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Reply to Letter to the Editor

Response to letter regarding "Stereotactic radiosurgery for nonfunctioning pituitary adenomas: meta-analysis and International Society of Stereotactic Radiosurgery (ISRS) practice opinion"

We would like to thank the editors for the opportunity to respond to the issues raised by Xu and colleagues and to clarify the key aspects of our meta-analysis of nonfunctioning pituitary adenomas (NFAs) treated with stereotactic radiotherapy.[1] We would also like to thank the authors themselves for broadening the discussion and seeking methodologic clarification.

As described in the Methods, a comprehensive review of the literature yielded several series which consisted of updates on prior reports from the same institution or multi-institutional studies with inclusion of already published patient cohorts. In these situations, duplicate studies were assessed for any updated data on treatment efficacy or toxicity with the latest report of the largest number of patients included in the final analysis: 35 unique studies. The intent of this was to minimize duplication to the greatest extent possible. In fact, we did provide a very detailed and specific evaluation of this issue in the discussion as a potential limitation. Taken verbatim, "every effort was made to prevent overlap of data across studies, and if multi-institutional patient level data were available, this was given preference over individual studies as they would incorporate data from centers which did not always publish individual outcomes. Also, different multi-institutional reports had overlapping time periods of data collection and therefore were included in order to evaluate the maximum number of patients, with partial but unknown quantity of overlap with subsequent studies."[1] Because individual patient level data from each publication are simply unavailable and unobtainable, the best that can be achieved is minimization of overlap, not complete negation of it.

One approach would be to completely reject all datasets with any possibility of overlap. Exclusion of these partially overlapped studies effectively eliminates significant data on 523 patients from multiple institutions, potentially adding even more selection bias. Such an attempt would not allow for representation of institutions that did not publish outcomes independently, and/or would eliminate data regarding longer-term outcomes from institutions that did not subsequently update their own series separately. In support of this, the two multi-institutional reports that were included with potential partial overlap actually addressed different aims. Lee et al only evaluated nonfunctioning adenomas (NFAs) treated with upfront SRS without any surgery (reporting on only 41 patients of a pool of 569 potential patients at 3 centers).[2] Cohen-Inbar et al reported on 357 patients from 8 centers examining the prognostic significance of corticotroph staining.[3] The collective consequence of this is a much smaller patient cohort from far fewer institutions with much shorter follow-up, creating an even more unreliable dataset. This decision is also consistent with the prior literature, including summaries and reports from these institutions, presumably for the same rationale.[4–6]

Xu and colleagues recalculated the pooled weighted effects and concluded that the disease control rate with single fraction stereotactic radiosurgery (SRS) is higher (5-y 98%) than that with hypofractionated stereotactic radiotherapy (HSRT) (5-y 97%). There are two key issues with this simple re-analysis. First, if the multi-institutional reports that Xu and colleagues are concerned about as containing some overlap are removed, then the methodology would require adding back in the single institution reports without duplication (a potential pool of at least 20 studies); this was not performed and therefore their analysis can only be viewed as incomplete. Second, given the inherent selection bias in treating patients with one technique versus another (SRS or HSRT), performing a statistical analysis without propensity matching is flawed and no comparative conclusions can therefore be derived.

In any case, both our original conclusion and that by Xu and colleagues support that stereotactic radiotherapy is an effective and safe treatment for patients with NFAs. Prospective studies will provide us with better evidence to guide our decision making and truly evaluate treatment outcomes in this population. We thank Xu and colleagues for a stimulating discussion.

Keywords

consensus | ISRS | nonfunctioning | pituitary adenomas | radiation therapy | radiosurgery

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