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AJNR Am J Neuroradiol published online 10 January 2013
http://www.ajnr.org/content/early/2013/01/10/ajnr.A3378

Published January 10, 2013 as 10.3174/ajnr.A3378

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ABSTRACT

BACKGROUND AND PURPOSE: T2-weighted MRI shows potential in early posttreatment assessment of the primary tumor. Residual masses composed entirely of low T2-signal scar tissue suggest local control and those ≥1 cm of similar signal to untreated tumor suggest local failure. The purpose of this study was to investigate the diagnostic accuracy of T2-weighted MR imaging early after chemoradiotherapy for identifying primary tumor treatment failure in squamous cell carcinoma of the head and neck.

MATERIALS AND METHODS: At 6 weeks after treatment, T2-weighted MR images of 37 primary tumors in 37 patients were assessed. Residual masses were divided into 3 patterns: pattern 1 = scar tissue only (flat-edged/retracted mass of low T2 signal intensity); pattern 2 = mass without features described in pattern 1 or 3; and pattern 3 = any pattern that included an expansile mass ≥1 cm of intermediate T2 signal intensity (similar grade of signal intensity to the untreated tumor). T2 patterns were analyzed for local outcome (Fisher exact test) and time to local failure (univariate and multivariate analysis of T2 pattern, age, T stage, and tumor size by use of the Cox regression model).

RESULTS: Residual masses after treatment were present in 34 (92%) of 37 patients. Local failures occurred in residual masses with pattern 1 in 0 (0%) of 14 patients; pattern 2 in 6 (55%) of 11 patients; and pattern 3 in 9 (100%) of 9 patients. Significant associations were found between local control and pattern 1 ($P = <.0001$; sensitivity, 74%; specificity, 100%; PPV, 100%; NPV, 75%; accuracy, 85%), and between local failure and pattern 3 ($P = <.0001$; sensitivity, 60%; specificity, 100%; PPV, 100%; NPV, 76%; accuracy, 82%). Pattern 2 showed no significant associations with local outcome. Univariate analysis of time to local failure showed that the T2 pattern was significant ($P < .0001$) and remained significant on multivariate analysis.

CONCLUSIONS: T2-weighted MR imaging is a potential tool for early posttreatment assessment of primary HNSCC treatment response. Awareness of correlation of the T2 pattern of any residual mass with treatment outcome at the primary site may contribute to patient treatment.

ABBREVIATIONS: CI = confidence interval; CRT = chemoradiotherapy; HNSCC = head and neck squamous cell carcinoma; NPV = negative predictive value; PPV = positive predictive value

Patients with HNSCC who have a residual tumor at the primary site after CRT benefit from salvage surgery.[1] It is generally considered desirable to perform salvage surgery 4–12 weeks after CRT in the window between acute and chronic treatment-induced effects,[2] and surgical outcome is reported to be better when the residual tumor is detected at an earlier T stage.[3] Posttreatment imaging is important for the identification of residual cancer, but scarce data exist regarding the accuracy of MR imaging in the early posttreatment period.[4,5] In addition, there is currently no clear consensus on the optimal criteria for assessment of posttreatment response with use of MR imaging. One scoring system that has been evaluated is based on the measurement of the size of a residual mass in the primary tumor bed. With this scoring system, which was developed for CT[6-8] and applied later to MR imaging,[4,5,9] the likelihood of residual cancer is assessed as low when there is an absence of a focal mass; indeterminate when a focal mass is <1 cm; and high when a focal mass is ≥1 cm. The absence of a residual mass is reported to correlate well with a low likelihood of residual cancer, but the presence of a residual mass has

Received June 1, 2012; accepted after revisions August 23.

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The work described in this study was fully supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04).

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http://dx.doi.org/10.3174/ajnr.A3378

shown less consistent correlations with outcome, and even masses ≥1 cm by CT/MR imaging have been reported to harbor residual cancers in ranges that vary from 90%–96%[6,7,9] to 8%–40%.[4,5,8] Incorporation of the MR imaging signal characteristics of a residual mass may improve the diagnostic accuracy of this scoring system. The T1-weighted postcontrast sequence is of limited value because both malignant and benign posttreatment masses show contrast enhancement.[10] On the contrary, the T2 signal is of potential value because scar tissue typically displays very low T2 signal intensity, whereas a tumor displays higher T2 signal intensity.[11-16] Although this difference in T2 signal intensity has been known for many years, there is a paucity of published data on the use of T2-weighted images in the early posttreatment period and, to our knowledge, none that combine this information with the scoring system based on the size of a residual mass.

Current MR imaging research into treatment response to head and neck cancer is focusing on functional MR imaging techniques such as diffusion-weighted imaging. Limited attention is being paid to the development of criteria based on conventional MR imaging; in particular, the potential value of T2-weighted MR imaging in the early posttreatment period is underappreciated. The aim of this study was to incorporate T2 signal intensity of any residual mass into the current size-based scoring system and to use the MR imaging criteria for determining treatment response in the primary tumor bed of HNSCC at 6 weeks after the end of CRT.

MATERIALS AND METHODS

Patients

A total of 43 patients with a primary HNSCC of the upper aerodigestive tract were recruited for either of 2 functional MR imaging studies between 2004 and 2008. These studies were performed with written informed consent and institutional review board approval. The patients underwent an MR imaging examination before treatment and 6 weeks after treatment and were available for 2-year follow-up in this retrospective study. Six patients were excluded because they died from nodal or distant disease before completion of 2-year follow-up of the primary site. The remaining 37 patients (34 men and 3 women) with a mean age of 57 years (age range, 45–71 years) who had primary tumors located in the oral cavity/oropharynx ($n = 17$), hypopharynx ($n = 13$), larynx ($n = 5$), and cervical esophagus ($n = 2$), underwent concurrent CRT with cisplatin and a course of accelerated concomitant boost radiation therapy ($n = 36$) or radiotherapy alone ($n = 1$). After this treatment, regularly scheduled clinical and radiologic follow-up examinations were performed, including MR imaging examinations at 6 weeks, 6 months, 12 months, and 18/24 months. Local failure was identified on histologic examination (biopsy or surgical resection), on endoscopic findings, or on an increase in the size of a mass at the primary site on follow-up clinical or imaging examination. Local control was determined by the absence of any new mass or increase in the size of any existing residual mass at the primary site during a follow-up period of at least 2 years.

MR Imaging

MR imaging was performed before treatment and at 6 weeks after treatment (mean, 42 days; median, 41 days; range, 32–53 days) on a 1.5T whole-body system (Intera NT; Philips Medical Systems, Best, the Netherlands) with a 30-mT/m maximal gradient capability. T2-weighted images were obtained in the axial plane by use of turbo spin-echo images with fat saturation (TR, 2500 ms; TE, 100 ms; echo-train length, 15; field of view, 22 cm; section thickness, 4 mm; intersection gap, none; and matrix size, 256 × 202). In addition, a full head-and-neck MR imaging protocol was performed, which included T1-weighted spin-echo images before and after intravenous contrast.

Image Analysis

To evenly cover the range of T2 signal from the low signal intensity of scar tissue to the high signal intensity of necrosis and inflammation, we divided the T2 signal intensity according to subjective visual assessment into 3 grades: 1) low T2 signal intensity (equal or lower than muscle), 2) intermediate T2 signal intensity (higher than muscle but lower than CSF), and 3) high T2 signal intensity (equal to CSF). Pretreatment primary tumors were assessed on MR imaging for T2 signal intensity, the presence or absence of any deep tumor invasion into adjacent tissues (tumor extending into the fat or muscles deep to the mucosa or submucosa was defined as deep extension), expansile or nonexpansile margins, and size (maximal dimension in the axial plane). The T stage was recorded according to the American Joint Committee on Cancer/ Union for International Cancer Control classification. The images from 6 weeks after treatment were analyzed. We reassessed the T2 signal intensity by using the same 3 broad grades described for the pretreatment tumor (an increase or decrease in signal within each grade was not assessed). In addition, the primary tumor bed was assigned to 1 of 4 T2 patterns (patterns 0–3). Pattern 0 denoted complete resolution, defined as no abnormality or expected symmetric changes without a focal mass. Residual focal masses were divided into pattern 1 = mass composed entirely of low T2 signal intensity with flat-edged/retracted margins, without any other T2 abnormalities in the residual mass; pattern 2 = mass without the features defined in pattern 1 or 3; and pattern 3 = mass of intermediate T2 signal intensity similar grade to untreated tumor ≥1 cm in size with expansile margins, irrespective of other T2 signal abnormalities in the residual mass. The size (maximal dimension in the axial plane) of any focal residual mass was recorded. Image analysis was performed by a single radiologist with >15 years of experience in head and neck radiology. An interobserver study was performed by a second observer with >5 years of experience in head and neck radiology. For pattern 2 residual masses, T2 signal intensities of these masses on follow-up MR imaging at 6 months were recorded.

Statistical Analysis

We examined associations between T2 patterns of a residual mass at 6 weeks and local outcome by using the Fisher exact test. We also calculated sensitivity, specificity, PPV, NPV, and accuracy. Time to local failure curves were constructed by the Kaplan-Meier method, and differences between curves were tested by the log-rank test. Univariate analyses of T2 pattern, age, T stage, and maximal tumor size were performed by use of the Cox regression model to assess time to local failure; hazard ratios and corresponding 95% CIs were calculated. Significant parameters were

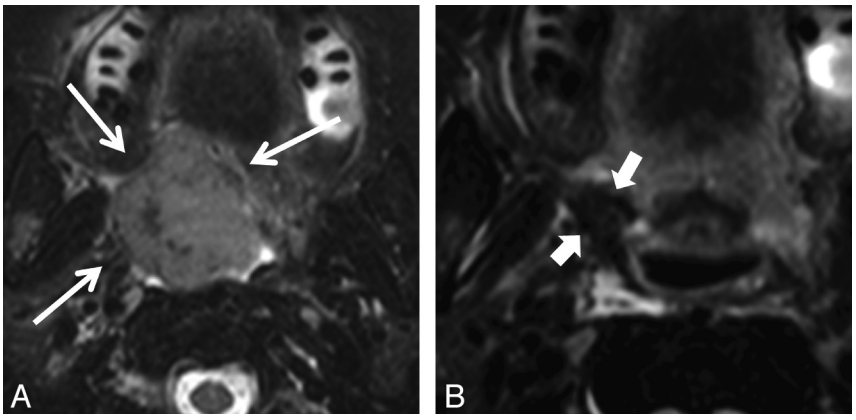

FIG 1. Tonsillar carcinoma control with a pattern 1 residual mass. Axial T2-weighted image shows that (*A*) before treatment the tumor forms an expansile mass of intermediate T2 signal (*thin arrows*) and (*B*) after treatment a retracted mass of low T2 signal mature scar tissue (*thick arrows*).

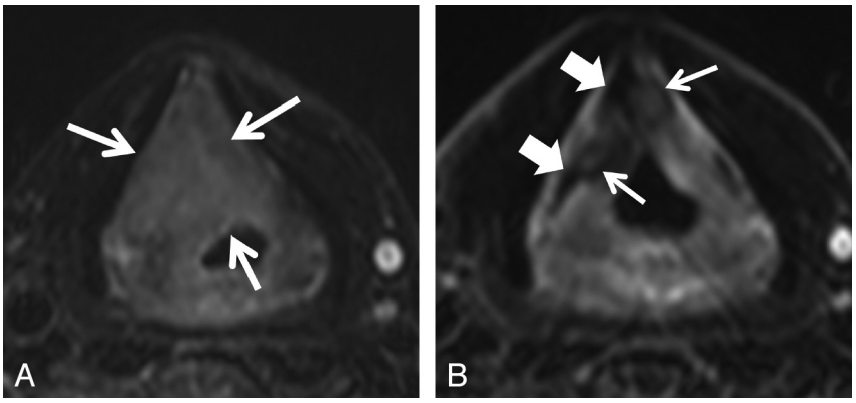

FIG 2. Laryngeal carcinoma failure with a pattern 2 residual mass. Axial T2-weighted image shows that (*A*) before treatment the tumor forms an expansile mass of intermediate T2 signal (*thin arrows*); (*B*) after treatment there is a residual mass of mixed appearance with both low T2 signal mature scar tissue (*thick arrows*) and indeterminate <1-cm expansile intermediate T2 signal (*arrows*). Six months later the expansile intermediate T2 signal component increased in size.

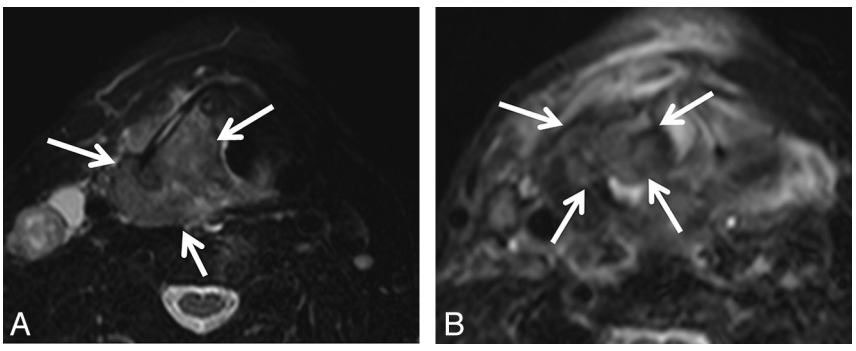

FIG 3. Hypopharyngeal carcinoma failure with a pattern 3 residual mass. Axial T2-weighted image shows a discrete expansile mass of intermediate T2 signal (*A*) before treatment (*arrows*) and (*B*) after treatment which is 1 cm in size (*arrows*).

included in a multivariate analysis. *P* values <.05 were considered statistically significant. SAS version 8.2 (SAS Institute, Cary, North Carolina) was used for the analysis. The agreement between 2 observers independently grading MR imaging examinations for the 4 ordered categories was evaluated by use of the weighted κ statistic.

RESULTS

MR Imaging Findings

Before treatment, all primary tumors were solid, expansile masses of intermediate T2 signal (Figs 1*A*, 2*A*, 3*A*). Some primary tumors also contained a few tiny foci of high T2 signal intensity within the tumor mass or in the overlying mucosa, but none showed any frank necrosis, and all were graded as intermediate signal intensity. T stages were T1 ($n = 2$), T2 ($n = 7$), T3 ($n = 9$), and T4 ($n = 19$) with a maximal size ranging from 1.4 to 7.3 cm (mean and median, 3.5 cm). The 6-week posttreatment MR imaging scans showed complete resolution in 3 tumor beds (pattern 0) and residual masses in 34 tumor beds: pattern 1 in 14 (41.2%) of 34 (Fig 1*B*), pattern 2 in 11 (32.4%) of 34 (Fig 2*B*), and pattern 3 in 9 (26.4%) of 34 (Fig 3*B*). For each T2 pattern (0–3), details of the primary tumors before treatment, range in the size of residual masses after treatment, and local outcomes are shown in the accompanying Table. The weighted κ for the 2 observers grading MR imaging examinations was 0.87 (95% CI, 075–0.98), which indicated a very good level of agreement. Observers agreed on 32 (86%) of 37 studies and differed by only 1 category for each of the 5 remaining cases.

Pattern 2 residual masses (those without features of pattern 1 or 3), consisted of 11 residual masses of mixed intermediate (<1 cm) and low T2 signal intensity, of which 2 had additional high T2 signal intensity areas (laryngeal necrosis and mucosal induration). Local failure occurred in 6 of 11 of these masses that included 1 of 2 masses with high T2 signal (laryngeal necrosis). Follow-up MR imaging in pattern 2 residual masses was performed at 6 months in 5 of 5 patients with local control and in 4 of 6 patients with local failure. All patients with local control showed an increase in the low T2 scar tissue component, whereas all patients with local failure showed an increase in size of the intermediate T2 signal tumor component.

Associations of MR Imaging Posttreatment T2 Patterns at 6 Weeks and Local Outcome

Local control was achieved in 21 (57%) of 37 patients, with median follow-up of 52 months (mean, 53 months; range, 25–81 months). In the 34 patients with a residual mass, when comparing pattern 1 with patterns 2 and 3, we found a significant association

MR imaging T2 patterns of 37 primary tumor beds in 37 patients 6 weeks posttreatment, pretreatment and posttreatment details, and clinical outcome at the primary site

Posttreatment T2 Pattern (0–3)	Pretreatment Primary Tumor	Size of Residual Masses (median in cm; range)	Local Failure[d]	Local Control[e]
0: Complete resolution No focal mass[a]	All tumors of expansile intermediate T2 signal without deep extension (size, 1.7–3.6 cm; stage, T4 = 0)	0 (0.0–0.0)	1	2
1: Scar tissue mass Flat-edged/retracted low T2 signal mass[b]	All tumors of expansile intermediate T2 signal with deep extension (size, 2.0–5.1 cm; stage, T4 = 4)	1.9 (0.7–2.5)	0	14
2: Indeterminate mass Mass without features defined in pattern 1 or 3	All tumors of expansile intermediate T2 signal with deep extension (size, 1.4–7.3 cm; stage, T4 = 7)	2.0 (1.3–3.2)	6	5
3: Residual cancer mass Focal expansile mass ≥ 1 cm in size of intermediate T2 signal[c]	All tumors of expansile intermediate T2 signal with deep extension (size, 2.9–7.3 cm; stage, T4 = 8)	2.6 (2.0–5.4)	9	0

[a] No abnormality or only expected symmetric changes.
[b] Without any other T2 abnormalities in the residual mass.
[c] Irrespective of other T2 signal abnormalities in the residual mass.
[d] Total = 16.
[e] Total = 21.

between local control and pattern 1 ($P < .0001$). Sensitivity was 74% (14/19), specificity was 100% (15/15), PPV was 100% (14/14), NPV was 75% (15/20), and accuracy was 85% (29/34).

Local failure occurred in 16 (43%) of 37 patients (median, 4.5 months; mean, 6.5 months; range, 2.5–17.0 months) and in 1 (33%) of 3 patients without a residual mass (pattern 0): a patient who had a marginal tumor recurrence identified by MR imaging at 12 months, and 15 (44%) of 34 patients with a residual mass (pattern 2 or 3). In the 34 patients with a residual mass, when comparing pattern 3 with pattern 1 or 2, we found a significant association between local failure and a pattern 3 residual mass ($P < .001$). In these findings, sensitivity was 60% (9/15), specificity was 100% (19/19), PPV was 100% (9/9), NPV was 76% (19/25), and accuracy was 82% (28/34).

No significant associations were found between a pattern 2 residual mass and either local failure or local control. The median time to diagnosis of local failure in patients with local failure in a pattern 2 residual mass was longer than that in patients with local failure in a pattern 3 residual mass (6.5 vs 3 months).

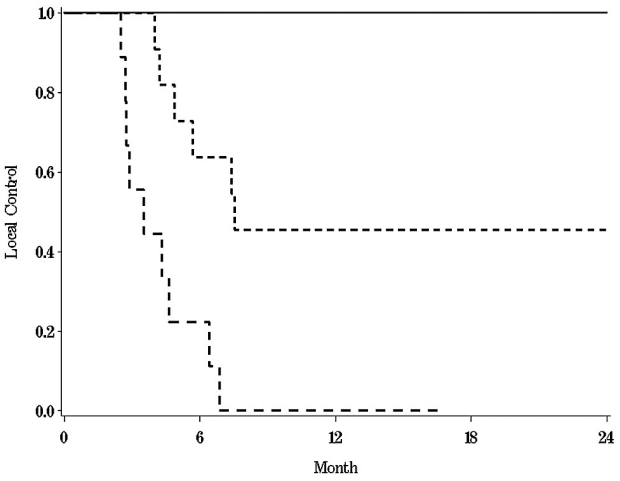

FIG 4. Kaplan-Meier curves showing local control rates for residual masses with patterns 1–3: pattern 1 (*solid line*), pattern 2 (*short long dashed line*), and pattern 3 (*long dashed line*).

Analysis of MR Imaging Posttreatment T2 Patterns at 6 Weeks and Time to Local Failure

Local failure rates at 2 years were 0% for pattern 1, 55% for pattern 2, and 100% for pattern 3 (Fig 4). When the log-rank test was used, significant differences were identified among the 3 patterns ($P < .0001$). On univariate analysis of time to local failure, T2 pattern ($P < .0001$; hazard ratio, 7.4; 95% CI, 3.1–17.7), maximal tumor size after treatment ($P = .0068$; hazard ratio, 1.1; 95% CI, 1.0–1.1), and stage T4 disease ($P = .015$; hazard ratio, 4.8; 95% CI, 1.4–17.2) were significant. On multivariate analysis, only the T2 pattern remained significant.

DISCUSSION

The results of our study show that early posttreatment T2-weighted MR imaging provides valuable information regarding the likelihood of residual cancer in the primary tumor bed of patients with HNSCC. As early as 6 weeks after the end of a course of CRT, the T2-weighted MR imaging sequence identified groups of patients with local control and local failure. A residual mass, regardless of size, which was composed entirely of scar tissue (low T2 signal intensity tissue with a flat-edged or retracted margin), identified patients with local control. A residual mass that included a ≥1 cm expansile area of similar T2 signal intensity to the untreated tumor (intermediate T2 signal intensity) identified patients with local failure.

T2 signal intensity is rarely used as an MR imaging criterion for assessment of head and neck cancer treatment response in the immediate posttreatment setting; when it is used, it is usually to identify residual cancer rather than scar tissue. Furthermore, when T2 signal intensity is used as a criterion for residual cancer, often it is grouped together with enhancement on T1-weighted postcontrast images,[10,17] so the value of the T2-weighted images alone is unknown. By using the system for grading T2 signal intensity described in our study, we determined that all residual cancers were of intermediate T2 signal intensity, similar to that of the untreated tumor (higher signal than muscle but lower than

CSF). When such areas formed a focal expansile mass ≥1 cm in size, the positive predictive value of MR imaging for identification of residual cancer was high. Therefore, this criterion has the potential to be used to direct the site of biopsy for early confirmation of disease. It is worth noting that, although some residual cancers also contained a few small foci of necrosis, high T2 signal intensity overall was a less valuable sign in treatment assessment because frank necrotic residual primary cancers were uncommon.

In addition to use of the intermediate T2 signal characteristics of tumors, the low T2 signal characteristics of scar tissue were also incorporated into the MR imaging assessment criteria. Residual masses that consisted entirely of such scar tissue, independent of size, were associated with a low likelihood of residual cancer. In this scenario, T2-weighted imaging could be used to avoid unnecessary biopsy or further investigation by fluorodeoxyglucose–positron-emission tomography. Low T2 signal scarring was observed to have formed even as early as 6 weeks after CRT and was sited deep to the mucosa and submucosa, being distributed along the underlying structures such as the muscles of the pharyngeal wall. Careful inspection could always identify scarring when the pretreatment tumor had shown deep invasion on MR imaging.

Not all patients in our study could be classified into the 2 groups discussed above. In approximately one-third of patients, the findings on T2-weighted MR imaging were judged to show an indeterminate likelihood of residual cancer. In most of these cases, there was a mass in the primary tumor bed with a mixture of both low T2 scar tissue and small (< 1-cm) areas of intermediate T2 signal intensity. A high proportion of residual masses with an indeterminate appearance developed tumor relapse; therefore, these patients require close clinical and imaging follow-up. In these cases, the 6-week T2-weighted MR imaging was a very useful baseline with which to compare the follow-up MR imaging several months later. Patients with local control showed an increase in the amount of low T2 scar tissue on the follow-up scan, whereas patients with local failure showed an increase in the size of the intermediate T2 signal areas of tumor.

Local tumor recurrence has been reported previously in those patients who show no abnormality, or only expected posttreatment changes, on posttreatment MR imaging.[4] In our study, 1 such patient, who did not have any residual mass on the posttreatment scan, subsequently developed a late marginal tumor recurrence. It is postulated that the residual tumor at the field margin was too small to identify on early posttreatment MR imaging, and this result supports the case for performing surveillance imaging in all patients.

Our study had some limitations, the main one being that it was a retrospective study in a fairly small group of patients. Therefore, the results will require validation by prospective studies with a greater number of patients. The study did not consider the percentage reduction in tumor size because the aim was to emphasize the value of the T2 signal intensity. Also, at present the additional value of use of a reduction of <50%[18] in the size of the tumor to evaluate residual masses measuring <1 cm is unknown.

CONCLUSIONS

Early posttreatment MR imaging has the potential to assess primary HNSCC response to CRT by using MR imaging criteria with T2-weighted imaging. Residual masses could be scored as follows: pattern 1 = focal mass composed entirely of low T2 signal intensity scar tissue, to indicate a low likelihood of residual cancer; pattern 2 = focal mass without features in patterns 1 or 3, to indicate an indeterminate likelihood of residual cancer; and pattern 3 = focal mass containing an area ≥ 1 cm in size of intermediate T2 signal intensity (same grade of signal intensity as the untreated cancer), to indicate a high likelihood of residual cancer. Future studies are required to validate these findings and determine whether combining T2 signal intensity with other MR imaging parameters, such as those obtained from percentage change in tumor size or functional MR imaging parameters, could improve the overall diagnostic accuracy of MR imaging in this challenging clinical setting.

Disclosures: Ann King—*RELATED: Grant:* Research Grants Council of the Hong Kong Special Administrative Region (China).* Chow Kwok Keung—*RELATED: Grant:* Hong Kong Special Administrative Region,* Comments: The work described in this study was fully supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04). Brian (Kwok-Hung) Yu—*RELATED: Grant:* fully supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04).* Kunwar Bhatia—*RELATED: Grant:* Grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04).* David Yeung—*RELATED: Grant:* Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04).* Alexander Vlantis—*RELATED: Grant:* Research Grants Council of the Hong Kong Special Administrative Region,* Comment: The work described in this study was fully supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. 4300/04). Anil Ahuja—*RELATED: Grant:* Research Grants Council of the Hong Kong Special Administrative Region, China, Project no. 4300/04.* (**Money paid to institution.*)

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