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ORIGINAL
RESEARCH

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BACKGROUND AND PURPOSE: To improve the resection rate of unexpected residual pituitary tumor under image guidance, iCT provides a less time-consuming and more convenient approach of promising the safety of the trans-sphenoidal surgery. However, iCT was thought to have worse image quality than MR imaging. This study was designed to determine the predictive concordance of iCT with standard postoperative high-strength MR imaging for the detection of residual tumors.

MATERIALS AND METHODS: From February to December 2009, 33 patients with pituitary macroadenomas were enrolled in this prospective study. All patients received endoscopic trans-sphenoidal surgery for tumor removal and underwent iCT before the surgery finished. If an accessible tumor remnant was suspected and resectable, the surgery was continued. To assess the accuracy of intraoperative evaluation of tumor resection, the intraoperative findings were compared with MR imaging findings obtained 2 to 3 months after surgery by individually calculating the residual tumor volume.

RESULTS: There were no statistically significant differences in the comparison between iCT and postoperative MR imaging findings ($P > .05$), and the predictive rates were also high (R^2 value >0.9). The GTR rate in the case of the noninvasive and fresh cases was 89% (17/19). The overall GTR rate was 58% (19/33), the second-look rate was 21% (7/33), and only one-fourth of the recurrent cases reached GTR.

CONCLUSIONS: The extent of resection in trans-sphenoidal surgery can be reliably assessed by iCT. Compared with postoperative MR imaging findings, the findings in this study provided quantitative evidence that iCT not only holds significant promise for maximizing the extent of tumor resection but also eliminates the unnecessary blind surgical manipulation, thus increasing the safety of the procedure.

ABBREVIATIONS: DLP = dose-length product; E = effective; GTR = gross-total tumor resection; iCT = intraoperative CT; iMR imaging = intraoperative MR imaging; NFPA = nonfunctioning pituitary adenoma; OR = operating room; STR = subtotal tumor resection

Trans-sphenoidal resection is a well known surgical procedure currently used in the treatment of sellar and parasellar lesions for $>90\%$ of all pituitary tumors. In certain cases, operative identification of the lesion and achieving a complete resection can be problematic.¹⁻³ Although technical advances have improved visualization of the sella, in some cases, the inability to directly visualize all of the tumor bed at the time of surgery contributes to suboptimal tumor resection. In these cases, residual tumor is typically treated by either a second operation or some form of radiation therapy, both of which present the patient with additional treatment-related risks.^{4,5} Intraoperative imaging

procedures have been devised in an attempt to increase the effectiveness of the surgery, including plain x-ray, fluoroscopy, ultrasonography, iCT, and iMR imaging.⁶⁻⁹ Plain x-ray and fluoroscopy are limited to defining bony anatomy, usually in a single plane, and they are primarily helpful in identifying the floor of the sella turcica. Ultrasonography has been used recently to detect both micro- and macroadenomas during trans-sphenoidal surgery.^{7,8}

The implementation of iMR imaging in standard neurosurgical procedures has been widely appreciated because of its ability to immediately control tumor resection. In addition, it offers more accurate intraoperative lesion localization and assessment of tumor resection, which allows intraoperative modification of the surgical strategy. Despite the reported improved outcomes in the extent of tumor resection with iMR imaging, its widespread use has been limited by its prohibitive cost, as well as the associated increase in the duration and logistic complexity of surgery.^{1,2,6}

However, iCT scanning is significantly faster and less expensive than iMR imaging, and the image quality from the volumetric CT scanner is excellent.⁹ In this study, a novel and scientific method was introduced to compare the accuracy of iCT and MR imaging.

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Materials and Methods

Patient Population

From February to December 2009, 33 patients who harbored pituitary macroadenomas were enrolled in this prospective study. All patients received endonasal endoscopic trans-sphenoidal surgery for tumor removal. Four of the patients had previous transsphenoidal pituitary surgery, and all patients underwent iCT (CereTom; NeuroLogica, Danvers, Massachusetts) before the surgery was completed. A routine postoperative MR imaging was obtained within 2 to 3 months after surgery. The patient details are summarized in the On-line Table. The local ethics committee approved the iCT, and signed informed consent was provided in each case. Approval also was obtained from the institutional review board.

Setup of OR

The iCT system consisted of a radiolucent adjustable, flexible, rotating operating table. This carbon-made OR table allows the patient to be placed in any position, including prone, supine, park bench, and sitting. Scanning is possible in all positions except sitting. The scanner is controlled by a wireless portable computer outside the OR. This setting enables CT image acquisition without any radiation exposure to personnel, because personnel are not required to stay in the OR during image acquisition. If needed during surgery, the portable iCT scanner is wheeled into position around the patient's head and guided into alignment with the assistance of a laser marker. CT images are then acquired and displayed in a multiplanar manner on the flat-screen video monitor within 3 minutes, for instant review, and the portable iCT is wheeled out of position.

Radiation Dose

Patient E doses were estimated by calculating the DLP, which was converted into an E dose by using an E/DLP conversion factor of $2.2 \mu\text{Sv}/\text{mGy cm}$. A typical scanning length is 19 cm, corresponding to an average DLP of 770 mGy cm. The resultant average patient E dose for every CereTom iCT examination is thus 1.7 mSv.^{10,11}

Trans-sphenoidal Surgery Assisted with iCT

Head fixation is not required in trans-sphenoidal surgery, and the entire procedure is identical to that performed in a regular OR. The surgery is routinely accompanied by endonasal endoscopy, by using 0 and 30° 4-mm rigid endoscopes (Karl Storz, Tuttlingen, Germany), which visualize the surgical site on a monitor. If the intraoperative imaging depicted some residual tumor that seemed to be accessible for further resection, surgery was continued when the procedure was deemed safe. After further resection, we did not perform a repeated iCT because it was possible to remove the residual resectable tumor via direct vision, thereby avoiding additional radiation exposure.

Imaging Interpretation

At the time of surgery, the surgeon interpreted the iCT imaging findings and then determined whether there was need for further resection. At a later time, the neuroradiologist, who was blinded to the earlier reading, provided an independent retrospective evaluation of the iCT, as well as the pre- and postoperative MR images, in an attempt to decrease the reporting bias. Postoperative MR imaging findings were interpreted as GTR if enhancement included solely normal pituitary gland and granulation tissue or as STR if residual enhancement other than that of the normal pituitary gland and granulation tissue was evident.

Subgroups and Tumor Volume Calculation

In this study, we divided patients into 2 groups, the GTR group and the STR group, and assessed in a quantitative manner whether the use of iCT could replace iMR imaging without compromising the extent of the tumor resection of pituitary macroadenomas. To quantitatively define the resection status, the volume of residual tumor tissue was assessed and calculated in the iCT, pre-, and postoperative 1.5T MR images, respectively, by using the software OsiriX (www.osirix-viewer.com). We determined the preoperative volume as volume A, the intraoperative volume as B, and postoperative volume as C and to minimize the calculating bias, volumes A, B, and C were the averages individually computed from the axial, sagittal, and coronal images. In addition, A_1 , B_1 , and C_1 stood for the tumor volumes of patient 1; A_2 , B_2 , and C_2 for those of patient 2, and so on ($n = 33$). We excluded 5 patients who did not receive repeated iCT after a second-look extended resection. As mentioned, in cases defined as GTR, the volume obtained was associated with normal pituitary gland and granulation tissue. To establish and standardize the average volume of normal pituitary gland and granulation tissue after a GTR of pituitary adenoma, we calculated the average volume of residual pituitary gland and granulation tissue, which was regarded as the baseline, of another 12 GTR patients who were followed up for a long time after trans-sphenoidal pituitary surgery. The values of B and C were obtained and compared in each patient to determine the predictive concordance of iCT with standard postoperative high-strength MR imaging for detection of residual tumor and the rate of GTR.

Statistical Analysis

Statistical analysis was performed by using SPSS 17.0 (SPSS, Chicago, Illinois). The Student *t* test (2-sample assuming unequal variances) and a simple regression test were used to compare the group means. The level used to determine statistical significance was a *P* value $< .05$. We did not apply the value B/A and C/A in the statistical analyses because in the GTR group, the volume of B and C was so tiny that the values of B/A and C/A varied considerably and therefore produced a significant bias. The values of B and C were compared in all of the 28 patients in the GTR and STR groups.

Results

In total, 33 patients with pituitary macroadenomas were enrolled in our study, including 21 men and 12 women, with a mean age of 49 ± 16.8 years (12–80 years), among whom 29 patients were fresh cases and 4 were cases of recurrent tumors. Ten of the patients had high-grade cavernous sinus invasion. The GTR group included 18 fresh patients and 1 recurrent patient (13 men, 6 women); the STR group included 14 patients (8 men, 6 women), 3 of whom were recurrent cases. Seven patients had a second-look operation after iCT, and 5 of these patients underwent further resection for residual tumor. These 5 patients were excluded (3 in the GTR group and 2 in the STR group) because they did not have another iCT after an extended second-look resection to avoid unnecessary additional radiation exposure. Their data were excluded from the statistical analyses. The mean tumor size was 3.1 cm (1.2–5.8 cm) in maximal diameter, and the mean tumor volume was 12.09 cm^3 ($0.82\text{--}56.35 \text{ cm}^3$).

There were no statistically significant differences in the comparison between volumes B and C in all 28 patients ($P = .876$), as well as in either the GTR group ($P = .085$) or the STR group ($P = .816$). By using the simple regression test, the pre-

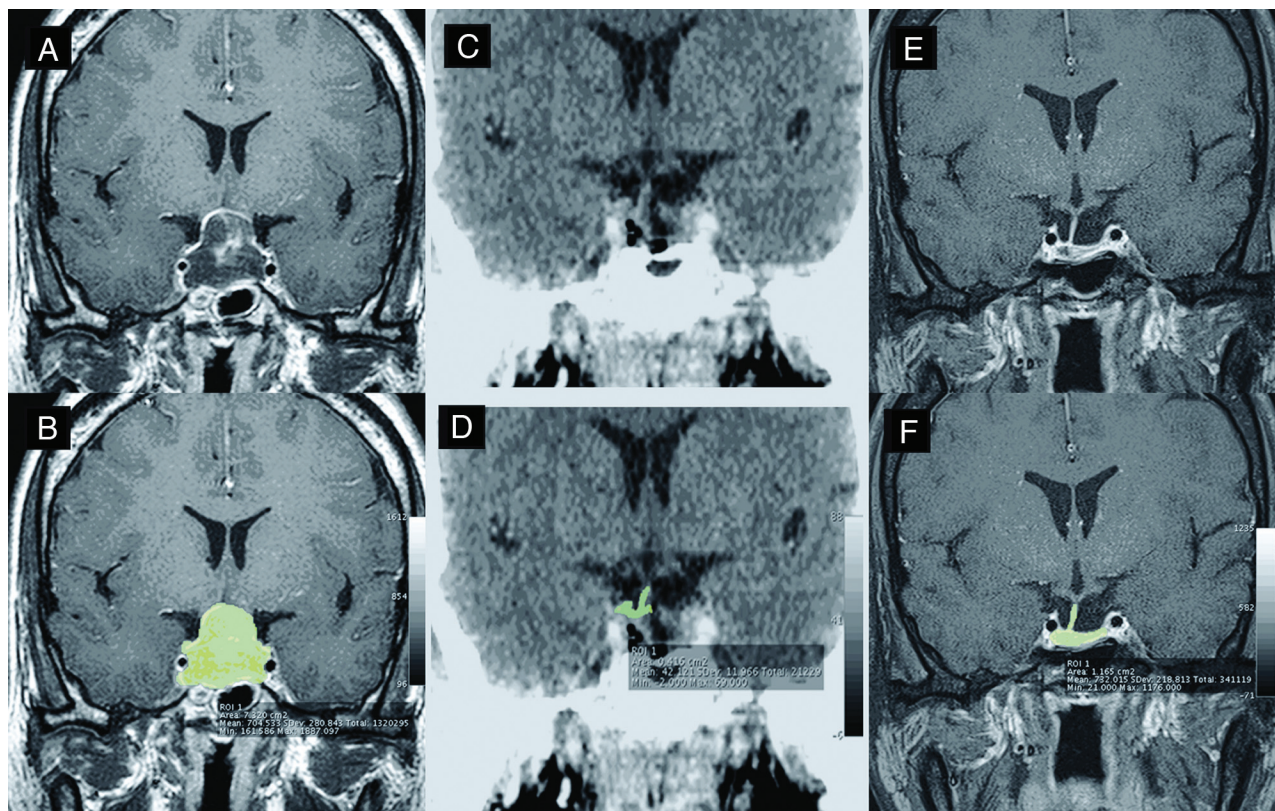


Fig 1. Case 22. Representative example of a correct prediction of GTR by iCT. *A*, Preoperative T1-weighted coronal contrast-enhanced MR imaging scan. *B*, The bulk of tumor is brushed in green. *C*, iCT images demonstrate only stalk and gland enhancement without residual tumor. *D* and *F*, The brushed normal stalk and gland are calculated to obtain the volume. *E*, Postoperative MR imaging demonstrates no residual tumor as well.

dictive rates were high between volumes B and C in all 28 patients (R^2 value = 0.971), as well as in the GTR group (R^2 value = 0.927) and the STR group (R^2 value = 0.957).

Another 12 GTR patients were followed up over an average of 25 months (12–43 months), and their mean calculated volume of normal pituitary gland and granulation tissue was 0.30 cm³ (SD, 0.05 cm³). In our series, the values of B and C in the GTR group were all distributed within the range 0.20–0.40 cm³ (0.30 cm³ ± 2SD).

The GTR rate in the noninvasive and fresh cases (the 2 failed cases were giant adenomas) was 89% (17/19). The overall GTR rate was 58% (19/33), the second-look rate was 21% (7/33), and only one-fourth of the recurrent cases reached GTR. No central nervous system infections or other disastrous complications occurred. Mild CSF leakage and diabetes insipidus were the 2 major complaints. Two cases illustrated the application of iCT and volume calculation during and after surgery. GTR was achieved and confirmed both in the iCT and postoperative MR images in a 49-year-old male patient harboring pituitary adenoma with suprasellar extension (case 22 in Fig 1). STR was demonstrated in the iCT and postoperative MR images in another 12-year-old male patient (case 10 in Fig 2) who had invasive pituitary adenoma.

Discussion

Trans-sphenoidal endoscopic surgery is a well-established, safe, and highly efficient therapy for pituitary adenomas and other sellar lesions. It allows decompression of the optimal neural structure and chances for endocrinopathy rever-

sal.^{6,11–15} Although little direct evidence shows that the maximal extent of resection minimizes the risk of recurrence, the size of the original tumor has been significantly correlated to tumor recurrence. Larger tumors correlate with a higher chance of postoperative residual tumor,^{16–20} and a higher recurrence rate. In addition, the size of the residual tumor has been shown to be an independent predictor of the response to adjuvant radiation therapy, with higher remission rates for smaller lesions.

For hormonally active lesions, excessively produced hormones can serve as tumor markers. For NPFA, however, an early prognosis of the outcome is not possible.²¹ In such cases, morphologic assessment of the radicality of tumor resection is more important, and it is the most sensitive diagnostic tool. However, the intraoperative assessment of the completeness of tumor resection is frequently very difficult, even for an experienced surgeon,³ who would expect a relatively high rate of intraoperative uncertainty with respect to the presence or absence of residual tumor. The ability to evaluate the precise extent of resection at the time of surgery is important to eliminate the need for unnecessary manipulation and further reoperation for the residual tumor; furthermore, the postoperative radiation treatment for the residual tumor can be decided as soon as possible.

Intraoperative imaging during surgical procedures offers the advantages of more accurate intraoperative lesion localization, assessment of tumor resection, and detection of complications. Among these procedures, iMR imaging provides valuable information that allows intraoperative modification of

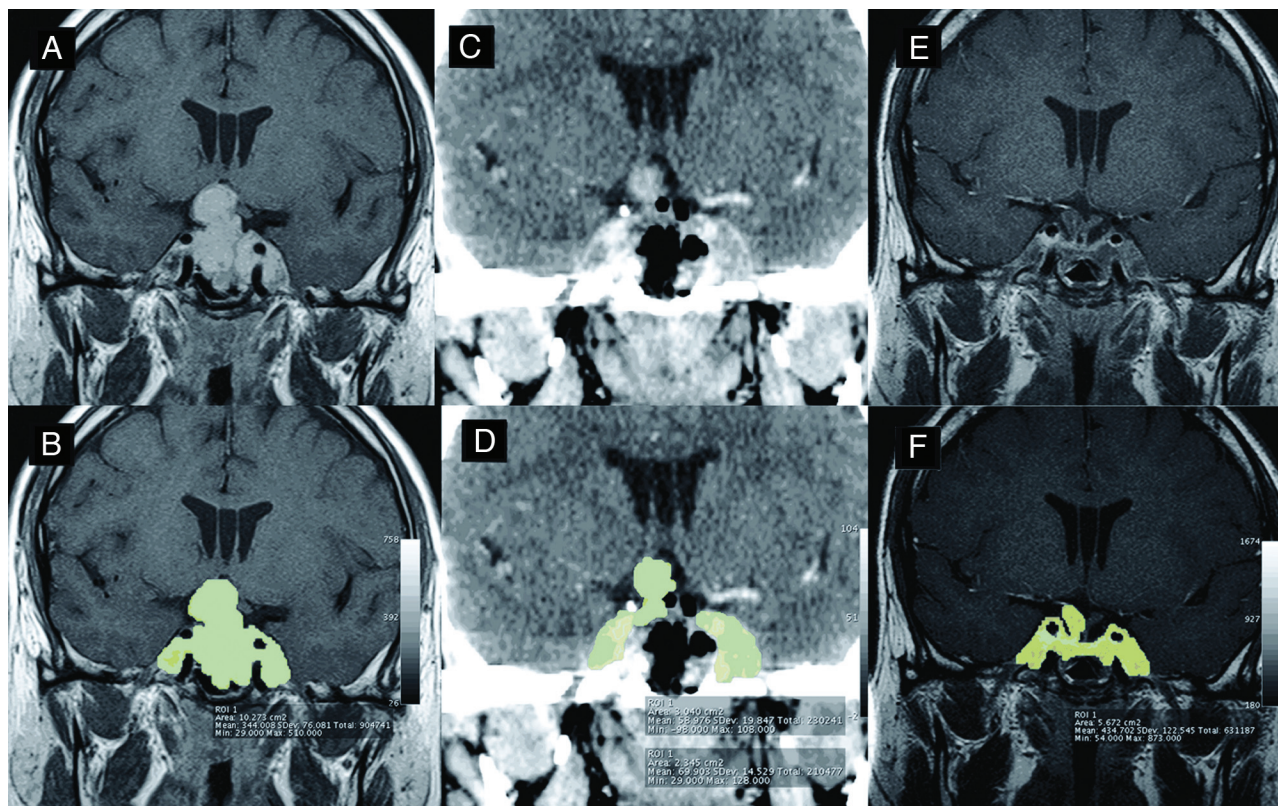


Fig 2. Case 10. Representative example of a correct prediction of STR by iCT. A, Preoperative T1-weighted coronal contrast-enhanced MR imaging scan discloses the invasiveness (Knosp classification grade IV). B, D, and F, The brushed areas are computed to obtain the volume. C, iCT image reveals partial resection. E, Postoperative MR imaging also demonstrates the residual remnants.

the surgical strategy. Investigators have reported enhanced resections when using iMR imaging, leading to complete tumor removal in a larger proportion of cases.²² In contrast, if the iMR imaging confirms complete removal, there is no need for imaging after 3 months; a regular follow-up after 1 year will be sufficient.

Since the mid-1990s, several new high- or low-field iMR imaging systems have been introduced.^{23–26} However, low-field iMR imaging is generally only useful in ensuring the removal of suprasellar tumors and provides unsatisfactory image quality. High-field iMR imaging has a great advantage over low-field iMR imaging in terms of image quality. Unfortunately, high-field iMR images are difficult to obtain because the centers having access to intraoperative high-field MR imaging are few. In addition, the implementation of iMR imaging calls for many ergonomic and financial considerations; the question concerning the capability of reconstruction measures and shielding of the OR, the available investment budget to purchase the iMR imaging system, and the requirements to use the scanner either strictly for intraoperative scans or also for diagnostic purposes.²⁷ In addition, the instruments and tools used need to be MR compatible, that is, the materials they are made of cannot be magnetically attractive. Electrical devices must not produce signals that interfere with image acquisition. Despite the reported improved outcomes in the extent of tumor resection with iMR imaging, its widespread use has been limited by its prohibitive cost, as well as the associated extension in operative time and complexity of surgery.

The iCT system is significantly faster, more easily operated,

and less expensive than the iMR imaging system and provides greater bony resolution, which is the primary concern for most sinus operations. In pituitary surgery, iCT is sufficient to detect tumor remnants in macroadenomas. The new generation of CT scanners offers a multitude of hardware and software improvements; with the modern technology of multislice scanners, image quality has greatly improved and acquisition time has become extremely rapid.^{9,28} Moreover, an iCT scan can detect an intracranial hemorrhage sooner than iMR imaging. In the case of hemorrhage from the sellar region, iCT was able to detect that blood ruptured into the third and lateral ventricles and thereby facilitated the rapid placement of an external ventricular drain. As mentioned, the resultant average patient effective dose for every iCT scan is thus 1.7 mSv. This radiation exposure is typical for head examinations performed on any CT scanner where adults receive between 1 and 2 mSv.^{10,11}

In this study, we compared iCT images with postoperative MR images to determine their concordance. The results demonstrated that there were no statistically significant differences between the volumes calculated from iCT and postoperative MR imaging not only in all patients but also in the 2 subgroups. This implies that iCT had a high concordance with the standard postoperative 1.5T high-resolution MR imaging. In another method, we used the simple regression test to assess the predictability between iCT and postoperative MR imaging, and it indicated that iCT is extremely helpful in delineating the extent of tumor resection during surgery and predicting residual tumor volume postoperatively. Furthermore, we

cannot overemphasize that the tumor volume obtained in GTR cases represents normal pituitary gland and granulation tissue rather than residual or recurrent tumor. In addition, to minimize the bias, we computed the normal pituitary gland and granulation tissue in another 12 GTR patients who were followed up for an average of 25 months. We found that the B and C values in the GTR group were distributed between 0.20 and 0.40 cm³ (mean $\pm$ 2SD), which indicates that in our GTR group the volume of B and C did not vary much over time and represented the real volume of normal pituitary gland and granulation tissue after GTR. As mentioned, we excluded the values B/A and C/A in the statistical analyses because of their significant variation.

After reviewing the reported series, the GTR rate of NFPA via the endoscopic trans-sphenoidal approach was achieved in 61.4%–70.2% of the patients, despite the large volume of NFPA at diagnosis.^{29,30} Although the GTR rate of large pituitary adenomas is approaching 50% in specialized centers, the results achieved in smaller surgical series seem less favorable, ranging from 14.3% to 43.1%.^{31–37} In our patients, the GTR rate reached 89% (17/19) in the noninvasive and fresh cases (the 2 failed cases were giant adenomas) with aid of iCT. The overall GTR rate was 58% (19/33) in all our patients, and 62% (18/29) in the fresh cases, despite the preoperative tumor volume and invasiveness, which seems compatible with the previous results.^{29,30} However, with the routine use of iCT and endoscopic direct vision, we believed that we could maximize the radicality of tumor resection as much as possible with iCT assistance, while simultaneously facilitating the earlier postoperative radiosurgical treatment of residual tumor. We also provided a more quantitative method for estimation of the extent of tumor resection. In addition, iCT was less time-consuming, less expensive, and more convenient than iMR imaging.

The second-look rate was 21% (7/33) in our patients, 5 of whom underwent further resection. To avoid extra radiation exposure, we did not repeat iCT. After further resection via the direct vision of the endoscope and the guidance of iCT, the demonstration of residual tumor volume reduction in the postoperative MR imaging implied that repeated iCT was not necessary. Another 2 patients underwent the second-look procedure, but due to the fibrous, fixed, and hard characteristics of the residual tumors, no further extended resections were performed.

Conclusions

The extent of tumor resection in trans-sphenoidal surgery can be reliably assessed by iCT. Compared with postoperative MR imaging, iCT provides good guidance for residual tumor resection, and it not only holds significant promise for maximizing the radicality of tumor resection but also increases the percentage of complete removals without any major complications. Simultaneously, it eliminated the need for blind surgical manipulation, which increases the safety of the procedure. The results of our study demonstrate that not only are the findings with iCT compatible with or even better than the iMR imaging findings but also that the iCT technique is less time-consuming, less expensive, and more convenient.

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