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Clinical Investigation

Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases

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Summary

Guidelines for contouring the clinical target volume for postoperative stereotactic radiosurgery after complete resection of brain metastases are lacking. Ten experts each contoured 10 cases with varying clinical scenarios and completed a survey regarding how they defined their target volume. All

Purpose: To propose contouring guidelines based on consensus contours generated by 10 international experts for cavity stereotactic radiosurgery (SRS), an emerging treatment option after surgical resection of brain metastases. No guidelines for contouring the surgical cavity volume have been previously reported.

Methods and Materials: Ten postoperative completely resected cases with varying clinical scenarios and locations within the brain were selected. For each case, 10 experts independently contoured the surgical cavity clinical target volume (CTV). All the contours were analyzed, and agreement was calculated using the simultaneous truth and performance level estimation (STAPLE) with the kappa statistic. A follow-up survey was also completed by each investigator to summarize their contouring rationale for a number of different clinical scenarios. The results from the survey and the consensus STAPLE contours were both summarized to establish contouring guidelines.

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contours were analyzed, and agreement was calculated using the simultaneous truth and performance level estimation with the kappa statistic. The present report summarizes the consensus contour and provides guidelines for contouring.

Results: A high level of agreement was found between the expert CTV contours (mean sensitivity 0.75, mean specificity 0.98), and the mean kappa was 0.65. The agreement was statistically significant at $P<.001$ for all cases. From these results and analyses of the survey answers, the recommendations for CTV include fusion of the preoperative magnetic resonance imaging scan to aid in volume delineation; contouring the entire surgical tract regardless of the preoperative location of the tumor; extension of the CTV 5 to 10 mm along the dura overlying the bone flap to account for microscopic disease extension in cases with preoperative dural contact; and a margin of $\leq$5 mm into the adjacent sinus when preoperative venous sinus contact was present.

Conclusions: Consensus contouring guidelines for postoperative completely resected cavity SRS treatment were established using expert contours and clinical practice. However, in the absence of clinical data supporting these recommendations, these guidelines serve as a baseline for further study and refinement.

Introduction

Surgery is an important treatment option for patients with symptomatic or large brain metastases. Until recently, postoperative whole brain radiation therapy (WBRT) has been the standard of care based on a historic randomized controlled trial demonstrating a decrease in local and distant brain recurrence (1). However, recent randomized trials aimed at clarifying the adverse effects of WBRT have confirmed the association of neurocognitive (2-5) and quality of life (2, 4, 6, 7) declines with WBRT, without any improvement in overall survival. Given the lack of a survival advantage with WBRT and the ability to monitor patients with serial magnetic resonance imaging (MRI) scans to detect new metastases and salvage at failure, a shift in practice has occurred for patients with limited intact brain metastases to undergo SRS alone and omit WBRT (8, 9). The success of SRS as the upfront therapy for patients with intact brain metastases has also been increasingly applied to the postoperative patient in the form of surgical cavity SRS, which is an emerging trend.

Several single-institution series and a few prospective trials specific to cavity SRS have been reported; however, only recently has a randomized trial compared cavity SRS and WBRT. The N107/CEC3 trial randomized patients with brain metastases after surgical resection to WBRT versus cavity SRS. Although SRS was shown to yield significantly better cognitive function and quality of life outcomes, with equivalence in survival rates, long-term local control was worse with cavity SRS (10, 11). Similarly, a smaller randomized trial from Poland also did not show better local control with cavity SRS (12). This was unexpected, given the higher biologically effective doses delivered with cavity SRS. One hypothesis is that of insufficient target coverage due to the lack of standardization of surgical cavity contouring. The steep dose gradients associated with SRS amplify the effect of inaccurate contouring and could potentially lead to treatment failure. In contrast, larger treatment volumes for SRS could also lead to greater toxicity (13).

The aim of the present study was to develop contouring guidelines for surgical cavity SRS using consensus contours from expert practice.

Methods and Materials

Ten cases of postoperative completely resected cavity SRS were selected from a prospective institutional registry of patients. The cases were selected to represent different locations in the brain (supra- and infratentorial, deep and superficial, with or without dural or venous sinus contact), different histologic features, different tumor and cavity sizes, and different degrees of edema and mass effect in the brain. Each case had a preoperative T1-weighted gadolinium-enhanced MRI scan and/or contrast-enhanced computed tomography (CT), a postoperative (2-4 weeks after surgery) planning T1-weighted gadolinium-enhanced MRI scan, and a noncontrast-enhanced planning CT scan. Ten international experts (2 neurosurgeons and 8 radiation oncologists) in cavity SRS, who have reported series or led clinical trials, participated in the present study. The combined numbers of cases performed by this group were estimated at >1000. For each case, a summary of the patient data, including age, histologic features, operative report, and time from surgery, were provided. For each of the 10 cases, the physicians were asked to use their institutional contouring system, fuse the images, and contour the clinical target volume (CTV) on the noncontrast-enhanced planning CT scan.

The finalized CTV contours for all the cases were returned to the coordinating center using the Digital Imaging and Communications in Medicine format and were imported into a commercial treatment planning system for initial review. All contours for each case were then exported to the Computational Environment for Radiotherapy Research, version 4.6, run through MATLAB, version 2016b (MathWorks, Natick, MA) for analysis. A kappa statistic was calculated for each case to quantify agreement between physician contours. Interpretation of agreement for the kappa results were as follows: <0, no agreement;

0 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1.00, almost perfect agreement (14). A consensus contour was generated with an expectation minimization algorithm, iteratively optimizing sensitivity and specificity, using the simultaneous truth and performance level estimation (STAPLE) (15-17) and applying a threshold of 80% to the resulting conditional probability distribution to obtain a binary segmentation. To aid in interpreting the results of the consensus contour, a survey was distributed and completed by each physician participant (Appendix E1; available online at www.redjournal.org). The survey consisted of questions focusing on details of the imaging used for contouring and the extent of the surgical or operative tract and dura or venous sinus included in the CTV.

Results

Ten CTV contours were obtained per physician for each case and analyzed (100 contours in total). The details for each case and the preoperative axial contrast-enhanced CT or T1-weighted MRI scan, postoperative axial contrast-enhanced T1-weighted MRI scan, and postoperative coronal contrast-enhanced T1-weighted MRI scan are provided in Figure 1. Eight cases were supratentorial tumors, 2 were infratentorial (cases 2 and 3), 6 had preoperative dural contact (cases 1, 2, 5, 6, 7, and 10), and 1 case had contact along the venous sinus (case 2). The CTV contours for the individual physicians (variety of colors in thin lines representing individual physicians) and the consensus CTV contour (thick red line) are displayed in the axial and coronal T1-weighted contrast-enhanced MRI scans. Appendix E2 (available online at www.redjournal.org) includes magnified MRI scans of the 10 cases, each in axial, coronal, and sagittal orientations, showing the individual physician and consensus contours.

Analysis of CTV contours

The results of the STAPLE analysis with the mean sensitivity, mean specificity, and kappa measure for each of the 10 cases are summarized in Table 1. Overall, a high level of agreement was seen among the physicians for the CTV contour (mean sensitivity 0.75, mean specificity 0.98). The mean kappa was 0.65, corresponding to substantial agreement. The agreement was statistically significant at $P<.001$ for each case.

The largest variability in contouring was seen with case 2 (kappa 0.43) and case 3 (kappa 0.52). Both were infratentorial tumors. Furthermore, the surgical cavity for case 2 was in close proximity to the transverse sinus and in contact with the dura. Also, although the tumor in case 3 was not in contact with a venous sinus or dura, significant blood products were present beyond the tumor bed, which likely caused the variability observed (Fig. 1 and Appendix E2; available online at www.redjournal.org). The degree of preoperative mass effect, which was most pronounced in cases 6, 7, 9, and 10, did not appear to have an appreciable effect on the extent of the CTV contoured.

Survey responses and contouring guidelines

Most of the responders did not use CT contrast during simulation (n=7). All responders used at least a T1-weighted gadolinium-enhanced MRI scan to contour the CTV. Other sequences that were commonly used included postoperative T2 fluid attenuation inversion recovery (n=8), and postoperative T1-weighted before gadolinium enhancement (n=5). All the responders contoured part of or the entire surgical tract as the CTV, except for 1 responder. If the tumor had been in contact with the dura preoperatively, the most common response (n=5) was to extend the CTV contour by 5 to 10 mm beyond the initial dural contact. If no contact had been present with the dura, most commonly (n=8), <5 mm of the dura was included in the CTV. When preoperative tumor contact with the venous sinus had been present, the responses were split. Of the 10 responders, 5 would restrict the CTV to include only the area of initial tumor contact along the sinus and 5 would extend the CTV another 5 mm beyond the preoperative contact with the venous sinus. The responders were also asked whether they would include a further margin beyond the contour for the surgical cavity. Of the 10 responders, 6 would include either a 1-mm (n=2) or 2-mm (n=4) margin and 4 would not include an additional margin. All but 1 of the responders preferred to perform cavity SRS within the first 4 postoperative weeks; the 1 responder preferred to wait >6 weeks.

Using the results of the consensus STAPLE contours and the follow-up survey, 5 recommendations were developed (Table 2).

Discussion

Surgical cavity SRS has been increasingly used in clinical practice as an alternative to WBRT after brain metastasis resection. This has been driven by the desire to provide good local control to the tumor bed, with sparing of the neurocognitive and quality of life decline associated with WBRT (3, 4, 6, 7, 18). With intact brain metastases, the target volume for SRS is well established and simply represents the enhancing lesion seen on CT and/or MRI. Postoperative target volume definition is much more complex and has not yet been defined. Our study has generated recommendations for completely resected cavity CTV contouring using consensus contouring among experts in the field and a summary of practice patterns determined from a written survey.

Each of the 10 selected cases was contoured by 10 experts, generating 100 CTV contours for analysis. The cases for contouring represented a wide variety of locations in the brain, including supra- and infra-tentorial, deep and

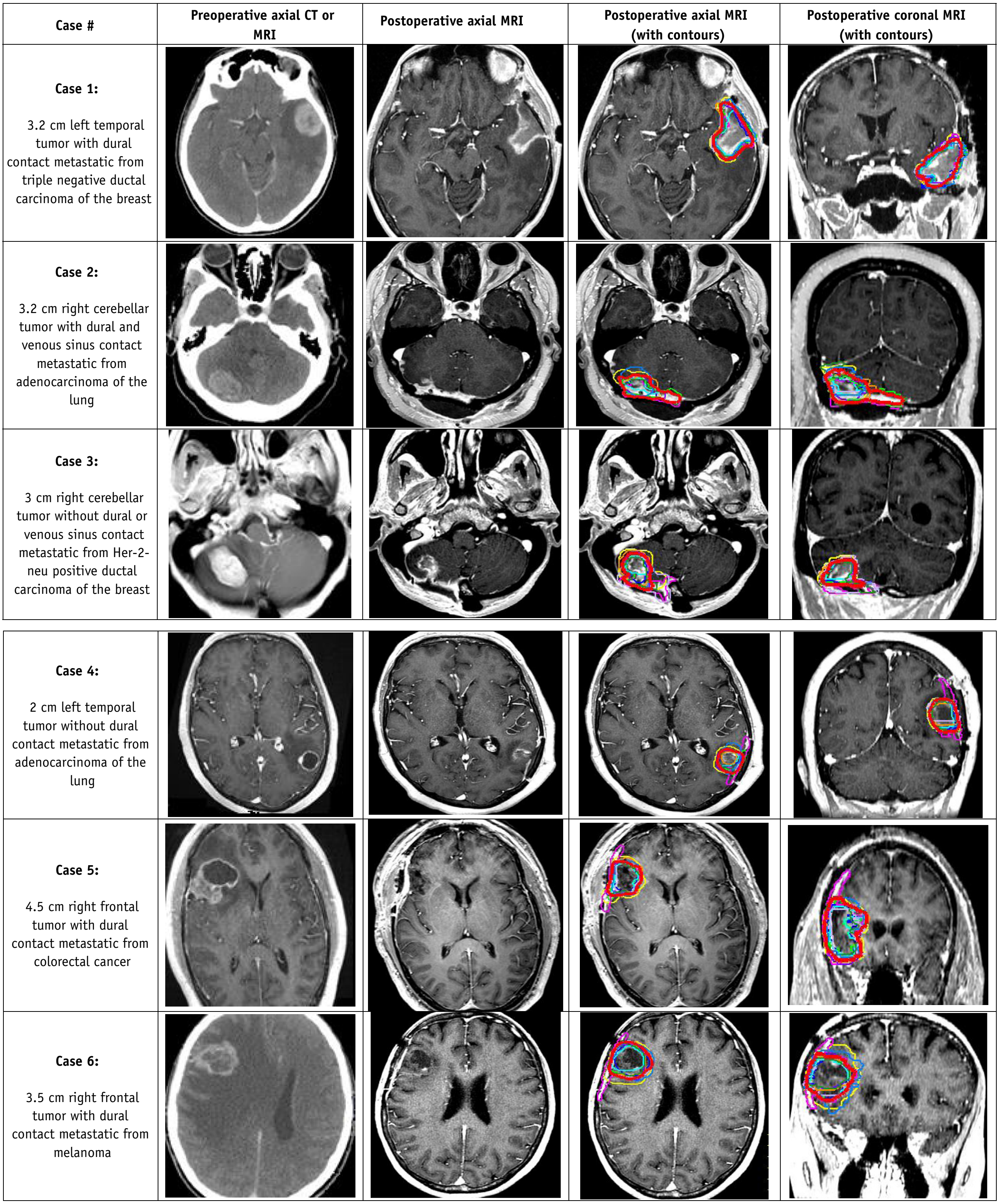

Fig. 1. Individual and consensus clinical target volume contours in resected brain metastases. Consensus contours shown in thick red and individual contours in other colors. *Abbreviations:* CT = computed tomography; MRI = magnetic resonance imaging.

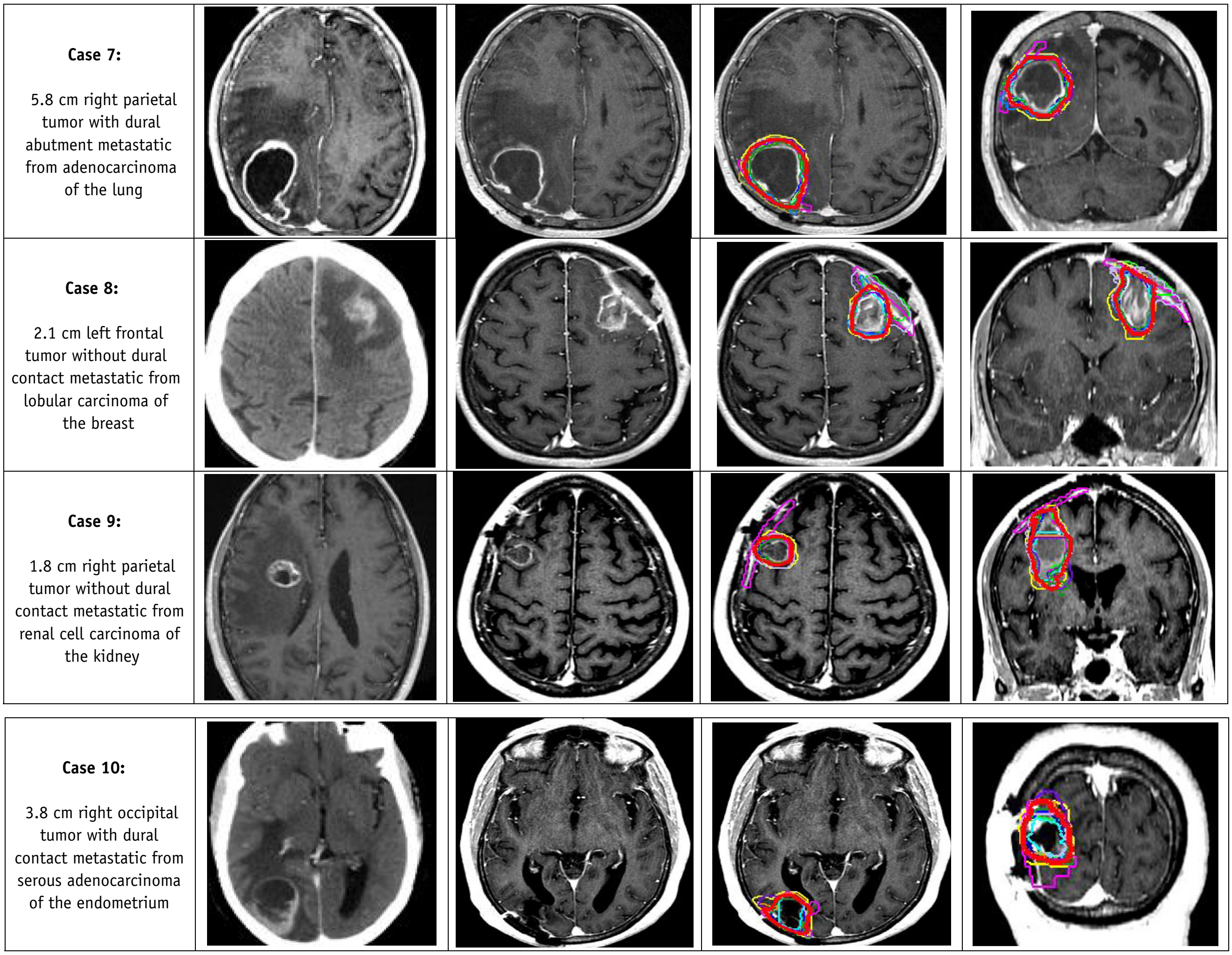

Fig. 1. (*continued*).

superficial, and dural or venous sinus contact. Overall, the level of agreement was high for each case's CTV contours (mean sensitivity 0.75, mean specificity 0.98). The largest variability was seen in the 2 cases of infratentorial metastases, with significant differences in the extent of CTV coverage along the bone flap (cases 2 and 3; Fig. 1). We hypothesized that the proximity to the venous sinus, contact with the dura, and extent of postoperative blood products contributed to this variability.

The consensus STAPLE CTV contour generated highlighted several consistencies. First, the surgical tract was typically included in the consensus contour even for deep tumors (eg, case 9). Second, for tumors with initial dural contact, the consensus CTV contour typically extended a few millimeters along the dura, overlying the bone flap (eg, cases 1, 2, 5, 6, 7, and 10). Finally, the consensus CTV contour extended a few millimeters radially beyond the initial sinus contact for the case with preoperative venous sinus contact (case 2).

The observations from the consensus CTV contours prompted a directed follow-up survey that was completed by the participants. The goal of the survey was to corroborate the observations seen for the consensus CTV contour. As a result of the survey and the observations among the consensus contours, 5 recommendations for completely resected cavity CTV contouring were generated (Table 2). Ultimately, these recommendations highlight that the surgical cavity CTV should not just encompass the preoperative volume but should also account for changes seen on the postoperative scan and encompasses potential adjacent areas of microscopic disease. Although this does increase the volume of normal tissue that could potentially be exposed to radiation, the late effects such as sinus stenosis and radiation necrosis were thought to be minimal. The N107C trial included a 2-mm expansion around the cavity; however, the surgical access tracks for deep lesions were not specifically targeted. Also, the patterns of failure relative to the CTV were not reported (10, 11). For another important study recently reported that had randomized postoperative SRS versus observation for patients with resected brain metastases (19), a separate abstract was presented at the International Stereotactic Radiosurgery

Table 1 Absolute kappa agreement, sensitivity, and specificity for CTV among participating clinicians using STAPLE analysis

Case no.	Sensitivity	Specificity	Kappa measure
1	0.81 ± 0.13	0.98 ± 0.02	0.74
2	0.51 ± 0.20	0.99 ± 0.02	0.43
3	0.71 ± 0.19	0.97 ± 0.05	0.52
4	0.75 ± 0.14	0.98 ± 0.03	0.64
5	0.71 ± 0.21	0.98 ± 0.03	0.62
6	0.74 ± 0.17	0.98 ± 0.03	0.63
7	0.92 ± 0.06	0.97 ± 0.03	0.83
8	0.83 ± 0.11	0.98 ± 0.02	0.74
9	0.71 ± 0.17	0.99 ± 0.01	0.66
10	0.81 ± 0.16	0.96 ± 0.05	0.65

Abbreviations: CTV = clinical target volume; STAPLE = simultaneous truth and performance level estimation.

Data presented as mean ± standard deviation.

Society. The authors analyzed the local failure patterns for the patients who had undergone SRS. Of the 64 patients randomized to postoperative SRS, 12 developed local failure. One-quarter of the local failures were at the margin, and all had had preoperative dural involvement. This suggests that CTV coverage along the meningeal margin might need to be more generous to improve local control. To accurately identify the preoperative tumor extent, including dural involvement, preoperative T1-weighted gadolinium-enhanced MRI is preferred; however, further study is required to clarify whether this will improve outcomes.

Several limitations in the present study are worth noting, including that the recommendations are limited to the clinical scenarios chosen for study. Unique scenarios such as whether the resection was subtotal, the presence of pre- or postoperative hemorrhage, and cases in which the surgical cavity is very difficult to visualize were not addressed in our guidelines; however, the method used in the present study could be used. Although the cases were selected to represent common clinical scenarios, clinical judgment is still required to address the unique factors in each patient's case. Additionally, these guidelines were not determined from pattern of failure analyses or treatment toxicity, and future clinical validation is necessary.

Table 2 Recommendations for CTV contouring for postoperative completely resected cavity SRS

Recommendation
CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding edema determined by MRI
CTV should include entire surgical tract seen on postoperative CT or MRI
If the tumor was in contact with the dura preoperatively, CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact
If the tumor was not in contact with the dura, CTV should include a margin of 1 to 5 mm along the bone flap
If the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1 to 5 mm along the sinus

Abbreviations: CT = computed tomography; CTV = clinical target volume; MRI = magnetic resonance imaging; SRS = stereotactic radiosurgery.

Conclusions

To the best of our knowledge, the present study is the first to establish guidelines for CTV contouring in patients undergoing cavity SRS after complete resection of brain metastases. These guidelines are designed to provide readers with recommendations for safe and effective treatment based on expert contours. However, issues such as the role of preoperative MRI, the extent of CTV contouring in the surgical tract, and expansion along the dura or venous sinus could be altered or refined with further data. Clinical judgment is still required on a case by case basis until these recommendations have been validated by clinical outcomes and patterns of recurrence.

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