INTRAOPERATIVE ULTRASOUND IN PATIENTS UNDERGOING TRANSSPHOIDAL SURGERY FOR PITUITARY ADENOMA: A SYSTEMATIC REVIEW

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Abstract

Background: Transsphenoidal surgery is the gold standard for pituitary adenoma resection. However, despite advances in microsurgical and endoscopic techniques, some pituitary adenomas can be challenging to cure.

Objective: To determine whether, in patients undergoing transsphenoidal surgery for pituitary adenoma, intraoperative ultrasound is a safe and effective technological adjunct.

Methods: The PubMed database was searched between January 1996 and January 2016 to identify relevant publications that (1) featured patients undergoing transsphenoidal surgery for pituitary adenoma, (2) used intraoperative ultrasound, and (3) reported on safety or effectiveness. Reference lists were also checked and expert opinion sought to identify further publications.

Results: Ultimately, ten studies were included comprising one cohort study, seven case series’ and two case reports. One study reported their prototype probe malfunctioned leading to false-positive results in two cases, and another study that their prototype probe was too large to safely enter the sphenoid sinus in two cases. Otherwise, no safety issues directly related to use of intraoperative ultrasound were reported. In the only comparative study, remission occurred in 89.7% (61/68) of patients with Cushing’s disease in whom
intraoperative ultrasound was used, compared with 83.8% (57/68) in whom it was not.

All studies reported that surgeons anecdotally found intraoperative ultrasound helpful.

Conclusions: Although there is limited and low quality evidence available, the use of intraoperative ultrasound appears to be a safe and effective technological adjunct to transsphenoidal surgery for pituitary adenoma. Advances in ultrasound technology may allow for more widespread use of such devices.

Keywords: Endoscopy; Neurosurgery; Minimally Invasive Surgery; Ultrasound
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Introduction

Transsphenoidal surgery is the gold standard for pituitary adenoma resection. Advances in microscopy and, more recently, endoscopy represent among the most important technological innovations in neurosurgery.\(^1\) However, some pituitary adenomas remain challenging to cure. In contemporary series’ approximately a third of patients undergoing transsphenoidal surgery for pituitary adenoma will have an incomplete resection.\(^2\)

Several adjuncts have been used to improve resection in patients undergoing transsphenoidal surgery for pituitary adenoma. Intraoperative CT and MRI offer high-contrast and high-resolution imaging that are familiar to all neurosurgeons, but have important limitations; the former results in exposure to ionising radiation, the latter requires specialised non-ferromagnetic instruments, and both are costly and significantly interrupt the surgical workflow and prolong the operating time.\(^3\) To this end, intraoperative ultrasound has become an increasingly popular tool in neurosurgery, and provides a relatively inexpensive and simple method of real-time feedback.

The technical specifications for ultrasound probes in transsphenoidal surgery are highly demanding and conflicting; they must be both slender enough to allow for their use within a narrow surgical corridor, and provide imaging of sufficient resolution to allow for meaningful analysis. Nonetheless, ultrasound technology has advanced considerably over the last 20 years, and several devices suitable for transsphenoidal surgery have now been developed.
The aim of the present systematic review was to determine whether, in patients undergoing transsphenoidal surgery for pituitary adenoma, intraoperative ultrasound is a safe and effective technological adjunct.

**Materials and Methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used in the preparation of this manuscript. The PubMed database was searched over a 20-year period between January 1996 and December 2016. The Boolean search term (microadenoma OR macroadenoma OR adenoma) AND (pituitary OR hypophysectomy OR transsphenoidal) AND (ultrasound OR ultrasonography OR sonography) was used. References lists of included articles were also reviewed, and expert opinion sought, to identify further eligible publications. Two authors (HJM and TV) independently identified articles using the above search criteria.

**Inclusion and exclusion criteria**

Titles and abstracts were screened to identify publications that (1) featured patients undergoing transsphenoidal surgery for pituitary adenoma, (2) used intraoperative ultrasound, and (3) reported on safety or effectiveness. Full articles were obtained and further assessed for eligibility. Discrepancies were resolved by discussion with the senior author.

**Data extraction**
The following data was extracted from eligible full articles: (1) study design, (2) study group characteristics including the number of patients and pathology, (3) ultrasound device details, and (4) safety and effectiveness including radiological and endocrine outcomes.

Corresponding authors and device manufacturers were contacted to provide supplemental data when required.

**Appraisal of evidence**

The Jadad and Methodological Index for Non-Randomised Studies (MINORS) scoring systems were used to guide evaluation of the quality of randomised and non-randomised studies respectively. Studies of greater quality were given greater weighting in the qualitative analysis.

**Results**

A total of 997 articles were pooled from the electronic databases, with an additional article identified following expert opinion (Figure 1). Of these, 981 articles were excluded on the basis of their title and abstract because they did not present original data, did not feature patients undergoing transsphenoidal surgery for pituitary adenoma, did not include intraoperative ultrasound, or did not report on safety or effectiveness. Full text screening of the remaining seventeen articles led to the exclusion of a further seven articles. In all, ten studies were identified that satisfied the inclusion criteria comprising one cohort study, seven case series’, and two case reports; no randomised studies were found (Table 1).
The quality of the included studies was variable (Table 2). Watson et al performed the only prospective comparative study, which was high quality (MINORS 20/24), although they did include non-contemporaneous controls. The remaining studies were retrospective case series’ and case reports; many included non-consecutive patients, inappropriate or biased assessments of endpoints, and inadequate follow up. None of the studies documented a prospective calculation of study size.

**Ultrasound devices**

Bao et al and Ota et al reported the use of Doppler ultrasonography but did not provide any device or manufacturer details.\(^7,10\) The remaining 8 studies reported the use of 10 different ultrasound systems.

Ultrasound systems vary greatly in their form and function. Ultrasound image quality depends upon the number of ultrasound elements; placing linear array probe elements on the side of a probe (side-viewing) allows for a more slender design, while placing these elements on the front of a probe (forward-viewing) allows for more intuitive imaging of sellar structures. Similarly, because of frequency-dependent attenuation of ultrasound waves, there is a trade-off between image resolution and depth.

Several studies used probes designed for transbronchial needle aspiration and transoesophageal echo (off-label use).\(^9,15\) Watson et al used two prototype ultrasound probes specifically designed for transsphenoidal surgery with long and rather thin shaft dimensions (150x11mm) operating at 12Mhz and 15MHz (Linscan Systems, USA). Solheim et al initially used a prototype side-looking ultrasound probe with a 3x4mm tip.
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A diameter and 4mm shaft diameter, operating at 10.3MHz (Vermon, France). In a subsequent study an improved prototype bayonet-shaped forward-looking ultrasound probe operating at 12MHz was used (Vermon, France). The improved probe was, however, more bulky with a transducer footprint of 12x8mm. Knappe et al used the only commercially available probe designed for pituitary surgery, the UST-534 probe (Hitachi, Japan), a forward-looking probe, 9mm in diameter, and operating at 12MHz.

Solheim et al described the integration of their prototype ultrasound probes with a neuronavigation platform (Sonowand, Norway). They reported that this allowed for improved image interpretation, particularly when viewing the unfamiliar image projections of the side-viewing probe.

Safety and effectiveness

Watson et al reported probe malfunction during one day of their study, leading to false-positive results in two cases (2.9%). Solheim et al found that their bayonet-shaped forward-looking probe was too large to safely enter the sphenoid sinus in two cases (8.3%).

There were no cases of operative mortality reported in any of the studies. Several operative complications were reported that were not directly related to use of intraoperative ultrasound. In one study a patient sustained injury to the internal carotid artery and subsequently underwent digital subtraction angiography and stent insertion and made a good recovery. Three studies reported panhypopituitarism, and two studies reported permanent diabetes insipidus as complications following transsphenoidal
surgery. Other complications included CSF leak, meningitis, monocular blindness, and cranial nerve palsies.

Several studies explicitly reported on the extent of radiological resection or endocrinological remission. The pooled rate of complete radiological resection in patients in whom intraoperative ultrasound was used was 67.1% (range 63.5 to 77.8%) and endocrine remission was 88.4% (range 76.0 to 100%). Watson et al found remission in 89.7% (61/68) of patients with Cushing’s disease in whom intraoperative ultrasound was used, compared with 83.8% (57/68) in whom it was not. Although this was not statistically significant (p = 0.45), the authors did subsequently perform a subgroup analysis of patients undergoing primary rather than revision surgery and found intraoperative ultrasound helpful. Notably, they found that the use of intraoperative ultrasound allowed for more frequent identification of adenoma tissue (90% versus 75%; p = 0.02).

Bao et al reported complete resection in 63.5% (33/52) of patients with pituitary adenoma invading the cavernous sinus (Knosp grade 3 and 4), and remission in 76.0% (19/25) of patients with functioning adenoma. Solheim et al reported complete resection in 77.8% (7/9) of patients in their initial and 70.8% (17/24) of patients in their subsequent study.

Knappe et al reported remission in 100% (18/18) of patients with Cushing’s disease.

All of the studies reported that surgeons anecdotally found ultrasound helpful in identifying intraoperative anatomy including the internal carotid artery and residual tumour tissue.
Discussion

Summary of evidence

At present, there is limited and low quality evidence on the safety and effectiveness of intraoperative ultrasound in patients undergoing transsphenoidal surgery for pituitary adenoma. Only ten studies met the inclusion criteria, including only one comparative study, which failed to demonstrate any statistically significant difference in the primary outcome. However, none of the studies reported any major safety issues directly related to use of intraoperative ultrasound, and all of the studies reported that surgeons anecdotally found intraoperative ultrasound helpful.

Comparison with other studies

The pooled rate of complete radiological resection in patients in whom intraoperative ultrasound was used was 67.1% (range 63.5 to 77.8%) and endocrine remission was 88.4% (range 76.0 to 100%). Although difficult to make direct comparisons between heterogeneous groups, these findings are broadly comparable to the reported outcomes of patients undergoing transsphenoidal surgery for pituitary adenoma with intraoperative CT and MRI. In a recent study, for example, Berkmann et al found an initial complete radiological resection rate of 43.5% without intraoperative MRI versus 65.9% with intraoperative MRI.\textsuperscript{17}

Intraoperative CT and MRI have been more widely used as adjuncts to improve the resection in patients undergoing transsphenoidal surgery for pituitary adenoma. In a systematic review, Patel et al identified 24 studies (2 CT and 22 MRI), with improved
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Recent guidelines by the Congress of Neurological Surgeons (CNS), however, found insufficient evidence to recommend their use, suggesting they may help improve immediate overall gross total resection of nonfunctioning pituitary adenoma but at the cost of removing normal tissue. Indeed, the present review also identified intraoperative ultrasound probe malfunction leading to false-positive results in two cases. These studies underscore the importance of experience in the interpretation of intraoperative imaging for surgical decision making, regardless of the modality used.

Limitations

The present systematic review has a number of limitations. First, the scarcity and small size of included studies, means it is likely underpowered to observe small effect sizes. Second, the fact that all but one of the included studies were retrospective case series’ and case reports makes it impossible to draw any firm conclusions on the safety and effectiveness compared to standard transsphenoidal surgery or other intraoperative modalities. Finally, the technical specifications of the intraoperative ultrasound devices used, and the experience of the operating surgeon, varied widely in the included studies making generalisations difficult. Advances intraoperative ultrasound and image guidance technology, including greater image quality, more ergonomic design, and automated interpretation, may improve their cost-benefit profile.

Conclusions
At present there is limited and low quality evidence to support the use of intraoperative ultrasound in patients undergoing transsphenoidal surgery for pituitary adenoma. Given the rapid advances in imaging technology, further prospective and comparative preclinical and clinical studies are warranted to determine the extent to which subjective benefits to surgeons correspond objective improvement in patient outcomes.

References


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Figures

287  Figure 1. PRISMA flow diagram of article selection.
Table 1. Summary of included studies. pts = patients; US = ultrasound

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Patients</th>
<th>Ultrasound devices</th>
<th>Safety</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson (1998)(^{14})</td>
<td>Cohort study</td>
<td>136 pts with Cushing’s disease and negative or equivocal pre-operative MRI; 68 pts with US and 68 pts without</td>
<td>Two prototype probes (Linscan Systems, USA), 150mm long x 11mm diameter operating at 12MHz and 15MHz respectively</td>
<td>Malfunction in probe in 2/68 (2.9%) leading to false-positive results; No operative complications reported</td>
<td>Remission in 61/68 (89.7%) with US versus 57/68 (83.8%) without US; in patients undergoing primary procedures remission in 54/57 (94.7%) with US versus 46/53 (86.8%) with US</td>
</tr>
<tr>
<td>Bao (2016)(^{7})</td>
<td>Case series</td>
<td>52 pts with pituitary adenoma invading the cavernous sinus (Knosp Grade 3 and 4) undergoing extended transsphenoidal approach</td>
<td>Doppler US (not specified)</td>
<td>Operative complications: carotid injury (1.9%), CSF leak (1.9%), meningitis (1.9%), permanent diabetes insipidus (1.9%), panhypopituitarism (3.8%), monocular blindness (1.9%), cranial nerve palsies (9.6%)</td>
<td>Complete resection in 33/52 (63.5%); Remission in 19/25 (76.0%) with functioning tumours</td>
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<td>Solheim (2016)(^{8})</td>
<td>Case series</td>
<td>24 pts; 20 with macroadenoma and 4 with microadenoma</td>
<td>Prototype bayonet-shaped forward-viewing probe (Vermon, France), 120 long x ca 10mm diameter, operating at 12MHz</td>
<td>Probe too large in 2/24 (8.3%); Operative complications: Permanent diabetes insipidus (4.2%), panhypopituitarism (4.2%)</td>
<td>Complete resection in 17/24 (70.8%); Remission in 9/10 (90.0%) with functioning adenoma</td>
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<tr>
<td>Author</td>
<td>Study Type</td>
<td>Participants</td>
<td>Imaging Details</td>
<td>Complications/Outcomes</td>
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</table>
| Ishikawa (2015) | Case series | 7 pts; 5 with pituitary adenoma | EB-530US probe for transbronchial needle aspiration (Fujifilm, Japan) for sagittal images, 6.7mm diameter, operating at 12MHz  
UST-52110S-5 probe for TEE (Aloka, Japan) for coronal images, 4.8mm diameter, operating at 3-8MHz | No operative complications reported |
| Furtado (2012) | Case series | 10 pts with pituitary adenoma | Nicolet Companion Micro transducer (Nicolet Biomedical, USA) for Doppler, 3mm diameter, operating at 10Mhz | No operative complications reported |
| Knappe (2011) | Case series | 18 pts with Cushing’s disease | UST-534 probe connected to an SSD-3500 SX system (Aloka, Japan), 9mm diameter, operating at 12MHz | Operative complications: panhypopituitarism (5.5%)  
Remission in 18/18 (100%) |
| Solheim (2010) | Case series | 9 pts | Prototype side-viewing probe (Vermon, France), 4mm diameter, operating at 10MHz | No operative complications reported  
Complete resection in 7/9 (77.8%) |
<p>| Arita (1998) | Case series | 23 pts; 18 with macroadenoma and 5 with microadenoma | EUP-ES533 biplane probe for TEE probe with EUB555 color Doppler system | No operative complications reported |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Patient Details</th>
<th>Equipment Description</th>
<th>Complications</th>
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<tr>
<td>Ota (2013)</td>
<td>Case report</td>
<td>One pt with pituitary adenoma</td>
<td>Hitachi, Japan, 800mm flexible shaft x 9.8mm diameter, operating at 7.5MHz; the probe has two tandem heads performing transverse and longitudinal imaging respectively</td>
<td>No operative complications reported</td>
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<tr>
<td>Yamasaki (1996)</td>
<td>Case report</td>
<td>One pt with acromegaly</td>
<td>MF20 and TC2-64 Doppler US probes (Eden Medizinsche Elektronik, Germany)</td>
<td>No operative complications reported</td>
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Table 2. Quality of studies using MINORS criteria

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<th>Inclusion of consecutive patients</th>
<th>Prospective collection of data</th>
<th>Endpoint appropriate to the aim of the study</th>
<th>Unbiased assessment of the study endpoint</th>
<th>Follow-up period appropriate to the aim of the study</th>
<th>Loss to follow up less than 5%</th>
<th>Prospective calculation of the study size</th>
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<th>Contemporary groups</th>
<th>Baseline equivalence of groups</th>
<th>Adequate statistical analysis</th>
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Records identified through database searching (n = 997)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 998)

Records screened (n = 998)

Records excluded (n = 981)

Full-text articles assessed for eligibility (n = 17)

Full-text articles excluded
- Not able to obtain full article (n = 1)
- No patients with pituitary adenoma (n = 1)
- No use of intraoperative ultrasound (n = 5)

Studies included in qualitative synthesis (n = 10)
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Abbreviations:
CT = Computed Tomography
MRI = Magnetic Resonance Imaging
CSF = Cerebrospinal fluid
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Disclosure:

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Conflicts of interest:

The authors have no conflicts of interest to disclose.