy MR Imaging in Predicting Risk of Pseudoprogression in Glioblastoma Patients. J Imaging. 2021 Jan 28;7(2):17. doi:10.3390/jimaging7020017.
23. McGarry SD, Hurrell SL, Kaczmarowski AL, et al. Magnetic Resonance Imaging-Based Radiomic Profiles Predict Patient Prognosis in Newly Diagnosed Glioblastoma Before Therapy. Tomography. 2016;2(3):223-228. doi:10.18383/j.tom.2016.00250
24. Wang ZH, Xiao XL, Zhang ZT, He K, Hu F. A Radiomics Model for Predicting Early Recurrence in Grade II Gliomas Based on Preoperative Multiparametric Magnetic Resonance Imaging. Front Oncol. 2021 Sep 2;11:684996. doi: 10.3389/fonc.2021.684996.
25. Lopez CJ, Nagornaya N, Parra NA, Kwon D, Ishkanian F, Markoe AM, Maudsley A, Stoyanova R. Association of Radiomics and Metabolic Tumor Volumes in Radiation Treatment of Glioblastoma Multiforme. Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):586-595. doi: 10.1016/j.ijrobp.2016.11.011.
26. Jeong J, Wang L, Ji B, Lei Y, Ali A, Liu T, Curran WJ, Mao H, Yang X. Machine-learning based classification of glioblastoma using delta-radiomic features derived from dynamic susceptibility contrast enhanced magnetic resonance images: Introduction. Quant Imaging Med Surg. 2019 Jul;9(7):1201-1213. doi: 10.21037/qims.2019.07.01.