Comparisons of the accuracy of radiation diagnostic modalities in brain tumor
A nonrandomized, nonexperimental, cross-sectional trial

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Abstract
Tumor morphology improved sensitivity, accuracy, and specificity of the diagnosis, but all diagnostic techniques have attenuation correction issues.

To compare computed tomographic (CT), positron emission tomographic (PET), and magnetic resonance imaging (MRI) characteristics of patients with brain tumor in a Chinese setting.

A nonrandomized, nonexperimental, cross-sectional trial.

Jining No. 1 People’s Hospital, China.

In total, 127 patients who had clinically confirmed a brain tumor were included in the cross-sectional study. Patients were subjected to brain CT, MRI, and PET. The tumors resected after brain surgery were subjected to morphological diagnosis. Statistical analysis of data of surgically removed tumor and that of different methods of diagnosis was performed using Wilcoxon test following Tukey–Kramer test. Spearman correlation was performed between diagnostic modalities and in vivo morphology. Results were considered significant at 99% of confidence level.

The data of diameter and volume of tumor derived from CT (Spearman r = 0.9845 and 0.9706), and MRI (Spearman r = 0.955 and 0.2378) were failed to correlate with that of the surgically removed tumor. However, prediction of diameter and volume of the tumor by PET (Spearman r = 0.9922 and 0.9921) were correlated with that of the surgically removed tumor. CT and MRI were failed to quantified pituitary adenomas.

The study was recommended PET for assessment of brain tumor.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CM = clinical manifestations, CT = computed tomography, DFOV = field of view, DICOM = Digital Imaging and Communications in Medicine, FDG = 18F-fluorodeoxyglucose, MRI = magnetic resonance imaging, PET = positron emission tomography, PFR = plain-film radiography, q = critical value for Tukey–Kramer multiple comparisons test, STARD = Standards for Reporting of Diagnostic Accuracy Studies, STROCSS = Strengthening the Reporting of Cohort Studies in Surgery.

Keywords: brain neoplasms, computed tomography, magnetic resonance imaging, positron emission tomography, serologic tests

1. Introduction
Brain tumor could be developed in the body over several days. It is difficult to screen out brain tumor without radiography. Addition of anatomical parameters including morphology of tumors could be improved sensitivity, accuracy, and specificity of diagnosis process. To study the morphology of tumor after surgical resection is an invasive and risky method. Therefore, there is a need for a noninvasive diagnostic method(s) for a brain tumor.

Physiological stress and surrounding impact are different for each individual. However, the clinical manifestations (CM) of brain tumor are conditions that most preferably found in the adjacent area of the brain. The development of the tumor can become in the right frontal part of the brain. However, the other parts of the brain could be normal.

Plain-film radiography (PFR) of brain tumor is provided nonspecific results. The currently available guidelines to use it are provided a rough idea of malignancies in brain tumor conditions. The brain tumor predicted by it could have more serious conditions. It has limited applications in brain tumor diagnosis and has more applications in traumatic brain injury.

The computed tomography (CT) was first made available for human subjects in 1974 by Ambrose, Hounsfield, and Cormack. It has the advantage of providing differences in electron densities among the tissues and used contrast(s), which helps to understand the functional and structural status of the clinically significant symptoms, for assisting the treatment decision-making. Magnetic resonance imaging (MRI), CT, and positron emission tomography (PET) are widely used methods for human neuroimaging.
Currently used CT has a capacity resolution with submillimeter at 90 s of acquisition time without contrast brain studies.\textsuperscript{16} It is easy to use.\textsuperscript{17} It is provided less information than MRI in brain diagnosis,\textsuperscript{18} but, at present, is used for diagnosis of Parkinson disease,\textsuperscript{19} aging,\textsuperscript{20} and head trauma.\textsuperscript{21}

Advanced MR sequences, for example, diffusion tensor imaging and perfusion MR imaging have advantages of differentiation of low-grade gliomas from high-grade gliomas,\textsuperscript{22} but these are efficient to distinguish radiation necrosis from residual gliomas after chemotherapy.\textsuperscript{23} Moreover, the exponential component-polynomial component is used for an unsupervised and robust gliomas.\textsuperscript{24}

There are several studies available for comparing 2 or more radiological diagnostic techniques in brain tumor, but all studies could not be succeeded in conclusion on any single accurate diagnostic technique because of attenuation correction issues.\textsuperscript{25}

The primary aim of the study was to diagnose brain tumor in patients who had clinically confirmed brain malignancies in a Chinese setting. The secondary endpoint of the study was to compare accuracy and efficacy of CT scan, PET scan, and MRI with parameters of the surgically removed tumor at the level 1 of evidence.

2. Materials and methods

2.1. Chemicals

\textsuperscript{18} F-fluorodeoxyglucose (FDG) was purchased from BV Cyclotron VU, Amsterdam, The Netherlands.

2.2. Ethical approval and consent to participate and publication

The trial had been registered in Research registry (www.researchregistry.com), UID No. researchregistry3395, dated June 25, 2014. The Jining No. 1 People’s Hospital review board had approved the diagnostic protocols for radiographical research of brain in human subjects under the law of China and 2013 Declaration of Helsinki. The work is reported in line with the STROCSS criteria (Strengthening the Reporting of Cohort Studies in Surgery). Written informed consent for radiology, anesthesia, surgeries, to have additional procedures done purely for research purposes, and patient information and images (if any) to be published in all formats (hard and/or electronics) irrespective of time and language were provided by the patients or their legally authorized representatives.

2.3. Inclusion criteria

In total, 127 patients who had problems with remembering, confusion, focal neurological deficit, abnormal behavior, and/or increased sleepiness admitted (clinically confirmed brain malignancies by serological tests) admitted to the department of the neuropsychology of Jining No. 1 People’s Hospital during July 2014 to December 2017 were included in the nonrandomized, nonexperimental, cross-sectional study. Patients who had aged >18 years were only included in the study.

2.4. Exclusion criteria

Patients <18 years of age and who did not follow-up protocols were excluded from the study. Patients who had no any suspected features of brain malignancy were excluded from the study. Patients who had rectal cancer, hepatic disorders, anemia, leukemia, neutropenia, and skin cancer excluded from the study (because these features may interfere with clinical pathology).

Demographical and clinical data of the patients before the diagnosis of brain tumor are reported in Table 1. STARD (Standards for Reporting of Diagnostic Accuracy Studies) flowchart of nonrandomized, nonexperimental, cross-sectional, diagnosis study is reported in Figure 1.

2.5. Diagnosis methods

2.5.1. CT scan. Patients were subjected to brain CT scan (SOMATOM Definition AS+, Siemens Healthcare GmbH, Germany). The images were recorded at 0.6 cm slice thickness, 80 kV voltage, 75 mA currents, 20 s/scan, and 360° rotation, and 5 mSv radiation dose. General anesthesia was administered to the patients during CT scan if required.\textsuperscript{26} Data related to the brain tumor were accessed using standard quantification guidelines of CT.\textsuperscript{27} All images were converted to patients’ DICOM file formats (field of view [DFOV] 51.2 × 61.5 cm).

2.5.2. PET scan. Patients had fasted overnight before scanning. There were 18.51 ± 0.01 MBq/100 g of body weight of FDG injected through a vein. Patients were subjected to brain PET scan (CT Secura, Philips) and PET images were collected at 5 mSv radiation dose. The PET images were reconstructed for decay, quiet time, normalization, photon attenuation, by the algorithm. The reconstructed size was 250 × 250 × 60 cube meter.\textsuperscript{28}

2.5.3. MRI. All patients were subjected to MRI (Achieva 3.0T XTX—Diamond, Koninklijke Philips N.V.) at axial fluid-attenuated inversion recovery and sequences visualizing (anatomical protocols). All types of MR images were converted to patients’ DICOM file formats (DFOV 31.3 × 25.0 cm).\textsuperscript{29}

2.5.4. PFR. Anteroposterior and lateral views of PFR of patients were carried out using 300 mA high-performance medical X-ray

### Table 1

Demographical and clinical data of the enrolled patients before diagnosis.

| Parameters                          | Population |
|-------------------------------------|------------|
| Sample size                         | 127        |
| Age, y                              | 51.35±2.58 |
| Sex                                 |            |
| Male                                | 69 (54)    |
| Female                              | 58 (46)    |
| Ethnicity                           |            |
| Chinese                             | 125 (98)   |
| Non-Chinese                         | 2 (2)      |
| Examination of Mini-mental state    |            |
| Poor cognitive state                | 15 (12)    |
| Normal state                        | 75 (59)    |
| Abnormal neurological symptoms      |            |
| Absent                              | 57 (45)    |
| Mild                                | 39 (31)    |
| Moderate                            | 27 (21)    |
| Abnormal neurological symptoms      |            |
| Severe                              | 4 (3)      |
| Focal neurological deficit          | 33 (26)    |
| Abnormal behavior                   | 67 (53)    |
| Karnofsky scoring status            |            |
| ≥70                                 | 73 (67)    |
| ≥40 but <70                         | 35 (26)    |
| <40                                 | 19 (17)    |
| Problems with remembering           | 24 (19)    |
| Confusion                           | 47 (37)    |
| Focal neurological deficit          | 33 (26)    |
| Abnormal behavior                   | 67 (53)    |
| Karnofsky scoring                   |            |
| ≥70                                 | 73 (67)    |
| ≥40 but <70                         | 35 (26)    |
| <40                                 | 19 (17)    |

* Karnofsky scoring—≥70: normal but few signs of diseases; ≥40 but <70: moderate signs of diseases; <40: the patient.

Continuous data were represented as mean±SD and constant data were represented a number (percentage).
machine (GE Healthcare, UK) at 0.01 mSv radiation dose. Data related to the brain tumor were accessed by visual observations of anteroposterior and lateral views of PFR.\textsuperscript{[28]}

All images were analyzed by authors who had at least 3 years of experience at the time of the study.

2.5.5. CM. CM of enrolled patients as worsening headache, fatigue, weight loss, bone marrow suppression, anemia, neutropenia, infection, lymphopenia, gastrointestinal disorder, anorexia, constipation, nausea, repeated vomiting, liver diseases, seizures, and the serum level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured. A headache, fatigue, gastrointestinal disorder, anorexia, constipation, nausea, and vomiting were reported by simply asking the question. The biochemical and serological analysis was performed using portable full automatic CE approved automated
hematology analyzer (HORIBA Medical Diagnostics Instruments & Systems, Kyoto, Japan).\[329\]

2.5.6. Post-surgery analysis. The tumor resected after brain surgery was subjected to morphological analysis as volume and diameter by Digital Electronic Carbon Fiber Vernier Caliper (Safeseed Electronic, China).\[330\]

2.6. Cost of diagnosis

The cost for PFR, CM, PET, MRI, and CT scan for every patient was evaluated.\[235\]

2.7. Statistical analysis

Statistical analysis between data of surgically resected tumor and that of different methods of diagnosis was carried out using Wilcoxon-matched pair test\[331\] after Tukey-Kramer multiple comparisons test (considering critical value \([q] > 4.03\) as the significant level).\[332\] The Spearmen nonparametric correlation was used to correlate parameters of volume and diameter of the tumor for all diagnostic techniques with that of the surgically resected tumor.\[333\] InStat (GraphPad, Inc., CA) was used for statistical analysis purposes. The results were considered significant at 99% of confidence level.

3. Results

During the diagnosis, 7 CT scans, 5 plain-film radiographs, 3 PET scans, 4 MRI scans, and 9 patients’ data of serum level of ALT and AST were failed to consider in statistical analysis because of missing information in DICOM files of patients while reporting by nursing staff. There were 19 patients refused to do brain surgery. Therefore, total, 108 patients’ tumor removed morphology data were used in statistical analysis.

CT, PET, and MRI scans were successfully quantified tumor and necrosis of cells. However, CM and PFR were failed to do so (Table 2).

Moreover, when the ancillary skull tumor was present, CT and MRI were failed to quantified tumor because CT images are simple tomographic images would not suffice for the diagnosis of pituitary adenoma (Fig. 2) and the white and grey matter of brain interrupted quality of MR images respectively (Fig. 3). In such conditions, PET was reliable for quantification of the tumor.

PET, CT, and MRI scan methods were succeeded in the quantification of tumor diameter and tumor volume. PFR had been shown less sized tumor diameter \([P < .0001, q = 17.284]\) and tumor volume \([P < .0001, q = 4.412]\) or provided approximate measurement than as that quantified by CT scan. However, CM had failed to provide a morphology of the tumor.

The data of diameter and volume for CT (Spearman \(r = 0.9845\) and 0.9706; Fig. 4A and B), PET (Spearman \(r = 0.9688\) and 0.9194; Fig. 5A and B), and MRI (Spearman \(r = 0.955\) and 0.2378; Fig. 6A and B) were failed to correlate with that of the surgically resected tumor. However, the prediction for diameter and volume by PET (Spearman \(r = 0.9922\) and 0.9921; Fig. 7A and B) were correlated with that of the surgically resected tumor.

The cost of diagnosis procedure was in the order of PET scan > MRI scan > CT scan > CM > PFR (Fig. 8).

### Table 2

Comparisons of different diagnostic techniques for brain tumor.

| Parameter | 1 (PSTA) (n = 108) | 2 (CT scan) (n = 120) | SA between 2 and 1 (P) | 3 (PFR) (n = 122) | 4 (CM) (n = 118) | 5 (PET scan) (n = 124) | 6 (MRI) (n = 123) | SA between 6 and 1 | \(P_{\text{corr}} \times 10^{-3}\) |
|-----------|--------------------|-----------------------|------------------------|------------------|-------------------|-----------------------|------------------|-------------------|-------------------|
| Tumor     | CD 107 (99)        | 106 (88)              | 0.5                    | 85 (70)          | 13.179 (99)       | 115 (83)              | 15.6             | 1.919 (89)        | 10 (12)           |
|           | NCD 1 (1)          | 1 (1)                 |                        | 31 (26)          | 9 (7)             | 9 (1)                 | 14 (11)          |                   |                   |
| Necrosis  | CD 107 (99)        | 102 (85)              | 0.0313                 | 65 (53)          | 15.088 (99)       | 116 (94)              | 31.3             | 1.688 (89)        | 10 (12)           |
| (tumor necrosis) | NCD 1 (1) | 1 (1) | 57 (47) | 63 (53) | 8 (8) | 15 (12) |

Data were represented as number (percentage).

CD = clearly detected, CM = clinical manifestation, CT = computed tomography, MRI = magnetic resonance imaging, NCD = not clearly detected, PET = positron emission tomography, PFR = plain-film radiography, PSTA = postsurgery tumor analysis, Q = assessment, SA = Statistical analysis. For statistical analysis, any of symptoms was quantified than considered as 1 and if not then considered as 0. Constant raw data were failed in software percentage raw data were used for numerical analysis.

Wilcoxon-matched pair test after Tukey-Kramer multiple comparisons test was used for statistical analysis. \(P < .01\) and \(q > 4.03\) were considered as significant.

*False positive.
4. Discussion

Compared with FDG PET, CT, MRI, and PFR had 0.97, 0.73, and 0.88 sensitivity. However, CM had not sensitive to a brain tumor. Because of complex anatomy and physiology of the brain, the diagnostic method is challenging\(^\text{[2]}\) and required extra features of brain tumors for proper diagnosis process.\(^\text{[3]}\) In respect to the diagnostic procedures performed for a brain tumor, a framework of 6 techniques was provided a competitive state-of-the-art for comparing different diagnostic modalities in brain tumor.

PFR was failed to provide morphology regarding diameter and volume of the tumor. Moreover, CM had not revealed the morphology of the tumor. Only CT, PET, MRI scan is succeeded in the prediction of the morphology of tumor.\(^\text{[30]}\) In consideration of techniques involved, the diagnostic cross-sectional study had demonstrated the choice of method, that is, CT, PET, MRI scan to assist the surgeons regarding surgery for brain tumor.

Considering CT as “gold standard” is a debatable issue. No controlled studies are available regarding sensitivity and specificity of CT scan for a brain tumor.\(^\text{[30]}\) In relation to lack of control, the diagnostic techniques demonstrated in the CT are required to perform with accuracy and precise method. CT images do not fully cover the field of view than MRI and PET scans.\(^\text{[33]}\) In respect to correction with surgically resected tumor data, the study stressed benefits of PET scan and MRI for a brain tumor diagnosis.

PET scan had excessive cost than MRI and CT. However, CT scan is relatively cheap than MRI.\(^\text{[30]}\) PET has increased the burden of radiation\(^\text{[25]}\) but has a high resolution\(^\text{[34]}\) than MRI. Moreover, PFR\(^\text{[7]}\) and CM\(^\text{[15]}\) have not quantified brain tumor morphology. MRI data are not easily be converted into attenuation values.\(^\text{[33]}\) Moreover, when the tumor is situated in the medulla oblongata, MRI is not an accurate method of...
Figure 5. Spearman nonparametric correlation curve between PSTA and PFR. (A) for tumor diameter, Spearman $r=0.9688$ (corrected for ties, 99% confidence interval: 0.98–0.9872); (B) for tumor volume, Spearman $r=0.9194$ (corrected for ties, 99% confidence interval: 0.9477–0.9662). Numbers of point = 84, $n=107$ for PSTA, and $n=85$ for PFR. PSTA = postsurgery tumor analysis, PFR = plainfilm radiography. Software generated figures.

Figure 6. Spearman nonparametric correlation curve between PSTA and MRI scan. (A) for tumor diameter, Spearman $r=0.955$ (corrected for ties, 99% confidence interval: 0.9695–0.9794); (B) for tumor volume, Spearman $r=0.2378$ (corrected for ties, 99% confidence interval: 0.414–0.5638). Numbers of point = 107, $n=107$ for PSTA and $n=109$ for MRI scan. PSTA = postsurgery tumor analysis and MRI = magnetic resonance imaging. Software generated figures.
In respect to the selection of diagnostic method, the study was provided more accurate data at comparatively loss cost to the patients. In limitations of the study, for example, the study was limited to spatial resolution for depth morphology of the tumor. The study was not used bioluminescence imaging technique for diagnosis of brain tumor. The study was not used for PET/MRI combined diagnostic technique. The study is limited to adult patients only. The large field of view was considered in separate CT, MRI, and PET. Anatomical conditions of patients as blood sugar level, use of steroids is also affected the diagnostic images. These factors were not discussed in the study. In the future work, PET study can be possible with $^{68}$Gallium-tagged DOTA-octreotate, which could be more cheap and accurate among all diagnostic modalities in brain tumor.

5. Conclusion

The nonrandomized, nonexperimental, cross-sectional diagnostic study was concluded that PET scan is adequate, reliable, and accurate diagnostic method to assess necrosis of tumor and morphology of tumor than the other diagnostic method in the brain. The surgeon can use positron emission tomography scan as a supplementary diagnostic technique for magnetic diagnosis.\[25]\n
Figure 7. Spearmen nonparametric correlation curve between PSTA and PET scan (A) for tumor diameter, Spearman $r=0.9922$ (corrected for ties, 99% confidence interval: 0.9885–0.9948); (B) for tumor volume, Spearman $r=0.9921$ (corrected for ties, 99% confidence interval: 0.9882–0.9947). Numbers of point $n=107$. n $= 107$ for PSTA and n $= 115$ for PET scan. PSTA = postsurgery tumor analysis, PET = positron emission tomography. Software generated figures.

Figure 8. Cost of diagnosis. Data were expressed as mean ± SD, n $= 127$ for all groups. PET scan had highest cost of diagnosis ($P<.0001$, $q = 31.726$) then after MRI scan ($P<.0001$, $q = 12.56$). CT scan had excessive cost of diagnosis than PFR ($P<.0001$, $q = 517.09$) and CM ($P<.0001$, $q = 357.95$). CT = Computed tomography, PFR = Plain-film radiography, CM = clinical manifestation, PET = positron emission tomography, MRI = magnetic resonance imaging. Wilcoxon-matched pair test following Tukey-Kramer multiple comparisons test was used for statistical analysis. $P<.01$ and $q > 4.03$ were considered as significant.
resonance imaging for quantification of a brain tumor before surgery.

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Author contributions
QL had performed conceptualization and data curation. YL had performed formal analysis, funding acquisition, and investigation. LL had performed visualization and written the manuscript for the intellectual content. WD had performed methodology and project administrator.

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