Pattern of Recurrence Analysis Following 3D Conformal Radiation Therapy with respect to Pre-RT MR Spectroscopic Findings

I. Park[1], G. Tamai[1], M. C. Lee[1], S. Cha[2], S. M. Chang[2], M. S. Berger[2], S. J. Nelson[1], A. Pirzkall[1]

[1]Radiology, University of California, San Francisco, San Francisco, California, United States, [2]Department of Neurological Surgery, University of California, San Francisco, CA, United States

Introduction: In order to enhance effectiveness of radiation therapy (RT) in brain gliomas while sparing normal tissue as much as possible, it is important to identify and distinguish cancer from normal tissue. The current 3D conformal radiation therapy (3D-CRT) target definition includes the gadolinium enhancing lesion on T1-weighted MRI with a uniform margin of 1 to 4 cm or the hyperintense lesion on T2-weighted MRI enlarged by several cm. These uniform margins are defined in an attempt to address several shortcoming with conventional anatomic imaging, i.e. MRI: serial biopsy studies show tumor cells occurring further than 3 cm from contrast enhancement (CE) region [1]; in addition, some tumors are not contrast-enhancing, and T2 hyperintensity may not distinguish tumor from edema, or the margin may miss the microscopic tumor area. Previous studies have shown that magnetic resonance spectroscopic imaging (MRSI) is valuable for mapping the extent of brain tumors and the target delineation for radiation therapy (RT) in high-grade gliomas, specifically by employing acholine-to-N-acetyl-aspartate abnormality index [2,3]. The goal of this study is to determine whether the combination of MRI and MRSI is of value for RT target definition if evaluated prior to RT.

Methods: Thirty patients with grade IV gliomas (22M/8F; 27-80 years; median 57 years) were evaluated. Each patient underwent a series of MRI and MRSI within 4 weeks after surgery but before RT and at two month followup (Fup) intervals after the beginning of RT. Seven patients were excluded due to the incomplete followup data. Among the eligible 23 patients, two had 1 Fup, eight had 2 Fup, four had 3 Fup scans , and the rest of the patients had more than 4 Fup scans (up to 7 Fup). Patients were scanned on a 1.5 T GE Signa Echospeed scanner (GE Medical Systems, Milwaukee, WI) prior to any intervention. The MRI protocol included axial T2-weighted Fluid Attenuated Inversion Recovery (FLAIR), and post-Gd-DTPA T1-weighted Spoiled Gradient (SPGR) sequences. 3D MRSI with lactate editing was acquired using Point Resolved Spectroscopic (PRESS) volume localization with spectral spatial pulses and VSS outer volume suppression bands (TR/TE=1000/144 ms, 1 cc nominal spatial resolution). Spectral values were normalized relative to the noise levels at the right hand end of the spectra. MRSI data were quantified offline to estimate absolute peak heights of various metabolites and a Choline- to-NAA Index (CNI) was automatically calculated as a indicator of metabolic tumor activity as confirmed by tissue samples [1]. Regions of interest (ROI) were manually contoured for T2-weighted hyperintensity (T2h), T1-weighted contrast enhancement (T1) and resection cavity (RC) and imported from the RT treatment planning system (the actually delivered RT dose map (60 Gy)), and automatically generated (point resolved spectroscopic box (PRESS), and CNI2. The details of analyzing CNI index have been presented elsewhere [2].

For the pre-RT scan, the volume of CNI2 outside the 60 Gy isodose line was calculated in order to evaluate whether the entire CNI2 is covered by the current conventional target definition and dose distribution. The combination of T2 and CNI2 (T2h+CNI2) within the PRESS volume was contoured and its volume and maximum extension distance beyond the 60 Gy region were calculated (Figure 1). For post-RT follow-up analysis, the volume and the maximum extension distance of CE at each follow-up scan outside the combined volume of T2, CE, RC and CNI2 from pre-RT (MRS/I) were calculated within PRESS (Figure 2). Also, CE inside CNI2 was estimated and analyzed to evaluate the degree of new/enlarged CE residing within CNI2 and to see whether the recurring CE was covered by 60 Gy. In addition, the total volume of CE as well as the volume of CE within PRESS were evaluated.

Results: Prior to RT, 21 of 23 patients exhibited contrast enhancing residual disease following surgery with CE volumes ranging from 0.39 to 41.99 cm^3. The CE inside the PRESS ranged from from 0.16 to 35.45 cm^3. In one patient the CE was not covered by the PRESS voilume. 43% (10/23) of patients had CNI2 regions not covered by the current conventional target definition and the subsequent 60 Gy isodose line at the pre-RT scan. The median and maximum volume that CNI2 extended beyond the prescribed dose volume was 3.46 and 29.21 cm^3 (range: 0.21 – 29.21 cm^3), and it extended as much as 43 mm from the edge of the 60 Gy volume (4.4 – 49 mm). This CNI 2 volume extending beyond 60 Gy was only minor (< 2 cc) in 5 patients. Among the 10 patients in whom the CNI 2 was found to extend beyond the 60 Gy volume, 30% (3/10) had new/increased CE occurring within the CNI 2 region that was not covered by 60 Gy. Of these three, one patient developed increased CE around a central necrosis 2 months after the start of RT. The second patient showed new CE located inferior to the resection cavity as well as enlarged CE around the resection cavity 6 months after RT. The third patient showed increasing CE 8 months after RT, and the CE region kept growing around the necrosis thereafter. Among, the remaining 7 patients, four had decreasing overall CE: one of these had no CE inside CNI2 and the other three had minor CE volume (< 2 cc). In one patient, it was impossible to assess because the CE was outside the PRESS volume prior to RT. In the last two patients who developed increasing overall CE, some of the CE was found inside the CNI 2 but they were all covered by 60 Gy isodose line Among all 23 patients, 8 patients showed increasing CE, 2 patients showed stable CE, 10 patients showed decreasing CE, 2 patients showed no CE, and 1 patient showed unstable CE, in which both total CE volume and CE volume inside the PRESS volume tripled at 2 months after RT, but reduced to 91% (total CE) and 70% (CE inside PRESS) compared to CE volume at pre-RT 4 months after RT. All 8 patients with increasing CE had CE residing within CNI2 at available follow-ups (ranging from 2 to 14 months after RT).

Recurring CE was found to reside within the pre-RT combined MRS/MRI lesion in 88% (7/8) of patients with increasing CE at 2 months (Table 1). Three of them had tiny CE volume outside the combined MRS/MRI lesion (< 0.4 cc), hence it was considered to be within the margin of error. The patient with recurring CE outside the MRS/MRI lesion showed an enlarged necrotic core and CE around necrosis was beyond the edge of the MRSMR/I lesion with the maximum margin of 19.4 mm. Out of all 8 patients with increasing CE, two patients had only one Fup scan, and one patient had only 2 Fup scans. At 4 months, all 6 remaining patients showed increased CE confined to the preRT MRS/I volume with minor extents considered within the error margin for the ROIs (range: 0.15 - 0.82 cm^3, median: 0.58 cm^3). At 6 months, in 40 % (2/5) of patients, recurring CE resided within MRS/I. Three exhibited a significant amount of CE outside MRS/I (range: 2.2 – 12 cm^3, median: 7.9 cm^3), and one had small CE volume outside MRS/I (0.39 cm^3). At 8 months after RT and at available scans thereafter, all recurring CE exceeded the combined MRS/MRI volume indicating an outgrowth from the original recurrence pattern that was confined within the MRSMR/I lesion.

Conclusion: This study demonstrated that the combination of MRI and MRSI can be of practical value for RT target definition. The CNI2 region in conjunction with T2 hyperintensity region covered the contrast enhancing region of recurrence in 88% of patients at 2 months, 100% at 4 months, and 20% at 6 months after the initiation of RT. While further follow-up is required to draw more refined conclusion, MRSI in combination with MRI may allow for a reduction and custom shaping of currently employed target volumes for RT in brain gliomas which would reduce the dose exposure to uninvolved normal tissue.

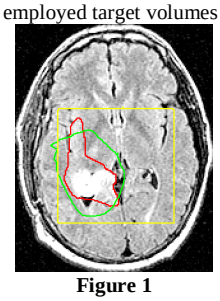

Figure 1

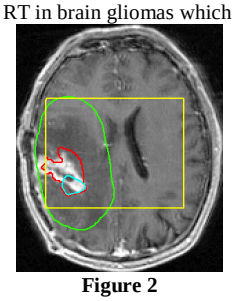

Figure 2

Time after RT (months)	*Total num. patients w/ increasing CE*	*Num. patients w/ CE ins MRS/I*	*% patients w/ CE ins MRS/I*	*Extentionvol. Median(cc)*	*Extension vol Maximum(cc)*
2	8	7	88	0.38	5.1
4	6	6	100	0.58	0.81
6	5	2	40	1.3	12

Table 1. Patients with recurring CE residing within the MRS/MRI lesion.

Figure 1. T2h image at pre-RT, overlaid with PRESS(yellow), 60Gy(green), and T2h+CNI2(red) ROIs
Figure 2. T1 SPGR with Gd contrast at 2 month follow-up, overlaid with PRESS(yellow), 60Gy(green), MRS/I(red), and CNI2(light blue) ROIs

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