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FULL PAPER

Cerebral cyst formation following stereotactic ablative irradiation for non-nasopharyngeal head and neck malignancies: imaging findings and relevant dosimetric parameters

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Objective: To describe the clinical characteristics, imaging findings and relevant dosimetric parameters of cases presenting with cerebral cyst formation (CCF) after single or oligo-fractionated stereotactic radiotherapy (SRT) for non-nasopharyngeal head and neck malignancies (HNMs).

Methods: We identified four cases with the follow-up duration of 5.7–9.1 years from SRT. The irradiated sites included the middle ear in one case and the ethmoid sinus in three cases, two of the latter possessed brain invasion. The chronological changes in MR images and the dose–volume histogram of the adjacent brain tissue were evaluated.

Results: CCF with or without multiple septi presented with a latency of 29–86 months (median, 45.5 months), which was preceded by either non-specific parenchymal enhancement or typical radiation necrosis. In three cases, CCF adjacent to the frontal base resultantly caused mass

effect, and two of these three cases required surgical intervention at 38 and 54 months, respectively, after SRT for alleviation of symptoms. The relation of the irradiated brain volumes to the biological equivalent dose based on the linear-quadratic (LQ) and LQ-cubic models was represented as a threshold.

Conclusion: When contemplating SRT for HNM cases, caution should be exercised to the dose–volume relationship of the adjacent brain tissue, especially the frontal base, as well as other critical structures, and long-term vigilant follow-up is also mandatory.

Advances in knowledge: CCF can occur as an unusual consequence of late brain injury with variable but mostly long latency following SRT for non-nasopharyngeal HNMs adjacent to the brain, even superficial parts that were previously irradiated via conventional radiotherapy.

Stereotactic radiotherapy (SRT) has emerged as a promising strategy for persistent or recurrent head and neck malignancies (HNMs) deemed not amenable to surgery or conventional radiotherapy (cRT).^{1,2} Data regarding the efficacy and safety based on long-term follow ups have been rather limited, whilst various types of severe late toxicities have been reported.^{1–3} Furthermore, the optimal dose fractionation scheme (DFS) has remained a controversial issue.^{1–3}

Brain radiation necrosis is one of the important untoward sequelae after radiotherapy, including SRT for HNM, especially nasopharyngeal carcinoma (NPC), with imaging findings being characterized by central loss of enhancement surrounded by feathery or reticular enhancement associated with perilesional oedema.^{4–7} Cerebral cyst formation (CCF) is an unusual subset of radiation-induced brain injury and is usually encountered in cases harbouring intracranial disorders

embedded in the parenchyma, such as arteriovenous malformation (AVM)^{8,9} or brain metastases,^{10,11} and rarely extra-axial tumours, such as meningioma¹² and neuroma,¹³ treated with stereotactic radiosurgery (SRS). CCF might also occur as a rare consequence of brain injury following definitive radiotherapy for NPC.^{14–16} However, CCF as a predominant manifestation of late brain injury in cases with non-nasopharyngeal HNM treated with SRS or SRT is extremely rare.

Herein, we describe four cases presenting with CCF following single or oligo-fractionated SRT for previously irradiated HNMs juxtaposed to the brain, focussing on the radiological findings and the relevant dosimetric parameters.

METHODS AND MATERIALS

Study populations

In our institution, 52 HNM cases with 60 lesions were treated with SRT based on the dynamic conformal arc (DCA)

Table 1. Clinical and treatment characteristics of the study populations

Case	1	2	3	4
Age at SRT (years), gender	56, female	69, female	36, male	40, male
Primary site	Middle ear	Ethmoid sinus	Nasal cavity	Maxillary sinus
Irradiated site	Middle ear	Ethmoid sinus	Ethmoid sinus	Ethmoid sinus
Histopathology	SCC	Basaloid SCC	Neuroblastoma	SCC
Situation	Initial	Recurrence	Recurrence	Recurrence
	cRT + SRT boost	cRT + SRT boost	SRT alone	Surgery + SRT
Previous RT (Gy)	50.0	40.0	40.0	60.0
Interval (months) ^a	0.8	0.3	44.0	49.5
CTV (cm ³)	16.0	7.6	0.6	11.7
Margin (mm)	2.0	3.0	2.0	2.0
PTV (cm ³)	27.7	19.2	1.8	19.9
PTV D95 (Gy × Fr)	8.8 × 2	9.0 × 1, 7.5 × 2 ^b	21.4 × 1	11.0 × 1
PTV D95 (BED10LQ)	33.1 (93.1) ^c	43.4 (91.4) ^c	67.2	23.1
PTV D95 (BED10LQC)	30.6 (90.2) ^c	40.4 (88.1) ^c	49.0	20.6
IDS (%) ^d	79.6	81.2	80.5	71.9
OTT of SRT (days)	8.0	15.0	1.0	1.0
Follow up (years) ^e	9.1 (9.4)	6.8 (10.0)	5.8 (9.5)	5.7 (9.2)
Treatment for cyst	None	None	Surgery (37.6 months)	Surgery (53.5 months)
Local control	NED	NED	NED	NED
Survival (KPS)	Alive (90)	Alive ^f (70)	Alive (90)	Alive (90)

BED, biologically effective dose; cRT, conventional radiotherapy; CTV, clinical target volume; Fr, fraction; IDS, isodose surface; KPS, Karnofsky performance scale; LQ, linear-quadratic; LQC, linear-quadratic-cubic; NED, no evidence of disease; OTT, overall treatment time; PTV, planning target volume; PTV D95, dose encompassing at least 95% of the planning target volume; RT, radiotherapy; SCC, squamous cell carcinoma; SRT, stereotactic radiotherapy.

^aInterval between the completion of cRT and the commencement of SRT.

^bDose was reduced in second and third fractions.

^cDose for SRT and the cumulative dose of cRT and SRT (parenthesis).

^dIDS fitting to the PTV D95 normalized to 100% at the isocentre.

^eFollow-up period from the commencement of SRT and the initial treatment (parenthesis).

^fThe patient harboured distant active disease at the last follow-up.

technique, either alone or in conjunction with cRT, between January 2005 and July 2012. Until November 2009, the delivery system was the “m3” micro-multileaf collimator (Brainlab AG, Feldkirchen, Germany) as an add-on device on the Clinac® 21EX (Varian® Medical Systems, Palo Alto, CA) with 6-MV X-ray, commissioned with the Brainscan v. 5.3 (Brainlab).^{3,17} Patients were immobilized with the Brainlab thermoplastic mask, and the set-up margin for target definition was usually 2–3 mm. We were forced to use a limited number of fractions (1–4) with non-daily delivery (1–2 fractions per week) owing to the limited machine capacity at that time, and the DFS was individually tailored to each patient, considering the heterogeneous backgrounds.³ In December 2009, the delivery system was supplanted by image-guided SRT using the Novalis Tx™ platform (BrainLAB and Varian Medical Systems) equipped with a six-dimensional verification and correction system,¹⁸ and since then the DFS of ≥5–10 fractions with daily consecutive delivery has been used, given the limitation of oligo-fractionated SRT in terms of ensuring safety.³ Among these 52 patients, we identified 4 cases (7.7%) developing CCF at the

latest follow up in December 2013: these constituted the study population. These cases were treated with the predecessor “m3” system without dedicated image guidance between January 2005 and February 2009, and the follow-up duration from SRT ranged from 5.7 to 9.1 years.

The follow-up MR images were retrospectively reviewed to elucidate the chronological change leading to CCF and the latency from SRT.

Dosimetric analyses

The dose calculation was based on a pencil-beam algorithm with the radiological path length for heterogeneity correction, with the grid size set to ≤1.0 mm. The dose encompassing at least 95% of the planning target volume (PTV D95) was used as a reference marginal dose.¹⁷ A part of the adjacent brain tissue of ≥12–15 cm³ was contoured, and each minimum dose to 0.5, 1, 2, 3, 4, 5, 7, 10 and 12 cm³ of the brain tissue was then computed. To compare different DFSs, the biologically effective dose (BED) was calculated according to the linear-quadratic (LQ)

Figure 1. Case 1: dose distribution of stereotactic radiotherapy (SRT) plan (left) and MR images 29–98 months after SRT (upper: post-contrast T_1 -[gadolinium- T_1]; middle and lower: T_2 weighted images [T_2 -WI]). Note the appearance of spotty parenchymal enhancement with slight oedema at 29 months (arrow). mo, months.

formula $BED_{n\text{ LQ}}(\text{Gy}) = \text{total dose} \times [1 + (\text{dose per fraction})/n]$, where n represents the α/β ratio, $\alpha/\beta = 10$ for antitumour effect and $\alpha/\beta = 2$ for normal tissue.³ The LQ model is the *de facto* standard method for comparing the different DFSs of SRT for HNM,^{1,3} but some investigators have refuted the applicability of the LQ model for dose per fraction of > 8 Gy.^{19,20} The BED was therefore also calculated using an alternative method: LQ-cubic (LQC) model.^{3,21,22} The BED based on the LQC model ($BED_{n\text{ LQC}}$) was defined as the total dose $\times [1 + (\text{dose per fraction})/n - (\text{dose per fraction})^2/(\alpha/\gamma)]$. According to Joiner,²¹ the survival curve becomes straighter at dose D_L by choosing $\gamma = \beta/(3D_L)$, and the LQC curve becomes a straight line at a dose, D_L , of 18 Gy.

For prior cRT, detailed dose–volume histogram data were unavailable for half of the cases. The same analyses for the brain dose–volume relationship in cRT were therefore omitted. The brain dose for cRT was then substituted as a point dose at the isocentre or near the reference point.

RESULTS

The clinical and treatment characteristics of four cases are summarized in Table 1. The irradiated lesions were located adjacent to the frontal lobe (gyrus rectus and/or orbital gyri) in three cases and the temporal lobe (occipitotemporal gyrus) in one case. Brain invasion was noted in two of the former cases, either pathologically (Case 4) or radiologically (Case 3).

Sequential MR images representing significant changes are demonstrated for each case in Figures 1–4. The chronological change on the MRI findings leading to CCF and the interval from SRT are summarized in Figure 5, whilst substantial interindividual variation in both the imaging findings and the latency was noted. The first manifestation of brain injury was the newly disclosed spotty parenchymal enhancement or enlargement of the pre-existing

lesion enhancement associated with mild oedema, which gradually progressed into typical radionecrosis or non-specific enlargement of the enhancing lesion with increased oedema. CCF subsequently appeared as a cystic change of a part or the entirety of the enhancing lesion preceded by a decrease in the enhancement and oedema at 29–86 (median, 45.5) months from SRT (Figure 5). In three cases, CCF adjacent to the frontal base resultantly caused mass effect 8–25 months later (37–79 months from SRT). In Case 3, radiological evidence of intracystic haemorrhage was noted at maximum enlargement of the cyst (Figure 3). These imaging changes in cases harbouring brain invasion treated with single fraction (Cases 3 and 4) appeared and progressed rapidly compared with fractionated SRT (Cases 1 and 2) (Figure 5).

Two out of three cases (Figures 3 and 4) required surgical interventions at 37.6 and 53.5 months after SRT for palliation of symptoms and also histological verification. Partial removal of the cyst wall was performed for decompression in both cases. Pathological examinations revealed no viable tumour tissue and otherwise similar findings to the reported cases of CCF:^{9,11} pseudocyst, non-epithelium-lined cyst, surrounded by congestive brain tissue associated with subacute and chronic haemorrhage, hyalinization of vessels, gliosis and perivascular lymphocyte infiltration,^{9,11} whereas no hypervascular/angiomatous lesion attributable to repetitive haemorrhage was identified.⁹ These patients recovered well after surgery. All patients retained no evidence of viable disease in and near the irradiated site and were alive with generally favourable performance status at the last follow-up visit (Table 1).

The BED2 of SRT alone and the sum of prior cRT and SRT, based on the LQ and LQC models, as a function of the respective irradiated brain volume are shown in Figure 6. The profile in Case 3 was quite different from the others in terms of relatively

Figure 2. Case 2: stereotactic radiotherapy (SRT) plan (left) and MR images 38–79 months after SRT (upper and lower: Gd- T_1 ; middle: T_2 -WI). Note the spotty multifocal enhancement with slight oedema at 38 months (arrows). mo, months.

high-dose irradiation to a small volume and *vice versa*. In Case 3, the irradiated isodose volumes, including the lesion *per se*, receiving at least 10, 12 and 22 Gy (V10/12/22 Gy) were 7.4, 5.7 and 1.8 cm³, whereas those in Case 4 were 34.0, 23.8 and 0.0 cm³, respectively.²³

DISCUSSION

The number of reports on CCF cases from various types of primary pathology have been increasing, whilst the aetiopathogenesis of

CCF remains to be elucidated.^{9,10} Repetitive haemorrhage from an abnormal angiomatous lesion located within or underlying the cyst wall was suggested as a plausible mechanism for cyst enlargement in AVM cases.⁹ The CCF in the present cases appeared more than 2–7 years after SRT, and are plausibly derived from a part or the entirety of pre-existing parenchymal injury rather than degenerative change of the necrotic tumour. The CCF was therefore considered as an unusual consequence of late brain injury related to SRT preceded by prior cRT.

Figure 3. Case 3: stereotactic radiotherapy (SRT) plan (left) and MR images 6–62 months after SRT (upper and lower: gadolinium- T_1 ; middle: T_2 -WI). Note the slight enlargement of the enhanced lesion with increased oedema at 6 months (arrows) and the fluid sedimentation level at 29 months (dashed arrow). mo, months.

Figure 4. Case 4: stereotactic radiotherapy (SRT) plan (left) and MR images 8–54 months after SRT (upper, lower: gadolinium- T_1 , middle: T_2 -WI). Note the irregular enhancement with slight oedema at 8 months (arrows) and subsequent appearance of enhanced lesion in the contralateral side at 12 months (dashed arrow). mo, months.

In previous cRT that ranged from 40 to 60 Gy, the brain tissue was not intentionally included in the clinical target volume in all cases, although it was included in the PTV for margin set-ups of approximately 5–10 mm. The V12/22 Gy for Case 3 treated with single fraction was sufficiently small for ensuring prevention of radionecrosis.²³ The profile for the dose–volume relationship of the adjacent brain in Case 3 was quite different from the others, suggesting that not only low-dose irradiation to large volumes but also high doses to limited small volumes can lead to CCF (Figure 6).²³

Deeply located lesions mainly embedded in the white matter and totally surrounded by parenchyma are more likely to be susceptible to damage from SRT than those located superficially in the grey matter.²³ The irradiated sites in the CCF causing mass effect were juxtaposed to the base of the frontal lobe in all three cases, suggesting that the frontal base might also be susceptible to SRT-induced damage among the cerebral cortices, even the superficial

parts that were previously irradiated with cRT. The present cases send out an extraordinarily cautious alarm to practitioners contemplating reirradiation for HNM adjacent to the basal brain via SRT, especially in an oligo-fractionated manner, and also suggest that long-term vigilant follow up with imaging surveillance encompassing the adjacent brain is mandatory, given the long latency for the appearance and progression into mass effect. Surgical intervention is indicated for cases presenting with unrelenting cyst enlargement causing symptoms or where underlying viable tissue is suspected.^{9,11}

Nonetheless, SRT contributed to the prolongation of survival with functional autonomy of more than 5.5 years after SRT and more than 9 years from the initial treatment, through sustained tumour control for the HNM cases deemed not amenable to surgery or cRT alone. Further optimization of SRT would therefore be required to ensure long-term safety, whilst retaining efficacy.

Figure 5. Chronological change of imaging findings with the interval (months) from stereotactic radiotherapy. Fr, fraction.

Figure 6. Biologically effective dose (BED) 2 of stereotactic radiotherapy alone (open shapes) and the cumulative dose with conventional radiotherapy (closed shapes) based on (a) the linear-quadratic (LQ) or (b) LQ-cubic (LQC) models as a function of irradiated brain volume.

Treatment planning and DFS must be tempered and optimized to circumvent these untoward sequelae. With regard to planning, the adjacent brain dose was undesirably increased in the present cases, due to rather skewed arc arrangement at the discretion of the then planner as a trade-off to reduce the critical structures located laterally, such as the optic apparatus or the brain stem. In DCA, the dose “hot area” is likely located at the cranial side within the target. These shortcomings of the delivered plans can be improved with modification of PTV geometry and its use as a surrogate for leaf fitting or manual adjustment of selected leaf positions on the beam’s eye view to sculpt dose distribution as exemplified by [Supplementary Figure A](#) for Case 1.¹⁸ The isodose surface (%) selection relative to the isocentre for target coverage would also be important to ensure that the dose fall-off outside the target is steep.^{24,25} Although the data for brain dose tolerance in oligo-fractionated SRT have been rather limited compared with SRS,^{4,26} the ablative DFS adopted in present cases would be unsuitable for cases adjacent to the basal brain tissue. The small-calibre vessels supplying the brain parenchyma are particularly susceptible to damage by large doses per fraction,²⁷ and the resultant vascular injury would be one of the major mechanisms underlying the pathophysiology in the development of CCF. To further minimize the risk of brain injury, more fractionated SRT regimen may be preferable. Current image-guidance systems provide more accurate daily patient set-up, thereby reducing the set-up margin.¹⁸ In our institution, we have encountered no such brain injury since starting to use the Novalis Tx platform.

We must declare several limitations in this study. Histopathological diagnosis was not obtained in half of the cases, and we can not therefore rule out any neoplastic disease as an underlying pathology in CCF. Notwithstanding the prolonged DFS with a fraction per week in two cases, neither the LQ nor LQC model takes the time factor, prolonged overall treatment duration, into account.²⁰ The presented dose–volume relationship as a threshold should therefore be refined by a more suitable

biological model for BED, if established. The BED for prior cRT was expediently substituted by the isocentre dose in as many of the dose–volume histogram analyses as were unavailable. The cumulative BED of cRT and SRT represented in [Figure 6](#) would thus be overestimated. In addition, we had no adequate data to identify the safe dose–volume relationship in cases, without causing CCF, owing in part to the insufficient observation periods or even to the unavailability for the dose–volume histogram analysis, and no evident threshold dose–volume parameters for the brain were therefore represented. Nonetheless, the adjacent brain dose must be reduced to sufficiently lower than the profile curves for the brain dose–volume relationship, when contemplating SRT for such HNM cases.

CONCLUSION

CCF can occur as an unusual consequence of late parenchymal injury with a variable but mostly long latency period of 2–7 (median, 3.8) years, and CCF can progress into a mass effect following single or oligo-fractionated SRT for non-nasopharyngeal HNM adjacent to the brain tissue, even the superficial part of which was previously irradiated via cRT. When contemplating SRT for such HNM, caution should be exercised to the dose–volume relationship of the brain tissue, especially the frontal base, as well as other critical structures. The dose–volume relationship of the brain tissue can serve as a threshold to reduce these untoward sequelae.

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