Editorial

Intraoperative magnetic resonance imaging and pituitary surgery

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Coburger et al. performed a retrospective study of 2 serial but nonconsecutive groups of patients in which microscope-based, paraseptal, fluoroscopically guided transphenoidal surgery (TSS) was performed for mostly pituitary tumors, in which intraoperative MRI (iMRI) was not used in the first group and was used in the second group. The authors claim that for those patients in whom gross-total resection (GTR) was intended there was a statistically higher rate of GTR in the iMRI group, and for the rest of the patients, in whom GTR was not intended, there was a significantly lower volume of residual tissue in the iMRI group. Based on these data they recommend the use of iMRI for pituitary surgery when the technology is available.

Although several prior studies have already shown that iMRI increases extent of resection, the control group has always consisted of the same patients whose surgeries were halted when the surgeon thought that all tumor was removed, and the experimental group consisted of the same patients after iMRI showed residual tumors. Such a study design leads to bias because the surgeons may have prematurely halted the surgery during the “control” period. The value of this current paper is that 2 supposedly similar groups of patients are compared and there was no iMRI waiting in the operating room during the control group surgery. However, although the authors should be commended for attempting to find a more rigorous control group, this paper is also marred by significant bias in study design, case selection, and surgical technique, and ultimately does not provide us with the most critical information required in establishing the value of iMRI.

The first design flaw is that patients were not contemporaneously randomized to groups with iMRI or no iMRI. The first group of patients underwent surgery between 2007 and 2008, and the second group between 2009 and 2011. The break in the middle occurred during the iMRI learning curve when cases were selectively chosen. The bias of such a study design is the learning curve of the surgeons for TSS. During the iMRI stage of the study the surgeons were also more experienced at performing TSS, and their results should naturally improve over time. Likewise, in the first group the surgeons used fluoroscopic imaging, and in the second group they used stereotactic navigation. Hence, their results could just as easily be a demonstration of the value of stereotactic navigation in TSS.

The second design flaw is that the authors separated out patients in whom GTR was the goal of surgery. Such a decision is inherently subjective. Did both surgeons have exactly the same criteria for choosing patients in whom a GTR could be achieved? Were cases evenly divided between these 2 groups? Was this determination made prospectively or retrospectively? The authors do not state that they kept a prospective database of patients who they thought could get a GTR, so it must have been done retrospectively. This is problematic, because the authors also knew which patients were in the iMRI group and thus were not blinded during this assessment.

Finally, the outcome measurement of the volume of residual tumor is not a good surrogate for extent of resection. Because the authors did not measure preoperative tumor volumes, it is possible that the first group of patients started out with larger-volume tumors and hence may have ended up with larger-volume residual but a similar extent of resection. Additionally, the volume of residual tumor was not statistically different between the 2 groups. The absence of preoperative volume measurements is even more of a concern because the percentage of patients with residual tumor was also not statistically different between the 2 groups. Only the percentage of patients with intentional subtotal resection who had residual intrasellar tumor was significant.

This finding is even less noteworthy because the iMRI group had a higher proportion of functional tumors, which are more likely to be smaller tumors, and the non-iMRI group had a higher percentage of suprasellar tumors, which are larger in volume.

With regard to the authors’ statistically significant findings, the power of their statistics is not robust given the sample size. For example, in the iMRI group there were 4 patients lost to follow-up. If only 1 of these patients did not have a GTR, the authors’ findings would not be statistically significant (p = 0.071; Fisher exact test). As for their second finding, as previously mentioned, the volume of residual tumor is actually not significantly different between the 2 groups; it is the presence of an in-
trasellar tumor remnant that is higher in the non-iMRI group. This is puzzling because these cases presumably were considered not totally resectable based on the presence of parasellar tumor, yet the significant residual lesion was found within the sella itself. The authors would then have to conclude that the primary value of iMRI is foremost for removing all of the tumor within the sella, which is generally considered to be the easiest part of the tumor to remove and the least likely to benefit from technical adjuncts.

Last, the Kaplan-Meier curve shows a trend for increased progression-free survival in the iMRI group. However, the authors have already shown that there were more tumors with suprasellar extent in the non-iMRI group and more functional tumors in the iMRI group, and thus probably more large tumors in the non-iMRI group.

Hence, it is not surprising that there were increased rates of recurrence in this group, particularly because the surgeons were also more experienced and were using stereotactic navigation for the second group. Whether the iMRI played a role in this trend is far from certain. The most robust statistics were that the use of iMRI increased the length of the surgery by 1.5 hours, and that there were 6 CSF leaks in the iMRI group and none in the non-iMRI group (p = 0.029, Fisher exact test); however, the authors did not calculate or report this latter statistic. Moreover, an increase in CSF leaks implies that the surgeons were more aggressive in this group, which may explain the higher rates of GTR.

As a final note on this paper, the authors fail to discuss the fact that the field as a whole is moving away from microscopic surgery to endoscopic surgery. The reason for this transition is that the visualization provided by the endoscope is superior to that of the microscope for nonsellar tumor (that is, suprasellar and parasellar locations). The primary motivation for using iMRI is to visualize residual tumor that is optically beyond the limits of the microscope. The literature substantiates the claim that one can achieve higher rates of GTR and extent of resection by using the endoscope and extended transsphenoidal approaches than can be achieved using the microscope, even with iMRI.

In this series, GTR was achieved in 40 (52.6%) of the 76 patients in the iMRI group, and in 91% when GTR was intended (possibly as low as 83% if you assume that the patients lost to follow-up had a subtotal resection). How does this rate compare with that in endoscopic series? Hofstetter et al. reported GTR of 76% of all tumors > 1 cm and in 92% of tumors in which GTR was the intention of surgery (regardless of suprasellar extent and cavernous sinus invasion). Dehenashiti et al. reported an 88% rate of GTR for all patients with pituitary tumors, and 96% when GTR was the intention of surgery. Finally, the Cincinnati group has shown that while iMRI increases extent of resection in 66% of their patients, they were only able to achieve GTR in 55% (16 of 29). When they adopted endoscopy, the rates of GTR were similar (55%; 15 of 27), with only 1 additional GTR achieved with iMRI. However, the increase in extent of resection was marginal (only 15%), which is remarkably similar to the only other publication that combined endoscopy with iMRI.

In conclusion, although iMRI probably increases extent of resection and rates of GTR for standard microscope-based TSS, the results do not compare to those that can be achieved with the adoption of the endoscope and extended transsphenoidal approaches. Moreover, the endoscope is far cheaper and does not increase the length of the surgery as dramatically as iMRI does. Whether iMRI offers a significant incremental improvement in surgical outcome above those provided by the endoscope and extended approaches is not clear, and will require further investigation, but at this time the data do not justify the incremental cost.

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Disclosure

The author reports no conflict of interest.

References


Response

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I thank Professor Schwartz for his comment, and I appreciate the opportunity to write a reply in this issue. There are several limitations in our study, due to its retrospective nature. The purpose was not to compare resection rates of iMRI-enhanced microsurgical technique with endoscopy, but to analyze the added benefit of iMRI in microsurgical resection of pituitary adenomas. From our point of view this comparison is still up to date, because the majority of neurosurgeons perform pituitary adenoma resection using...
the microsurgical technique. Furthermore, the increasing number of iMRI-equipped neurosurgical operating rooms makes MRI-based intraoperative resection control available to a growing number of surgeons.

There are several ways to overcome the challenges of decreased visibility in a narrow corridor during TSS. Both iMRI and endoscopy are used faithfully in many clinical centers for transsphenoidal pituitary surgery. However, no Class I evidence exists, either for endoscopy or for iMRI, that these techniques are superior to conventional TSS.

We provide the first report of a direct comparison between the conventional transsphenoidal approach and iMRI-assisted surgery. The manuscript addresses one of the key issues in intraoperative imaging: does it improve the extent of resection? Most studies published so far for iMRI and for endoscopy have assessed only the “additional” resection achieved by iMRI or endoscopy by using the same patients as a control group. This, as Professor Schwartz states, has a strong bias. Furthermore, a direct comparison of different studies from different centers and cohorts is of low validity. The retrospective design using 2 historical cohorts in our study shows specific biases. However, it provides the first comparable information about which patients benefit most from iMRI and about respective rates of complications. Furthermore, we show the first description of progression-free survival in conventional surgery compared to iMRI-guided surgery.

The nonrandomized design led to a selection bias, as pointed out by Professor Schwartz. As shown in Table 1 in our paper, more complex cases were treated using iMRI. The selection bias in our study clearly favors negative results for iMRI. Given this fact, it is noteworthy that our data show a significant benefit for the use of iMRI in patients with and without GTR.

Professor Schwartz suggests a possible bias due to a learning curve for the surgeons. However, as mentioned in the manuscript, 90% of surgeries were performed by surgeons who were far beyond their learning curve, with more than 15 years of experience in pituitary surgery. One could rather argue that the first iMRI cases were biased negatively by a learning curve still present in 2009, which again favors negative results in the iMRI group. As reported in the Results section, we tested for a learning curve in the iMRI cohort, comparing results of the first 20 with the last 20 cases, and found no significant differences.

The surgical technique was identical in both groups, except that neuronavigation was only used in selected cases in the conventional group. The routine use of intraoperative neuronavigation is part of the iMRI concept and not a specific bias in our series. Based on our data we are not able to discriminate between the effect of iMRI and neuronavigation, yet we do not regard stand-alone neuronavigation as a relevant factor influencing the extent of resection. Thomale et al. published a retrospective assessment addressing the benefit of neuronavigation in pituitary surgery, and the authors found a value only for complex and recurrent cases. In contrast, we showed that there is a benefit when using iMRI, especially in the “simple straightforward” cases. This finding is one of the most relevant novelties from our point of view.

We think it is very important to distinguish between cases with an intended GTR and cases in which the tumors are not completely removable. As shown in Table 1, the rate of intended GTR negatively correlates with the rate of parasellar extension; a tumor with significant extension into the cavernous sinus is usually not a target for resection, independently of the use of any intraoperative imaging. Especially in these cases, decompression and maximal tumor reduction is the goal. Usually, tumor left behind in the folds of the diaphragm will descend into the sella and present as intrasellar residual tumor at follow-up. From our point of view, volumetric assessment of residual tumor is a good surrogate marker to compare extent of resection in invasive tumors, assuming equal distribution of initial tumor volumes in both groups. Professor Schwartz refers to a higher proportion of larger tumors in the non-iMRI group; however, the opposite is the case. Additionally, in the subgroup of parasellar tumors no functional tumors were present. Although more complex cases were performed in the iMRI setting, progression-free survival of patients in the iMRI group, with and without GTR, tended to be longer in comparison to conventional cases in our series.

Professor Schwartz addressed the fact that there was a higher rate of postoperative CSF leaks in the iMRI group. A significant difference concerning the rate of complications was not found. The rate of CSF leakage was 8% in the iMRI group. Given the fact that a higher share of recurrent disease and larger tumors were found in the iMRI group, the rates are even lower than the typical 10% rate for CSF leaks found in the literature. So far no significant increase of complications when using iMRI has been found in the literature. In endoscopic series the rate of CSF leaks has been reported at a level from 5% to 11%. In small comparative series an increased rate of CSF leaks was found for the endoscopic approach; however, a significant difference with the rate for microsurgical approach was not seen. Techniques like iMRI and endoscopy that are increasing the extent of resection are suspected to increase the rate of CSF leaks. A further evaluation is needed in this regard.

In these days many large neurosurgical centers that do perform TSS on a routine basis host iMRI apparatus. Usually these centers do not acquire such a system for pituitary surgery but for resection control in gliomas. Therefore, the systems are readily available, sometimes even as a two-or-more—room solution for a “quick” pituitary case. Thus the issue of higher costs of an iMRI system in comparison to an endoscopic system is not the main point.

Increased GTR is the aim of any additional imaging technique in pituitary surgery. As pointed out by many experienced pituitary surgeons, the unparalleled view obtained using an endoscopic system is of great benefit in pituitary surgery. Even though using the endoscope enables a surgeon to see around the corner, which might lead to a further detection of residual tumor, it does not enable us to “look behind” structures. A typical example is a suprasellar tumor remnant hidden behind a plica of the diaphragm. Even a low-field iMRI system will easily detect the residual tumor, whereas an endoscopic inspec-
tion might not reveal it without additional risk of incidental opening of the diaphragm.

The recently published rates of GTR performed using the endoscopic transsphenoidal approach are similar to the rates published for high-field iMRI.6,7 Nevertheless, the data so far published allow only limited comparisons of endoscopic and microsurgical techniques in the resection of pituitary adenomas. Much less clear is the role of iMRI as an adjunct to the endoscopic technique. In our study we did not intend to prove the superiority of one or the other technique, or even to make comparisons thereof. The aim was to perform a critical evaluation of the additional benefit of iMRI in microsurgical resection of pituitary adenoma, based on a retrospective comparison of contemporary and historic results in our department.

The published data do not allow one to conclude whether the endoscopic approach or the iMRI-based microsurgical technique is superior or can substitute for each other. Nevertheless, we showed a significant benefit of high-field iMRI as an adjunct to microsurgical transsphenoidal pituitary surgery. A large randomized prospective trial would be needed to address whether similar results can be achieved using the endoscopic approach alone if only a small difference in resection rates is postulated. However, as Schwartz et al.9 stated in 2006, both techniques provide complementary information that can assist the surgeon in maximizing the extent of resection.

References


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