Ultrasound guided surgery in patients with intracranial tumours

Thesis for the degree of philosophiae doctor

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NTNU
100 skapende år

“X-rays will prove to be a hoax.”
Lord Kelvin, 1895

Ultraveiledet kirurgi ved intrakraniale svulster

Intrakraniale svulster omfatter svulster i selve hjernen, svulster i hypofyseregionen og svulster i hjernehinnene. Målsetningen ved operasjoner av intrakraniale svulster er ofte, foruten å sikre diagnosen gjennom prøver som sendes til histopatologisk undersøkelse, å fjerne så mye svulstvev som mulig, samtidig som man ønsker å minimere risikoen for skader på normalt hjernevev. På denne måten er målsetningen å redusere plagene, forlenge overlevelsen og i noen tilfeller helbrede pasienten for sin svulstsykdom.

Gjennom mange år vært et aktivt ultralydforskningsmiljø i Trondheim. Det er blant annet utviklet ultralydbaserte navigasjonssystemer for å veilede hjernesvulstoperasjoner. To - og tre-dimensjonale bildedata basert på MR og ultralyd gjør at kirurgen kan orientere seg i anatomien hos den enkelte pasient under inngrepet. Avbilding med ultralyd gjør at kirurgen kan få oppdatert bildeinformasjon om strukturer som ligger under overflaten i operasjonsfeltet.

I denne avhandlingen, som består av fem separate arbeider, var hensikten å prøve ut og utvikle ny teknologi samt å evaluere ultralyd som hjelpemiddel under intrakraniale svulstoperasjoner. Hovedfunnene var:

- Tredimensjonal ultralyd kan være av potensiell nytte ved operasjoner for store hjernehinnesvulster
- En prototyp ultralydprobe ble tatt i bruk i hypofyseoperasjoner via nesen. Ultralyd kan brukes til å trygge kirurgens anatomiske orientering, og kan også være potensielt nyttig til å identifisere svulstvev som ellers ville blitt oversett under operasjonen
- Man fant en assosiasjon mellom ultralyd bildekvalitet og behandlingsresultatene ved operasjoner for en type hjernesvulst (høygradige gliomer). Dette tolkes som en antydning om at bedre ultralydteknologi fører til bedre kirurgi
- Overlevelse for glioblastom (en ondartet type hjernesvulst), behandlet med kirurgi og strålebehandling, har økt i årene etter at ultralydassisert hjernesvulstkirurgi ble tatt i bruk i Trondheim
- Moderne hjernesvulstoperasjoner for gliomer (en gruppe hjerne svulster) synes ikke å ha verken positiv eller negativ effekt på pasientenes selvopplevde livskvalitet i gjennomsnitt, men nye nevrologiske utfall på grunn av skader på hjernen etter inngrepet er assosiert med et betydelig fall i pasientenes selvopplevde livskvalitet

Samlet gir artiklene ny kunnskap og innblikk i nytteverdien og resultatene ved ultralydassisert kirurgi for intrakraniale svulster. Ny teknologi for ultralydassisert hypofysesvulstkirurgi ble utviklet og vil videreutvikles som følge av prosjektet.

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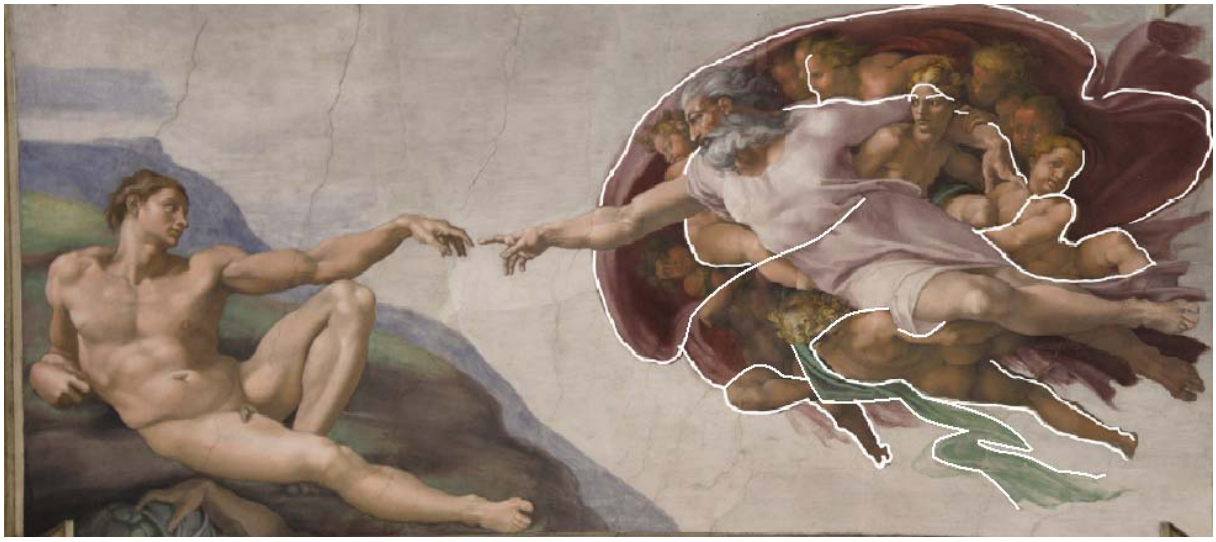

On the subjectivity of image interpretation:

The creation of Adam - or the creation of God?

The subjective nature of image interpretation is a factor to consider in most publications regarding medical imaging, and perhaps ultrasound imaging in particular. This subjectivity of image interpretation may also be encountered in the analyses of classic masterpieces in art. The famous, unnamed section of Michelangelo's fresco in the Sistine Chapel ceiling was painted around 1511. For centuries the painting has been analyzed by historians, dissected by critics, and debated by theologians and intellectuals, most of whom were content with the "obvious" interpretation as the "creation of Adam". However, nearly 490 years later, Frank Meshberger (JAMA 264:1837-1841, 1990), a medical student at the Indianapolis School of Medicine, flipped through a book about Michelangelo. He was immediately struck by the shape of the image surrounding God and the angels as he recognized the outline of the human brain. First he noticed that the swirling green robe corresponded with the vertebral and basilar artery, which follows an irregular path upward toward the pons. Then he noticed the angel's leg and bifid foot that matched the anterior and posterior lobe of the pituitary gland. Then he noticed the general outline of the Sylvian fissue, which separates the frontal from the temporal lobe. Perhaps Michelangelo was not painting God's "creation of Adam", but just the opposite: Man's creation of God? Was Michelangelo expressing that any human concept of God is a creation of the human brain?

Contents

1 Acknowledgements

In my early days as a neurosurgical resident, I was lured to apply for a PhD-scholarship in medical technology. At the time I was somewhat hesitant as I was more interested in pure clinical research, and also more eager to master new surgical procedures than to dig deep into the speckled world of ultrasound imaging. Nevertheless, I was persuaded to join the intraoperative ultrasound research group. For this I am now exceedingly thankful. In 2007, I received a research grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU) and was allowed to combine research and clinical work in a favourable and rewarding way. The welcoming, enthusiastic and innovative environment of the multi-disciplinary collaborative research group is unique and soon made me recognize the great potential impact of research in medical technology, and the advantages of conducting such research in Trondheim. The close collaboration between clinical and technical researchers from St. Olavs University Hospital, SINTEF, and the Norwegian University of Science and Technology offers an outstanding environment for innovative research, especially in ultrasound and image guidance. I am very thankful for the great opportunities I have been offered and would like to express gratitude to my supervisor, Professor Geirmund Unsgård, both for luring me into medical technical research, for his support in my projects, and for his inspiring stamina and great enthusiasm with both his clinical and academic work. Thanks also to my co-supervisor, Professor Øystein Petter Nygaard who with his brilliant pedagogic skills has provided valuable clinical guidance and support these years.

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Finally, I am thankful for my family and extraordinarily and forever thankful for my fantastic and loving wife, Tora.

Trondheim, November 2010

Ole Solheim

2 List of papers

PAPER I

Ole Solheim, Tormod Selbekk, Frank Lindseth, Geirmund Unsgård:
Navigated resection of giant intracranial meningiomas based on intraoperative 3D ultrasound
Acta Neurochirurgica. 2009 Sep; 151(9): 1143-51

PAPER II

Ole Solheim, Tormod Selbekk, Lasse Løvstakken, Geir Arne Tangen, Ole Vegard Solberg, Tonni Franke Johansen, Johan Cappelen, Geirmund Unsgård:
Intrasellar Ultrasound in Transsphenoidal Surgery: A Novel Technique
Neurosurgery. 2010 Jan; 66(1): 173-85

PAPER III

Ole Solheim, Tormod Selbekk, Asgeir Store Jakola, Geirmund Unsgård:
Ultrasound guided operations in unselected high grade gliomas – Overall results, impact of image quality and patient selection
Acta Neurochirurgica. 2010 Jul 21. Nov;152(11):1873-86

PAPER IV

Carl Andrew Sæther, Magne Torsteinsen, Sverre Helge Torp, Stein Sundstrøm, Geirmund Unsgård, Ole Solheim:
Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? - a retrospective analysis of 192 primary operations
Submitted

PAPER V

Asgeir Store Jakola, Geirmund Unsgård, Ole Solheim:
Quality of life in patients with intracranial gliomas - the impact of modern image guided surgery
Submitted

3 Abbreviations

2D	Two-dimensional
3D	Three-dimensional
5-ALA	5-Aminolevulinic Acid
CI	Confidence Interval
CT	Computer tomography
CUSA®	Cavitron Ultrasonic Surgical Aspirator®
EEG	Elecroencehalogram
FLA	Flat Linear Array
GTR	Gross total resection
HR	Hazard rate
KHz	Kiloherz (1000 Hz)
MHz	Megaherz (1,000,000 Hz)
MR	Magnetic resonance
MRI	Magnetic resonance imaging
nm	Nanometers
NTR	Near total resection
FPA	Flat Phased Array
PR	Partial resection
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
WHO	World Health Organization

4 Errata

In paper I, the affiliation to SINTEF of the 2nd and 3rd authors is missing
In paper II, figure 13 B, the symbol ¤ is exchanged with the symbol Є in the legends.

5 Introduction

5.1 History and current state of navigation, visualization and imaging in neurosurgery

5.1.1 Navigation in neurosurgery

Landmarks, palpation and radiographs

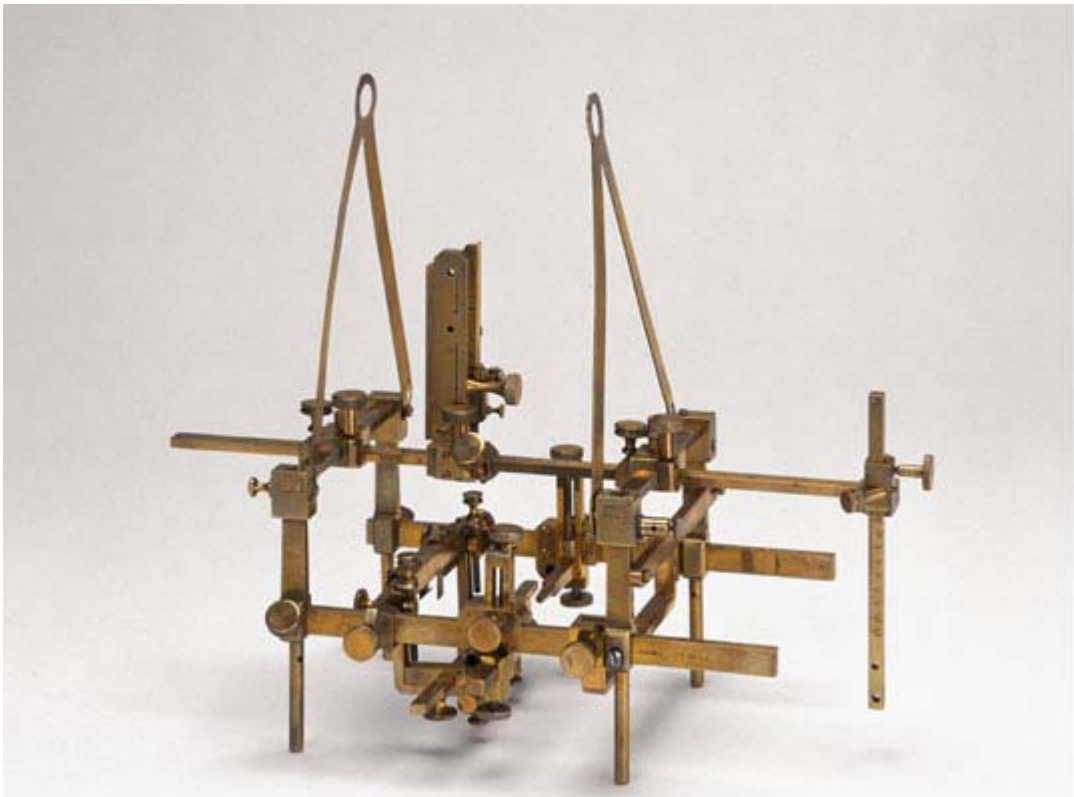
In 1881, Dr. Macewen from Glasgow, Scotland, reported in The Lancet the first successful removal of an intracranial tumour. In a 14-year old girl, he removed what is later thought to have been a meningioma. Hyperostosis of the skull above facilitated the localization of the tumour [1]. By the late 19th century the functional anatomy of the brain had been much described through observations and ingenious experiments by Jackson [2], Ferrier [3] and Horsley [4]. Based on this knowledge of functional neuroanatomy, Dr. Bennett was in 1884 able to localize a cerebral tumour based on clinical findings alone – an abnormal fundus of the right eye and a left hemiparesis. By using various anatomical landmarks, the surgeon, Godlee could make a relatively small craniotomy and removed the tumour near the middle third of the of the rolandic fissure on the right side [5]. X-rays were discovered by Röntgen in 1895 [6]. In the following, plain skull radiographs could be used to identify shift of the pineal calcification, sellar enlargement due to tumours, or erosion from elevated intracranial pressure, as well as to detect abnormal calcifications, bone destruction, or hyperostosis of the calvaria. However it was not until the introduction of the pneumoencephalogram, by Dandy in 1918 that intracranial lesions to some degree could be localized visually prior to surgery [7]. Through the injection of air directly into the ventricles or through lumbar subaracnoidal punctures, contrast in the plain x-rays was enhanced. Pneumoencephalograms were used to explore the presence of posterior fossa or cerebelloptine angle lesions, pituitary tumours and intraventricular masses [8]. As cerebral angiography was introduced by the Portuguese neurologist Moniz in 1927 (who is more famous for his Nobel

price in 1949 for discovering the therapeutic value of lobotomy), the visualization of vessels could serve as indirect markers of intracranial mass effect [9]. However, from now clinical neurosurgical imaging was practically unchanged the next four decades. Due to the limitations of the available imaging techniques, large and standardized surgical approaches were utilized. If the lesion was not localized where expected, the surgeon would palpate the brain directly or use a puncture needle to feel for resistance representing a deeper lesion.

Stereotaxy

The term stereotaxy is used to describe techniques that enable three-dimensional localization of structures within the brain. In the 1890s, the Russian anatomists Zernov and Altukhov described an “encephalometer”, a skull-fixed arc used for localization of intracranial anatomy based on superficial landmarks. In 1908, Horsley and Clarke described the first stereotactic procedures on small animals [10]. A fixed frame registered to anatomical landmarks such as the external auditory canals, inferior orbital rims and cranial midline were used to guide the placement of electrodes in the brain. However, the technique was quite imprecise as variations in normal anatomy limited localization of areas in the brain extrapolated from variations external landmarks. The accuracy of stereotaxy was greatly improved as Spiegel and Wycis in 1957 described a calibration of stereotaxy through neuroimaging [11]. Preoperative or intraoperative pneumoencephalograms were used to visualize the pineal gland and the foramen of Monro as intracranial reference points. After positive contrast agents for ventriculography were developed, the anterior and posterior commissures and the intercommissural line became the most commonly used intracranial landmarks. Despite improved accuracy, the positioning of structures perpendicular to the imaging plane were often associated with inaccuracy as imaging was still only two-dimensional. Still, in the following decades, the relatively fine precision of frame-based stereotaxy used in functional neurosurgery was in immense contrast to contemporary brain tumour surgery.

Preoperative image diagnostics relied on indirect markers of mass effect by angiography and or pneumocephalography and tumour surgery was characterised by large and standardized explorative approaches.



Science Museum Library, London (Science & Society Picture Library)

Stereotactic apparatus used by Sir Victor Horsley and Richard Clarke to explore physiology through positioning needles inside the brain of animals

Computed Tomograpy and Magnetic Resonance imaging

The invention of Computed Tomography (CT) in 1973 [12] enabled an enormous progression in the field of neurosurgery as lesions from now on could be seen and evaluated preoperatively in terms of location, size, shape or growth rate. This advanced preoperative planning and enabled more targeted surgical approaches. Postoperative imaging enabled closer evaluation of complication and surgical results and permitted better follow-up of patients. Stereotaxy was also improved as CT data could be used to calibrate the stereotaxic frames. The development of of Magnetic Resonance Imaging (MRI) was another enormous leap for the quality of neuroimaging [13, 14]. Together with the introduction of the microscope in the operating rooms [15], the stage was now set for safer and much more precise neurosurgery.

Neuronavigation based on preoperative images

The progress in computer and robot technology and advances in neuroimaging during the 80s and 90s, enabled the development of more sophisticated devices for stereotactic surgery based on preoperative images. Both frame-based and frame-less technologies were developed [16-22]. Frame-based techniques are very exact but the frame and the stereotactic arches are bulky and may obstruct surgical exposure. The more flexible frameless stereotactic systems may use optical, electromagnetic, ultrasonic sensors or mechanical arms to track the position of surgical tools and instruments intraoperatively, but are less accurate. Neuronavigation based on preoperative MR images is today widely employed in most neurosurgical departments. Frame-based techniques are today typically reserved for extremely accurate procedures like stereotactic biopsies in eloquent areas or deep brain stimulations, while frame-less techniques are utilized in tumour surgery. A small retrospective study claims that neuronavigation increases the radicality in the resection of malignant astrocytomas and may improve survival [23]. The same conclusion is reached in a case-control study design [24]. A randomized study, however found no benefit in routine use of neuronavigation [25].

5.1.2 Intraoperative imaging and tumour visualization

Systems based on preoperative images cannot provide the surgeon with information about changes that occur intraoperatively. The brain shift due to positioning of the patient, removal of CSF, spatulas, brain swelling and resection of tissue will diminish the value of spatial information acquired preoperatively [26-28]. This is the rationale for intraoperative imaging.

Intraoperative ultrasound

The German neurologist Dussik published in 1941 in the article "Über die Möglichkeit hochfrequente mechanische Schwingungen als diagnostisches Hilfsmittel zu verwerten" where he proposed transmission and registration of pulsed ultrasonic vibrations on opposite sides of the head to localize the ventricles of the brain [29]. The following pioneers [30-36] assessed cerebral ultrasound echoes in one-dimensional so-called A-mode displays. The received ultrasound energy from certain depths was presented as amplitudes in an oscilloscope. Although the depth of tumours could be assessed along with gross estimates of lesion sizes, the challenges of interpretation and lack of real anatomical information limited widespread utilization. The introduction of B-mode, one-dimensional display where the brightness of dots corresponds to the amplitude of the reflected sound wave, made the interpretation somewhat easier. However, it was not until the early 80s when three different research groups almost simultaneously started using real-time B-mode sector scans [37-39] that intraoperative imaging in neurosurgery was born. Surgeons could now obtain updated neuroanatomical images at any time during surgery. In the following, two-dimensional (2D) ultrasound has been employed and evaluated in different neurosurgical settings [40, 41], including intracranial brain tumour surgery [42-45], shunt surgery [42], spinal surgery [43-49], neuroendoscopy [50], vascular neurosurgery [51-54] and transsphenoidal operations [55-57]. Ultrasound imaging through burr-holes could be used as a substitute for convensional stereotaxic guidance procedures [58-60] and even a skull-mounted apparatus for ultrasound

guided stereotaxy was described and evaluated [61, 62]. Still, real-time 2D ultrasound images can be associated with variable quality and with ill-defined scan planes that may challenge perception.

By combining different technical concepts, the evaluation of brain-shift and the interpretation of ultrasound images became easier. The first three-dimensional (3D) display of ultrasound images were explored by Koivukangas and colleagues using holistic displays already in 1986 [63]. In 1994, Trobaugh published a different method of obtaining 3D ultrasound images based on a B-mode scanner. Light-emitting diodes were attached to the probe for tracking its position [64]. The technique was also used in comparison with preoperative CT/MR images to evaluate brain shift during surgery [16]. In 1993, Koivukangas described a arm-based computer-assisted neuronaviation system with interactive reconstructions of preoperative CT and MR images as well as corresponding intraoperative ultrasound images [65]. Frameless stereotactic neuronavigation systems that allowed navigation in real time 2D-ultrasound images while displaying corresponding preoperative image data based on CT or MR were developed [66, 67].

SonoWand Invite ®

Grønningsæter and colleagues from Trondheim described in 2000 an integrated neuronavigation system with optical tracking based on an ultrasound scanner. This single-rack system (SonoWand) enables frameless neuronavigation based on pereoperative MR or CT data along with intraoperative 3D ultrasound data [68]. The integration of ultrasound imaging and navigation technology enables acquisition of 3D ultrasound volumes, typically generated from 200-300 image

slices. The ultrasound image volumes can be readily acquired when needed during surgery, and the data are displayed with preoperative MR data on the navigation monitor when using tracked tools such as a pointer or ultrasound aspirator. 3D navigation may offer easier anatomical orientation due to data displayed as orthogonal (patient related slices) or reformatted according to the position of the tracked tool (tool related slices).

Based on the experience from several surgical series it has been suggested that the use of intraoperative ultrasound may ease intraoperative delineation and facilitate extent of resection of various intracranial lesions [69-75], but no controlled trials have been conducted. It is pointed out by several authors that as ultrasound often provide a good delineation of lesions before starting the resection [76], tumour remnants and infiltrated brain tissue in the resection cavity wall may be undetected after gross resection due to image artefacts [77, 78]. In addition, not all brain tumours are well delineated by intraoperative ultrasound [71, 75, 79, 80], perhaps reflecting the physical principles on which the images are based.

Intraoperative CT and MR imaging

Intraoperative CT imaging was described already in the early 80s [81], and refined in the late 90s [82, 83], but has not been much employed. This is presumably due to inferior image quality and exposure to ionizing radiation. In 1995, the first neurosurgical procedure was performed in the 0.5 Tesla intraoperative MR suite, the General Electric “double doughnut” in Boston. Updated MR images of the surgical field could be obtained while the surgeons operated in a 56 cm gap in the centre of the magnetic core [84]. In 1997, Tronnier described the use of a 0.2 Tesla magnet installed adjacent to one of the operating theatres for intraoperative imaging. A specially designed patient transport system carried the patient in a fixed position to the scanner and back to the surgeon [85]. The concept of intraoperative MRI has been further developed and explored in various high- and low-field scanners located within or next to the operating

theatres [86-91]. Low-field scanners are associated with inferior field of view and inferior image quality that lower rates of detected tumour remnants [86], but can today be installed under the operation table. The implementation and use of high field intraoperative MRI is on the other hand very expensive, requires skilled technical support, and often associated with logistic challenges in the operating room. There is need for MR-compatible, non-ferromagnetic, equipment and electromagnetic shielding around the scanners. Also the image acquisition and processing can be time consuming, extending operating times. Only one small and probably underpowered case control study has compared the value of intraoperative MRI to conventional surgery [92]. This study failed to demonstrate an increased efficacy of surgery in patients with grade IV gliomas compared to conventional methods.

Image fusions and updated neuroimaging

The information in preoperative images becomes more and more outdated as surgical resection and brain shift progresses. Overlay-techniques or side-by side display enable the detection and evaluation of brain shift when navigating in intraoperative image volumes together with preoperative MRI volumes. This is possible with the SonoWand system, but the surgeon has to mentally correct for brain shift if he or she seeks to extend the value of information in preoperative images. This may for example be advantageous in eloquent lesions if functional MRIs have been recorded prior to surgery [74, 93]. To recycle the outdated information in peroperative MR images, some methods and models have been proposed [94, 95]. In 2003, Lindseth proposed an image fusion between preoperative MR data and intraoperative 3D ultrasound images from the SonoWand neuronavigation system [96]. Another group have also suggested a method of intraoperative display and evaluation of brain shift using preoperative MR data and the SonoWand neuronavigation system [97]. Recently, a biomechanical brain deformation model driven by intraoperative ultrasound data was proposed to generate updated MR images [98]. However so far, outdated MRI data cannot be restored for clinical use.

Fluorecence guided neurosurgery

Malignant tissue is known to preferentially synthesize or accumulate fluorescent and photosensitizing endogenous porphyrins after excess administration of 5-aminolevulinic acid (5-ALA), a naturally occurring precursor in the heme biosynthesis pathway. This phenomenon can be utilized in malignant brain tumour resections. Three hours before the induction of anesthesia, 5-aminolevulinic acid can be administered orally. Intraoperatively, fluorescence is observed through a 455-nm long-pass filter after excitation with violet-blue (375-440 nm) xenon light. In a histopathological study the sensitivity was 85% and specificity was 100% for the detection of malignant glioma tissue [99]. The efficacy of this method has been documented in a randomized controlled multi-centre trial in a selected population of malignant gliomas [100].

Comparative studies

Three small comparative studies of intraoperative ultrasound and intraoperative MRI have been published so far. None of the studies are randomized nor controlled and both modalities were used in all study subjects. In a small series of 7 patients, intraoperative 3D ultrasound was compared to 0.2 Tesla intraoperative MRI. Detection of metastases and high-grade gliomas and intraoperative delineation of tumour remnants were comparable in the two imaging modalities. Better visibility was achieved with ultrasonography in one case of a low-grade glioma. Still, intraoperative findings after resection were difficult to interpret and it was concluded that intraoperative MR is superior to intraoperative ultrasonography in terms of resection control in glioma surgery [101]. In a comparative study in 26 patients, 1.5 Tesla Intraoperative MRI was compared to 2D ultrasound with the SonoWand 1.4 system. Intraoperative MR imaging was more precise in detecting small tumour remnants than 2D ultrasound. Still, the authors acknowledge that ultrasound may be used as a less expensive and less time-consuming alternative that provides almost real-time feedback information [102]. In a recent study from Turkey, intraoperative ultrasonography was used in 52 of 56 low-grade gliomas operated with a 3

Tesla intraoperative MRI system. Before proceeding to the acquisition of intraoperative MR images, residual tumour tissue was detected with intraoperative ultrasound in 4 cases (7.7%). In 21 (43.8%) of the remaining 48 cases, the following intraoperative MR images revealed residual tumour tissue that had not been evident on the intraoperative ultrasonography performed immediately before MR imaging. The authors conclude that intraoperative ultrasonography could detect only 16% of residual tumours in low grade gliomas [103]. Together, these small comparative studies, published by intraoperative MRI enthusiasts, suggest that the sensitivity of intraoperative ultrasound is lower than intraoperative MRI in the detection of tumour remnants. This is probably a valid conclusion, at least in comparison with high magnetic field systems, since the definition of “remnant tumour” is today by based on the MR modality. Thus, the sensitivity of ultrasound can by definition only be inferior, or at best equal to the MR modality. However, to be considered, the reliability of such image technology comparisons may be low as the usefulness of any method will depend on the type equipment in use, the knowledge of know to use it, and the experience and enthusiasm of the interpreter.

5.2 Technical and physical aspects of ultrasound imaging

5.2.1 Fundamental principles of ultrasound

Ultrasound is waves with frequencies higher than the upper limit of human hearing; i.e. more than 20 KHz. Medical applications of ultrasound typically require wave frequencies above 1 MHz and are generated from piezoelectric materials. When a voltage is applied across materials that exhibit the piezoelectric effect, the solid undergoes a mechanical distortion that generates waves. Medical ultrasound is compression waves since shear waves are heavily attenuated in soft tissues if frequencies are above 1 MHz. As ultrasound echo back from tissue interfaces towards the probe with piezoelectric ceramic probe elements, the process is revered and an electric field is generated in response to the applied mechanical stress from the reflected waves. The depth of the different reflections is calculated based on how long it took the echo to be received from when the sound was transmitted. The strength of the echo, i.e. wave amplitude determines the brightness of the echo displayed in so-called B-mode ultrasound images.

Ultrasound waves travel through tissues with a propagation velocity (c) while an oscillation in the pressure with the frequency (f) is observed. The relationship between the wavelength (λ), propagation velocity (c) and frequency is given by:

$$\lambda = c/f$$

The ultrasound waves that leave the probe are focused either by the shape of the transducer, and/or a lens in front of the transducer, and/or through a complex sequence of pulses from the ultrasound scanner, so-called beamforming. Electronic beamforming and steering utilize the Huygens–principle of wave propagation; the advancing sound wave as a whole may be seen as the sum of all waves arising from the probe elements.

The sound propagation velocity is related to the mass density (ρ) and the volume compressibility (κ) of the tissue:

$$c = 1/\sqrt{(\rho\kappa)}$$

When the transmitted ultrasound pulse meets boundaries between tissues or structures, for example between normal brain tissue and a tumour, the pulse is partially reflected backward and partially transmitted forward. Variations in acoustic impedance (Z) between two materials cause such reflection of the ultrasound, i.e. echo back towards the probe. The acoustic impedance (Z) is given by mass density (ρ) and the sound velocity (c):

$$Z = \rho c$$

The greater the impedance difference, the more is reflected. For interfaces between soft tissues, for example between white and gray matter in the brain, reflection is quite small and most of the energy is transmitted forward. If ultrasound propagate to a tissue with higher acoustic impedance than the surroundings, such as most brain tumours, the magnitude of back-scattered signals make the lesion appear brighter than the surrounding tissue, so-called hyperechoic. If ultrasound spread through interfaces to soft tissues with lower acoustic impedance, such as cysts or necrotic tumour tissue, such lesions appear darker than the surrounding brain tissue, i.e. hypoechoic. If ultrasound spreads through a lesion with the same acoustic impedance as the adjacent

tissue, no delineation of the lesion will be possible as the lesion is isoechoic. For interfaces between soft tissues and bone, the difference in impedance is so great that most of the energy is reflected, limiting further propagation of the sound waves, resulting in shadow artefacts behind the tissue interface in the images.

Some ultrasound energy is lost due to reflections that attenuate the transmitted wave. Most of the energy is however lost due to absorbed energy when wave is converted to heat. Thus, attenuation increases with distance away from the probe. The attenuation of ultrasound energy also increases with frequency (f).

5.2.2 Ultrasound image resolution

Axial resolution, i.e. pixel length along the ultrasound beam path, is determined by the wavelength of sound pulses. As the wavelength is inversely related to the frequency, and as attenuation and penetration is inversely related to the frequency, there is a constant trade-off between resolution and penetration. As a consequence it is difficult to obtain high resolution in deeper lesions. Lateral resolution, i.e. pixel length perpendicular to the beam path is dependent on beam width and is generally poorer than axial resolution. The beam width is dependent on the probe footprint, i.e. the aperture in number of ultrasound elements, transducer frequency and focusing of the sound beam. In addition resolution may be affected by gain settings as the sound beam will become wider with increased gain. For 3D-imaging, the azimuth pixel length is also important. Focusing through lenses or electronic focusing affects the narrowness of sound beams in the azimuth dimension.

5.2.3 Ultrasound image artefacts

Several artefacts of ultrasound may limit image quality. Most ultrasound scanners assume that the speed of sound is constant at 1540 m/s in any tissue. However, as mentioned, the speed of sound varies with the acoustic impedance of the tissue. For brain tissue, the speed is plus or minus 3% of 1570 m/s. This may to some degree cause errors in distance and size measurements. This is however more often a problem in imaging in less uniform locations than in the brain. Variations in attenuation and scattering of ultrasound waves in transitions between different tissues may cause artificial enhancements or shadows in the image. The rim enhancement in saline filled resection cavities is well known. Tumours that are well delineated prior to resection, may be overestimated during resection due to rim enhancement [77]. Likewise, shadow artefacts in air-filled cavities or in calcified lesions may be encountered. Reverberation artefacts can be seen when ultrasound beams are reflected several times back and forth between two strong reflectors. Ghost images of hyperechoic structures may be a result of misdirected ultrasound energy. Side lobes and grating lobes are both unwanted parts of the focused ultrasound beam that can produce image artifacts due to error in positioning the returning echo.

6 Aims and methodological considerations

The overall aim the thesis was: Clinical evaluation of and development of new applications for ultrasound in intracranial tumour surgery

PAPER I

Navigated resection of giant intracranial meningiomas based on intraoperative 3D ultrasound

We sought to present experience from the use of 3D ultrasound in surgery for giant meningiomas, a type of lesion were image guided surgery is usually not utilized.

PAPER II

Intrasellar Ultrasound in Transsphenoidal Surgery: A Novel Technique

We sought to present our initial experience utilizing a prototype 6.2 -14.3 MHz side-looking, linear array, catheter shaped, ultrasound probe for intraoperative imaging during transsphenoidal surgery.

PAPER III

Ultrasound guided operations in unselected high grade gliomas – overall results, impact of image quality and patient selection

We sough to determine resection grades and clinical outcome in a consecutive, population-based sample of high grade gliomas, 95% of which were operated with use of the SonoWand system. We also sought to explore the variation in and importance of ultrasound image quality. The relationship between surgical results and patient selection was also described.

PAPER IV

Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? - a retrospective analysis of 192 primary operations

In retrospective study we sought to compare survival before and after the introduction of neuonavigation and 3D ultrasound in glioblastoma surgery in our department.

PAPER V

Quality of life in patients with intracranial gliomas - the impact of modern image guided surgery

We sought determine the impact of modern image guided glioma surgery on patient reported QoL. We also compared how QoL is related to traditional outcome parameters and explored possible predictors of QoL.

6.1 The patients

Patients were selected according to the inclusion and exclusion criteria of the studies. Patients were scheduled for tumour surgery in the department of Neurosurgery, St.Olavs University Hospital. The retrospective inclusion of patients in papers I and IV were done through systematic search in hospital records.

6.2 The ultrasound equipment

The commercially available ultrasound-based neuronavigation system (SonoWand version 1.4, Trondheim, Norway) was used in the operations that were carried out in studies I, III, IV and V. A few operations in study III and V were performed with the new system (SonoWand Invite).

In paper II, we utilized a prototype ultrasound probe. The probe was produced by Vermon (Tours, France) and equipped with a connector for a commercial system (Vivid 7, GE Vingmed, Horten, Norway), and a specialized application for the probe was developed on this scanner. Acoustic measurements in the ultrasound laboratory of NTNU verified that thermal and mechanical indexes were within FDA safety regulations, and the ultrasound probe was further electronically tested and approved by the technical department of St. Olavs University Hospital before being used in patients.

6.3 Ethics

The studies were approved by the regional Ethics Committee. Storage of data was approved by the Norwegian Social Science Data Services. All patients included in study II and V, and most patients included in study III gave written, informed consents. Studies I, III and IV were also approved by the Norwegian

Ministry of Health, which allowed for review of patient data without informed consent.

6.4 Statistics

The statistical analyses are described in detail in the papers.

The Kaplan-Meier method displays the probability of survival against time, and can for example be used to estimate median survival or survival at given times after inclusion such as, one-, three-, or five-year-survival rates. In a long term observational study, the case mix may change over time due to change in diagnostics, incidence, classification or because new forms of treatments are introduced. The Kaplan-Meier method, however assumes that the probability of survival is the same for subjects recruited early and late in the study period. This is for example an issue in study IV as adjuvant treatment has changed in the inclusion period.

The hazard is the probability of a patient to experience the endpoint (e.g. death) at a given time. The hazard ratio, a type of relative risk, is a comparison of such probabilities between groups of patients. The hazard ratio does however not convey any information about how much faster death may occur in days or months. Thus, a statistical significant hazard ratio may still be clinically irrelevant. This may be kept in mind when looking at hazard ratios presented in study IV.

6.5 Classification of intracranial tumours

Central nervous system tumours are most often classified according to the widely accepted WHO classification system [104]. Classification is based on the notion that each type of tumour results from the abnormal growth of a specific cell type. The behaviour of a tumour correlates with its basic cell types. Although some entities are histologically and biologically benign, the nature of the brain often blurs the distinction between benign and malignant. A relatively small, slow-growing tumour with no metastatic potential may become lethal if located in a region where it is difficult to reach and remove. Although the histopathological classification of lesions is for now the gold standard to which other diagnostic tools are compared and by which adjuvant treatment is decided, there is a considerable inter-observer-variability among neuropathologist for many types of lesions. 11% and 27% discordance is reported for glioblastomas and anaplastic gliomas, respectively [105]. This may be an issue when comparing results from various publications, such as in paper III.

6.6 Classification of ultrasound image quality

In the questionnaire for the surgeons, good ultrasound image quality was defined as cases with a clear definition of tumour borders in the ultrasound images. Medium ultrasound image quality was defined as cases with difficult, but possible delineation of tumour borders. Poor ultrasound image quality was defined as cases where it was impossible to visualise tumour borders in the ultrasound images. This classification of ultrasound image quality used in paper III and V was not validated. However, almost identical three-step scales have been utilized by others [71, 106]. While image resolution may be calculated objectively, image quality is undoubtedly a subjective matter. There is a well known learning-curve of both acquisitioning and interpreting of intraoperative ultrasound images and artefacts. A known limitation of intraoperative ultrasound

are the various artefacts in surgical cavities that contribute to a deterioration of ultrasound image quality and tumour delineation during resection [77].

6.7 Measurements of tumour resections

In most neurosurgical tumour publications, the extent of resection has not been measured objectively. In several studies the extent of resection has only been quantified on the basis of the surgeons' impressions alone. Such estimates are clearly inaccurate [107]. This was also confirmed in our study number III, despite the widely employment of neuronavigation and intraoperative ultrasound imaging. Thus, presumed resection grades, as presented in study number IV may, be of questionable value. Resection grades can be dichotomized to resection versus biopsy or gross total resection (GTR) versus partial resection (PR). Some use a three-step-scale of GTR, subtotal resection or biopsy. GTR is often defined as no residual tumour seen in postoperative MR images, although some classify any extent of resection >90% as GTR [108, 109]. Some introduce the term Near Total Resection (NTR) if extent of resection is between 90 and 99% [110] or only rim enhancement of the resection cavity was noted on postoperative MR imaging in high grade gliomas [111]. Even though some recent studies attempt to measure resection more objectively, results are complicated by the use of different imaging modalities or sequences, different methods to quantify tumour volumes and irregular timing of the postoperative imaging. Comparisons of results among published case series may therefore be difficult.

In paper III and V we calculated volumes of spherical shaped lesions by applying the ellipsoid volume formula ($4/3 \cdot \pi r_1 r_2 r_3$) based on the maximum tumour diameters in the available image dimensions. In cup-shaped residual tumours, volume was calculated by subtracting the ellipsoid shaped resection cavity from the volume of the tumour/cavity-complex. The accuracy of this method is clearly not perfect, but still an improvement compared to more crude measures. In some cases with more complex tumour configuration, tumour

borders were segmented manually in each slice. Tumour volumes were calculated based on the voxel resolution and the total number of voxels segmented. This method is however extremely time consuming. As any volume calculation also requires a subjective interpretation of tumour borders in the medical images, such quite accurate measurements can still never be 100% objective.

6.8 Radical and complete resections

A common prerequisite for surgically curable cancers is radical removal of lesions together with a safety margin of normal tissue, without contaminating the surgical field with tumour cells. The possibility of such en bloc resections with a substantial safety margin is naturally problematic in the brain. Diffuse brain tumours are therefore generally operated from within and towards the periphery, and ending resection when normal tissue is reached. In the 1920s, Dandy performed right sided hemispherectomies in malignant glioma patients with preoperative left hemiplegia [112]. Still, despite his and others' heroic efforts [113], recurrence was always seen. Decades ago Matsukado showed that more than half of untreated malignant gliomas had already reached the contralateral hemisphere [114]. Many diffuse brain tumours are quite advanced at the time of diagnosis, limiting the possibility of a cure after even the most radical surgical resections. It is still worth considering that the surgical technique used by neurosurgeons in brain tumour removal would yield (just as) catastrophic results if applied in cancer surgery in other organs. Radical attempts of en bloc resections have not been repeated in modern times, after the introduction of neuronavigation and modern neuroimaging that theoretically could enable detection and en bloc resection of some small lesions at an early stage. Modern surgery for diffuse malignant brain tumours is for now, only a palliative form of treatment. The challenge is the often delicate balance between achieving extensive resections that matter, in terms of extending survival or postponing

progression, while avoiding complications and neurological deterioration due to the operation itself.

The gold standard and definition of complete resection (or GTR) of many intracranial tumours is based on various MRI sequences. As the instruments of imaging improve, the definition of complete resection may be pushed further away from the safe margins of resection. One must also bear in mind that all image modalities are associated with false positives and negatives. The smallest dot or voxel seen in modern MRI images is approximately 1 x 1 x 1 millimeters and can contain around 0.001 ml or 1 million tumour cells. It is known that strength of the magnetic field [86], timing of the contrast agent [115] or different image modalities such as MR spectroscopy [116, 117] has implications for what will be defined as tumour. False positive contrast enhancement may occur after and during operations [118-120]. Oedema or gliosis may sometimes be mistaken for tumour in both MRI and ultrasound images. The sensitivity of MRI in detection of residual tumour tissue varies between types of lesions. In functional pituitary adenomas the sensitivity of MRI is for example quite low compared to hormonal assays. For gliomas, the true tumour volume is almost always larger and more diffuse than observed in any current imaging technology [114, 121-123]. It is so far unknown if the tumour seen on MRI scans is closer to reality than the same tumour seen on ultrasound images. The cut-off of what is tumour and what is not is therefore not straightforward, and will change with the evolution of imaging technology. The ideal cut-off to be used for intraoperative navigation in diffuse lesions is one that maximizes survival and minimizes the risk of resecting functional tissue.

7 Summary of results

7.1 Paper I

Objective: To present experience from the use of 3D ultrasound in surgery for giant meningiomas, a type of lesion were image guided surgery is usually not utilized.

Design: Technical application report illustrated by a retrospective case series.

Study subjects: 15 consecutive meningiomas with a diameter of more than 5 cm operated with guidance of intraoperative 3D ultrasound

Results: Ultrasound guided intracapsular gross total resection of tumour tissue was done before the tumour capsula was carefully removed from adjacent normal tissue. Major feeding arteries and adjacent normal arteries could be identified by ultrasound power-Doppler angiography. In one patient we were not able to indentify important venous structures

Conclusions: We describe a method of 3D ultrasound guided resection of giant meningiomas. The method enables image guided resection through narrow approaches that minimize traction.

7.2 Paper II

Objective: To present our initial experience utilizing a prototype 6.2 -14.3 MHz side-looking, linear array catheter shaped ultrasound for intraoperative imaging during transsphenoidal surgery.

Design: Technical note illustrated by case presentations

Study subjects: 9 patients with pituitary macroadenomas

Results: We present 2-dimensional, high-resolution ultrasound images. The small side-looking, high-frequency ultrasound probe can be used to ensure orientation in the midline for the surgical approach to identify important neurovascular structures to be avoided during surgery and for resection control and identification of normal pituitary tissue.

Conclusions: We believe that the concept of intrasellar ultrasound can be further developed to become a flexible and useful tool in transsphenoidal surgery

7.3 Paper III

Objectives: To determine resection grades and clinical outcome in a consecutive, population-based sample of high grade gliomas, 95% of which were operated with use of the SonoWand system. We also sought to explore the variation in and importance of ultrasound image quality. The relationship between surgical results and patient selection was also described.

Design: Prospective cohort study

Study subjects: 156 consecutive malignant glioma operations carried out 2007, 2008 and 2009 in the department of Neurosurgery, St.Olavs University Hospital, Norway.

Results: 142 (91%) were resections whilst 14 (9%) were only biopsies. We achieved gross total resection (GTR) in 37% of all high-grade glioma resections. There was a worsening of functional status in 13%, as assessed by the modified Rankin Scale. The risk of getting worse was significantly higher in reoperations, resections in eloquent locations, resections in cases with poor ultrasound image quality, resection when surgeons' resection grade estimates were inaccurate, and in cases with surgery-related complications. Aiming for GTR, unifocality of lesions, non-eloquent location and medium or good ultrasound image quality were identified as independent factors associated with achieving GTR.

Conclusions: We report good overall results, both in terms of resection grades and functional outcome in consecutive malignant glioma resections, in which intraoperative ultrasound was used in 95%. We observed a possible dose–response relationship between ultrasound image quality and clinical and radiological results. This may suggest that better ultrasound facilitates better surgery. The study also clearly demonstrates that, in terms of surgical results, the selection of patients seems to be much more important than the selection of surgical tools.

7.4 Paper IV

Objective: In retrospective study we sought to compare survival before and after the introduction of neuronavigation and 3D ultrasound in glioblastoma surgery in our department in November 1997.

Design: A retrospective case study with a historical control group

Study subjects: 192 glioblastoma patients who received surgery and postoperative radiotherapy in St.Olavs University Hospital between 1990 and 2005.

Results: We observed an increase in survival for patients in the last study period, 9.6 (n = 85) versus 11.9 months (n =107); HR = 0.7; p = 0.034. Significant improvement in the latest time period was sustained after adjusting for age, WHO performance status (≥ 2), type of radiotherapy (normofractioned or hypofractioned), and chemotherapy (yes/no), p = 0.034.

Conclusions Our study demonstrates a statistical significant improvement in survival after the introduction of neuronavigation and 3D ultrasound. The case mix has changed in the study period and the use of a historic control group is a weakness. The improvement was still statistically significant after adjustment for known major prognostic factors. The demonstrated association is a necessity for causation, but given the nature of this study, one must be cautious to claim causality.

7.5 Paper V

Objective: To determine the impact of modern image guided glioma surgery on patient reported QoL. We also sought to compare how QoL is related to traditional outcome parameters and explored possible predictors of QoL in these patients.

Design: Prospective follow-up study

Study subjects: A selection of 88 patients with intracranial gliomas operated in the department of Neurosurgery, St.Olavs University Hospital, in the years 2007, 2008, and 2009.

Results: The median EQ-5D index value was 0.76 (range -0.59 to 1.00) preoperatively and 0.75 (range -0.24 to 1.00) 6 weeks postoperatively (p= 0.419)**.** 35.2 % reported an improvement, 20.5 % reported no change and 44.3 % reported a deterioration in QoL following surgery. Occipital lesions (p=0.033), no use of ultrasound for resection control (p=0.009), new motor deficits (p=0.002), new language deficits (p=0.037) and new unsteadiness and/or ataxias (p=0.002) were independent predictors for worsening of QoL following surgery.

Conclusions: The study indicates that modern glioma operations per se do not have a detrimental overall effect on QoL in the average patient – however it is of paramount importance to avoid new deficits as this has a major undesirable effect on QoL. Previous studies that have reported positive associations between GTR and postoperative QoL probably are affected by selection bias since extensive resections are more often carried out in patients in a good preoperative condition. The EQ-5D scores correlate to traditional variables, but also offer a more detailed and presumably more unbiased description of outcome, adding the patients' point of view.

8 Discussion

8.1 Association or causation?

A correlation between two variables does not automatically imply that one causes the other, but a correlation is necessary for causation, and can indicate possible causes or areas for further investigation. Does intraoperative ultrasound improve brain tumour surgery? Sir Austin Bradford Hill proposed in 1965 nine criteria to appraise when an association might be considered causal, such as: strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence and analogy [124].

In paper III we explored correlations between surgical results and various factors. For example was medium or good ultrasound image quality, independent of other studied factors associated with higher odds for obtaining GTR. The correlation was quite strong with an odds ratio of 7.6. A strong association is more likely to be causal than a weak association. There may still be confounders that are perhaps not quantifiable. For example, so-called reverse causation could exist if operations with poorer surgical results increased the chances of the surgeons scoring intraoperative image quality as poor. In paper III we also found that the surgeons' ability to correctly estimate the extent of resection was associated with the reported intraoperative ultrasound image quality. Again, there may be confounders, but this relationship may suggest a biological gradient, supportive of a causal relationship between the use of ultrasound and surgical results. We also found that the risk of neurological worsening following surgery was significantly higher in cases with poor ultrasound image quality. In paper V we found that active use of ultrasound in resection control, but not ultrasound image quality was independently associated with change in patient reported QoL following surgery. This could imply that surgery is safer if resection is guided by active use of ultrasound, although again, there may be confounders. One possible explanation is that active use of intraoperative ultrasound may reflects the surgical mentality in the

single patient – when no or only one intraoperative image acquisitions are carried out, this could reflect therapeutic nihilism in cases with less hope of benefits from surgery. Due to weaknesses associated with a historic control group and the possibility of confounders we were also reluctant to claim causality in paper IV, but the study demonstrates that survival has improved in the same period that intraoperative ultrasound and neuronavigation was introduced and established in our department. The demonstrated association is a necessity for causation, but there is still room for doubt.

8.2 The levels of evidence in neurosurgery and medical technology

Neurosurgery is a practical speciality where procedures and skills traditionally have been developed through the learning of own mistakes and triumphs, or those of others. Much of surgical practice is determined by common habits or simply because “this is how I was taught”. Surgery is usually complex interventions, ivolving sereval steps and phases. There are few standardized surgical procedures, and indications, approaches, techniques, and preferred technical aids may vary much from surgeon to surgeon and from centre to centre. Such mentioned variations often raise questions about the validity of surgical research, contrasting the often easily standardized interventions in medical drug trials.

The evidence supporting the use of even acknowledged technical aids in surgery is often surprisingly scarce. While new medical drugs are compelled to document the safety and document benefits in a standardized manner involving pre-clinical studies and phase 0-IV clinical trials (first-in-human studies, small group of volunteers, randomized multicenter trials and post marketing surveillance trials), the requirements to new medical technology are far less stringent. It is usually sufficient to demonstrate a likely technical feasibility along with an argumentation for patient safety before marketing of technical tools.

Systematic post market surveillance or controlled documentation of benefits is seldom seen. It is a common problem in medical technology that “the proof of the pudding is in the eating“, and new tools are introduced, used and perhaps abandoned without much evidence at all [125]. Another challenge is that technology constantly evolves so that an evaluation of today’s technology may not be true next year.

Over the last two decades the concept of evidence-based practice has evolved in both medicine and surgery [126]. It has been postulated that “applying what we know already will have a bigger impact on health and disease than any drug or technology likely to be introduced in the next decade” [127]. Evidence based surgery involves the systematic and scientific use of current best evidence in making clinical decisions. Evidence and research findings may be classified in hierarchic categories. The most widely utilized classification system is by the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net):

Level of Evidence in therapy/prevention, aetiology/harm	***Requirements (2009):***
Ia	Systematic reviews (with homogeneity) of Randomised Controlled Trials
Ib	Individual RCT (with narrow Confidence Interval)
Ic	Met when all patients died before the X became available, but some now survive on it; or when some patients died before the X became available, but none now die on it.
IIa	Systematic review (with homogeneity) of cohort studies
IIb	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
IIIa	SR (with homogeneity) of case-control studies
IIIb	Individual Case-Control Study
IV	Case-series (and poor quality cohort and case-control studies
V	Expert opinion without explicit critical appraisal, or based on physiology, bench researchor "first principles"

As seen, randomised controlled trials can provide higher levels of evidence than other types of studies. A much raised criticism towards the evidence based approach is exemplified by the humorous fact that no randomised trial supports the use of a parachute if jumping off an airplane [128]. Indeed, many clinical or technical aspects can not be easily investigated in RCTs, especially, complex treatments, those that require long term follow-up, rare entities, and those that require unethical experiments. However, it should still be noted that the use of parachutes may be regarded as level Ic evidence according to the Oxford criteria, since it observational data indicate that people who fell from aeroplanes before the invention of parachutes all died, while survival of parachute jumpers is now close to 100%.

Evidence based surgery is about much more than RCTs. Evidence-based medicine (or surgery) is the conscientious and explicit use of clinical expertise and current best evidence in making decisions about the care of individual patients [129]. Sometimes, some forms of treatment are not appropriate for our individual patient. Often, the exclusion criteria of the available RTC may exclude individuals like our patient. Even more often, there are no available RCTs, and one has to rely on other levels of evidence. Also, the position of the RCTs is also often weaker in surgery than in medicine, due to the limited availability of RCTs in surgery and due to the often lower quality of surgical RCTs. While well designed RCTs may provide the highest level of evidence, poorly designed RCTs may be misleading because their design affords them unwarranted credibility [130]. Only 4% of the clinical neurosurgical literature found in EMBASE and only 3% of the neurosurgical clinical trials found in MEDLINE are randomized controlled trials, and only about half of such trials are of good quality [131]. Lack of statistical power is a common problem [132]. Extremely few randomised trials assess medical technology.

There are several obstacles that limit the possibility of obtaining the highest levels of evidence in surgical research. Randomisation may be particularly challenging in surgery due to several factors; patients may not want their

operations to be selected by randomisation, standardisation of the surgical intervention may be difficult, urgent or emergency surgery makes inclusion challenging for many procedures, the potential learning curve effect in surgical skills may complicate the interpretation of results. The timing for randomised trials in surgery can also be difficult. Surgeons may be reluctant to randomise while a procedure or technique is being developed, and may still be reluctant after steady state is reached, since they are then using the technique routinely and may be convinced of its value. There is also often limited funding for surgical RCTs and there are the ethical obstacles associated with blinding or sham interventions.

Nevertheless, despite frequent use of inferior scientific methods it is noted that practical neurosurgery is progressing and has gone through a metamorphosis in few decades. The progress has largely been due to the introduction of and refinement of new technology, and usually not tested in high quality clinical trials. Modern surgical methods are safer and peri- and intraoperative technology allow for more accurate surgery, better patient selection, better planning of surgery, better pre- intra and postoperative surveillance of patients, and better evaluation of outcome or complications. Still, almost no tools or techniques utilized in modern neurosurgery have been evaluated in high quality controlled studies, including pre- or postoperative MRI, intracranial pressure monitoring, various types of neuronavigation, electrophysiological neuromonitoring, direct microscopy or endoscopic visualization techniques, intraoperative fluoroscopy, ultrasound aspirators, various minimal invasive techniques, different surgical approaches, and practically all aspects of neurointensive care.

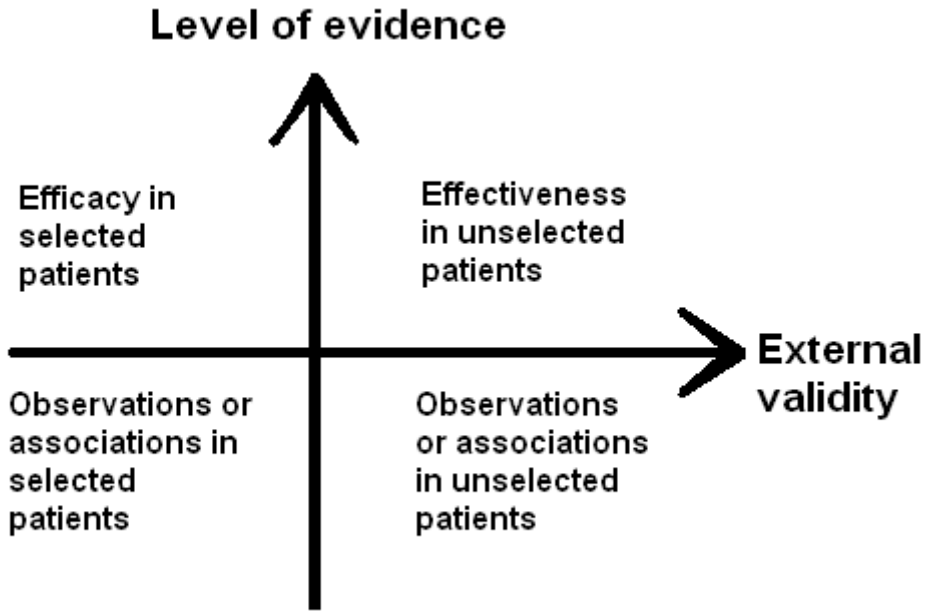
8.3 Efficacy - effectiveness - efficiency

Efficacy is the extent to which an intervention works under ideal circumstances, e.g. in carefully selected randomised controlled trials. *Effectiveness* is the extent to which an intervention works under the non-ideal, usual circumstances of healthcare practice, e.g. in observational studies of unselected patients or in patient registries. *Efficiency* depends on whether an intervention is worth its cost to patients or society, e.g. as assessed in cost-efficiency analyses [133].

Several technical solutions are proposed to increase resection grades in high grade gliomas, including fluorescence guided surgery, intraoperative ultrasound, intraoperative contrast-enhanced high field or low field MRI. So far, only the efficacy of 5-ALA fluorescence guided resection has been assessed in a high quality RTC [100]. Although plausible or feasible, for a technology to affect overall treatment results in such patients it needs to be widely employed, not only in small project-like series. Increasing operating time, high costs and uncertainty about benefits may be the reason why few neurosurgical departments routinely employ various technical aids in unselected patients. Intraoperative ultrasound with 3D-reconstructions enables close to real-time intraoperative imaging for updated maps during navigation, and there is no need for new surgical instruments or a modified operating theatre. Ultrasound devices are also quite cheap compared to competing technology like intraoperative MRI. As intraoperative ultrasound technology does not alter operation logistics or prolong operation times much, it can be applied routinely in most brain tumour operations, as done in our department.

Although the efficacy of an intervention may only be proved beyond doubt through well conduced RCTs, effectiveness may usually not be assessed in randomised controlled trials due to the often carefully chosen inclusion and exclusion criteria. Results reported in RCTs may therefore be misleading, if extrapolated to unselected patients. To provide higher levels of evidence

(i.e.demonstrate efficacy) and to provide high external validity (i.e. demonstrate effectiveness) may therefore often be conflicting abilities in study design:



Cost-efficiency analyses are becoming more relevant outcome measures. There is increasing need for health care prioritizations since treatment options, costs, and demands are growing rapidly. One approach is measuring treatment and complication costs together with quality of life measurements with a generic instrument, such as the EQ-5D. A QALY (Quality Adjusted Life Year) gives an idea of how many extra months or years of life of a reasonable quality a person might gain as a result of a treatment. The cost per QALY is a measure of the cost-efficiency of the treatment. For certain neurosurgical interventions, such as high grade glioma surgery, the gain in terms of extra months with a reasonable quality of life is presumably quite modest. The cost-efficiency of technical adjuncts may therefore also be marginal. New technology may increase cost-efficiency either by prolonging survival through increasing the frequency of gross total resections, by avoiding a loss of quality of life due to neurological deficits from surgery, or by lowering costs.

8.4 Uncontrolled data – common limitations

The papers I, II, III and V are based on cases without controls. Case series without controls are common in the neurosurgical literature. Much evolvement of surgical techniques and surgical knowledge has traditionally been based on the communication of uncontrolled "personal series" with questionable external validity along with strong personal opinions by famous surgeons. The transsphenoidal approach to pituitary tumours was for example practically abandoned for 30 years after Harvey Cushing, ("the father of neurosurgery") spoke in favour of the subfrontal route in 1929. In modern times, the validity of surgical case reports or observational case series has been questioned [134]. However, the practical nature of surgery and the obstacles and limitations associated with controlled trials in surgery still leaves a role for this type of research. Case series may also serve as valuable audits for the conducting surgeons and institutions, and as an equivalent of phase IV drug trials, i.e. "post-marked surveillance" of the procedure, tool or intervention. How interventions work in non-ideal and everyday settings, i.e. the effectiveness can be and is studied in such observational case studies. However, the assessment of own data is a common source of bias in surgical outcome studies. It is also known that studies with excellent surgical outcome are more likely to be published. Results from literature reviews or meta-analyses may therefore be misleading [135]. Community-based prospective registration of all patients who underwent surgery (such as from treatment registries), providing a sampling free from publication bias should therefore be encouraged [136]. The estimation of causal effects from observational data is however difficult. Associations observed in such studies may be due to: a) statistical chance, b) bias, c) confounding, d) reverse causality, e) causation.

It should also be remembered that the placebo effect of surgery may be even higher than for medical interventions. There are several awaking examples of established and popular surgical treatments and techniques that have not stood the test of sham controlled trials.

8.5 The value of the presented research

Although image based intraoperative ultrasound has been employed in neurosurgical operations for almost 30 years, only level IV or V evidence (Oxford Centre for Evidence-based Medicine) like technical reports or case-series without controls have been published so far. Due to the scarce evidence avaliable, there is much room for personal opinions. Consequently, the utilization of ultrasound, like most other tools in neurosurgery, varies much from surgeon to surgeon and from centre to centre. There are both enthusiasts and critics. The evidence in support of both the ultrasound and the neuonavigation part of the SonoWand system is also quite limited. There has therefore been a call for more clinical evidence. The results presented in this thesis are from both feasibility studies of technical applications (paper I and II) and attempts to collect more clinical data related to the use of this technology (papers III, IV and V). The external validity is presumably quite high in papers III, IV and V. In these papers we presented circumstantial evidence concerning the use of ultrasound in brain tumour surgery. In paper III we reported an association between ultrasound image quality and surgical and clinical results. In paper V, active use of ultrasound in resection control was independently associated with improvement of QoL after surgery. However, as there may be confounders, no causal relationships are claimed in the papers. The use of a historic control group and the retrospective study design is a weakness in paper IV, but the attempt to correct for confounding factors may perhaps be sufficient to still claim class III evidence. Still, despite the acquisition of some new circumstantial evidence, the current thesis is not able to demonstrate definite causal relationships. There is therefore still room for sceptics.

8.6 The popularity of technical aids

Lars Leksell, the inventor of the gammaknife, was familiar with the principles of stereotaxy early in his career and stated that *"I anticipated a rapid development in this area, but I did not recon with the neurosurgeons' conservatism and resistance to any technique deviating from the routine".*

The popularity and variation in utilization of different medical technology is not only depending on the levels of evidence. Trends develop and pass and some technical solutions are saluted or regarded as promising for decades, while others quite quickly are considered obsolete. Such trends may be affected by clinical anecdotes, rumours among colleges, or strong opinions by a few leading clinicians, but also by successful marketing strategies. It should be noted that surgeons may be an easy prey for successful marketing strategies of medical technology. While the pharmaceutical industry has to present phase I-IV studies to support their marketing, often challenged by independent and comparative studies and strict government requirements for reimbursement, the manufactures of medical technology are often left with proving the "pudding by serving it". The "pudding" is served at practical demonstrations and by lending out new equipment for neurosurgical departments to try out. This rather unscientific nature of medical technology testing, marketing and distribution could leave important tools unrecognized and other techniques overrated.

Intraoperative ultrasound in neurosurgery suffers from the fact that it has been around for a long time without being extensively utilized around the world. The poor image quality and artefacts from the early B-mode technology that resembled some kind of radiological *tasseography* [fortune-telling method that interprets patterns in tea leaves or coffee grounds], may perhaps be remembered and associated with the technology today. Many clinicians may therefore perhaps intuitively consider ultrasound inferior to contemporary imaging technology based on MRI or CT. New technical developments in CT and MRI sequences and hardware are readily seen and much appreciated by

clinicians. However, the simultaneous developments in ultrasound technology may be largely unknown. Also, while CT or MR machines are upgraded or replaced as technology develops, old ultrasound scanners are still found in many hospitals and neurosurgical centres. Most neurosurgeons are also very familiar with and skilled at interpreting preoperative and postoperative CT and MR images. Intraoperative imaging based on a different type of technology is therefore unfamiliar and may be associated with more scepticism. For any new technology to gain acceptance, it must not only adequately fill a true need, but must also function optimally within the confines of coexisting technology and concurrently available support systems [137].

9 Future perspectives

Curiously, the only doctor to receive the Nobel Prize for a neurosurgical technique was the Portuguese neurologist Antonio Egoz Moniz who received the price in 1949 for the development of frontal lobotomy. It is not easy to predict what techniques that will be rewarded and which that will be discredited in the future, as further exemplified by the quotation by Lord Kelvin on the third page of this thesis.

9.1 Seeking higher levels of evidence?

It is possible that the future of ultrasound in neurosurgery is more dependent on intuitive and convincing technical developments than future clinical trials with the existing technology. There is still a demand for higher evidence and ideally randomised trials to clarify the efficacy of intraoperative ultrasound. However, the levels of evidence in support of most neurosurgical opererations *per se* are also low. Thus, to evaluate if a technological surgical aid or tool has an impact on relevant patient outcome parameters is challenging, since it may not even be known that the surgery per se is helpful. It has for example been claimed about malignant glioma surgery, that some technical aids are almost absurd attempts to improve the course of a condition that is not much affected by surgery whatsoever [138]. It may still be argued that, even if the course of some malignant brain tumours may only be marginally affected by surgery, new technology may lessen the negative impacts of surgery by facilitating safer resections. It is however, noteworthy that despite the expensive and fine tools and techniques that are developed, published, sold, and utilized to lower the incidence of neurological deficits, very few researchers have actually asked their patients how they are doing after the tumour surgery. Traditional outcome parameters where surgeons evaluate their own patient's outcome in a gross functional scale should be replaced by more objective evaluations, more nuanced scales, and preferably also QoL measurements. Cost efficiency analyses based on generic

QoL data are probably also increasingly relevant to ensure that increases in costs in health care are associated with clinically important result improvements.

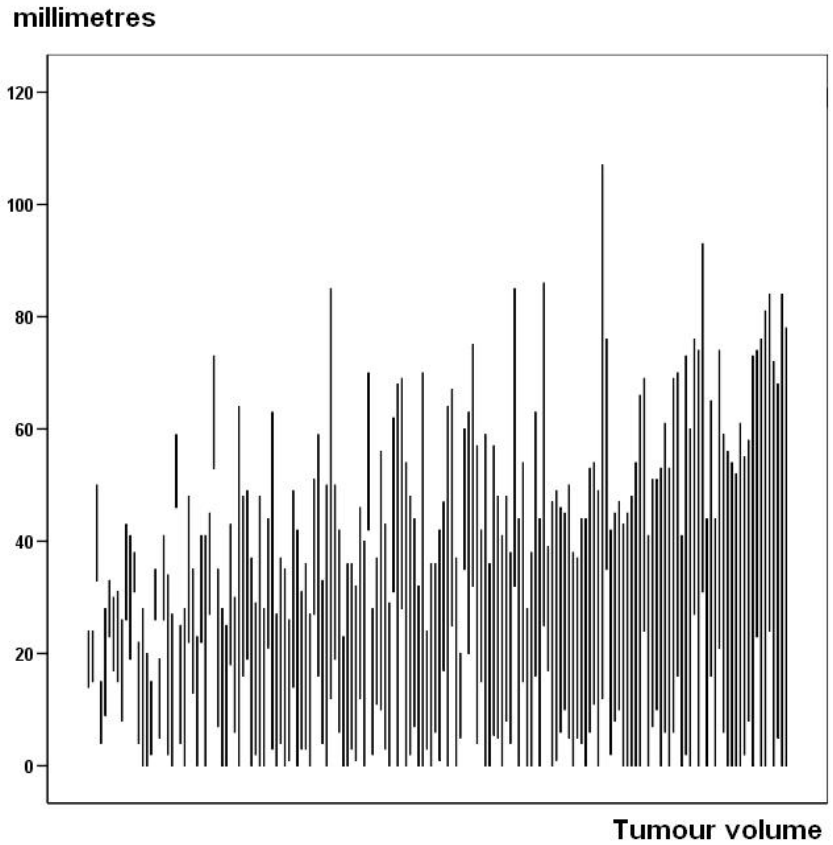
Ideally, the implementation of a new therapy or technology over currently available best practice should require the demonstration of improved results, or the same results at reduced costs or risks [139]. However, since a demonstration of effects is usually not required for marketing, the medical technical industry is usually more focused on innovation than evaluating clinical efficacy. Neurosurgical everyday practice is also still much influenced by personal experience, local treatment traditions and local, or less local experts, not necessarily always advocating evidence based practice. The offered treatments and preferred techniques and tools may therefore differ to a surprising extent between surgeons and centres, even in the Norwegian socialized health care system, despite quite evenly distribution of recourses and uniform licensing and training of health professionals. However, as trials are conducted and scientific evidence is mounting, there will likely be a need for more evidence based treatment guidelines.

There are still extremely few randomised trials in brain tumour surgery. The institutional case volume of brain tumours is too low for obtaining a sufficient sample volume for a high quality randomised trial in almost all neurosurgical centres. Fortunately, the number of multicentre trials is increasing along with the quality of neurosurgical research [131]. The expense and time involved in designing and administrating high quality clinical trials in medical technology is enormous, and the funding of non-pharmaceutical trials can be difficult to obtain. Together with the lack of power, limited external validity and methodological limitations often associated with randomised trials in surgery, it may perhaps be more feasible to gain further evidence through a strengthening of national treatment registries or to develop international treatment registries. High quality observational data after neurosurgical or neuro-oncological interventions, preferably including QoL and neuroimaging data, could be used

for quality control and to identify treatment subgroups or modalities that are associated with exceptionally poor or good outcome.

9.2 New technical perspectives

It is somewhat paradoxical that while cardiologist or echo-technicians, who use ultrasound for imaging of a much smaller organ, utilize several different probes, depending on the clinical setting, most publications on intraoperative ultrasound in neurosurgery report of using the same probe in all operated cases. With the SonoWand 1.4 system that was utilized in articles I, III, IV and V we utilized a FPA 5 (4-7) MHz and also a smaller FPA 10 (5-10) MHz probe. These two probes have optimal focus properties from 3-6 cm and 0.5 – 4 cm respectively. Outside the focal range, image resolution and quality is inferior. As seen in figure below, the distance from the ultrasound probe to the proximal and distal tumour borders vary much from lesion to lesion, and a number of tumour borders are outside the optimal focus range of the probes.



Bars representing depth of proximal and distal tumour border from the surgical approach (and ultrasound probe) in 170 ultrasound guided glioma resections in relation to lesion volume (unpublished data).

Ultrasound probes have so far usually not been developed for the sole purpose of neurosurgical use, but are selected more or less carefully from the marked of transducers developed for various medical purposes. The optimal focus range, the type of array, footprint size and probe shape vary among different transducers. The resolution and penetration of ultrasound energy as well as occurrence and type of image artefacts will differ depending on the probe in use. In probe design, there are always trade-offs between resolution, probe size and penetration. There may be a great potential in the development and refining of probes for specialized neurosurgical use. Separate probes may be developed for different operations, as exemplified with our pituitary probe. Future ultrasound probe elements can probably be made smaller and the probes can be become slimmer. Special probes can be designed for burr-hole procedures such as lesion biopsies or ventricle drains, or for specially designed for certain surgical approaches.

So far, ultrasound images of brain tumours have been acquired from outside the lesions. As exemplified with the pituitary probe, it is possible to make high resolution images from within lesions as well. This shortens the distance between the probe and the tissue of interest, which can enable the use of higher frequencies that provide far better image resolution. There may be a potential in developing very high resolution probes to be inserted inside tumours or resection cavities to be used only for resection control. Images from such probes may be displayed on top of the usual ultrasound image from lower frequency probes with larger fields of view. Such cavity probes may for example be tightly curved, high frequency, linear array probes that may be leant directly to the tissue in areas where the surgeon is uncertain about the extent of resection. Such small probes may also record images without the removal of spatulas. This reduces brain shift and increases accuracy. The bright rim artefact that degrades ultrasound image quality during subsequent phases of

resection may be much reduced if ultrasound arrays may be put in directly contact with the tissue instead of being immersed in saline in surgical cavities.

As suggested in study number III in this thesis, the clinical usefulness of ultrasound in neurosurgery may increase with image quality. Several of the new techniques are still in research phase or in the early stage of commercialization. Ultrasound elastography or strain imaging are promising methods to delineate tumor borders and has been applied in breast [140], prostate [141] and brain imaging [142]. A recent commercially available method for exploring and imaging the mechanical properties of tissue is called acoustic radiation force intensity (ARFI) imaging. The method uses radiation force to generate localized displacements and shear waves in the tissue, which can subsequently be used for mapping of mechanical properties of the tissue [143]. A related technique, supersonic shear imaging (SSI) has been developed in France and has been used in examinations of breast and liver [144, 145]. The reports of these new techniques for mapping of mechanical properties of tissue are promising and this technology may become a conjunct to conventional B-mode imaging, and might contribute to better contrast and less false positive or false negative findings in tumor diagnostics and border detections. Another interesting technique for high-frequency contrast imaging has been developed by the ultrasound group at NTNU. Second order ultrasound field (SURF) imaging is a dual band method in which the SURF-probe simultaneously transmits a low-frequency pulse to manipulate the contrast bubbles and a high-frequency pulse for image reconstruction [146]. The benefit is that the method is able to detect and image the micro-bobbles of a contrast agent, even above its resonance frequency, allowing for high frequency contrast imaging. This makes the method potentially suitable for use in brain surgery, where frequencies between 5-12 MHz are of most interest. SURF contrast imaging can potentially be used for both imaging of vascular structures and for delineation of tumours. The probe development into multi-row and 2D arrays will continue, and is likely to be increasingly used also in brain surgery in the coming years. This will increase resolution in the azimuth plane and therefore contribute to better 3D ultrasound reconstructions.

9.3 A future for ultrasound in transsphenoidal surgery?

The inspiring initial results from paper II has lead to a mutual project, involving technical reserchers at NTNU, researchers at SINTEF, and SonoWand A/S to further develop new ultrasound technology for transsphenoidal surgery. A new forward-looking prototype is developed, but is so far not approved for testing in patients. A new side-looking probe with smaller element sizes and even higher resolution may also be developed. We are also exploring the possibility of making 3D reconstruction of 2D ultrasound images from the pituitary probes to allow for neuronavigation and perhaps guided resections with navigated curettes. Commercially available technical solutions for pituitary surgery of will probably be marketed by SonoWand in the near future.

10 Main conclusions

- 3D-ultrasound may be a feasible tool for navigated resection of giant meningiomas
- 2D intrasellar ultrasound may be useful in transsphenoidal surgery, both to ensure anatomical orientation, and to detect residual tumour tissue
- There is an association between ultrasound image quality and clinical and radiological results in high grade gliomas. This may suggest that better ultrasound technology facilitates better surgery
- The selection of patients is crucial for surgical results in case series. Aiming for gross total resection, unifocal lesion, good or medium ultrasound image quality and non-eloquent lesion location were independent predictors of achieving gross total resection in high grade gliomas
- Survival has increased in glioblastoma patients treated with radiotherapy in the years after the introduction of intraoperative neuronavigation and ultrasound in our department. These results may not necessarily reflect a causal relationship, but in the lack of harder evidence, do at least not weaken the use of intraoperative ultrasound in such patients
- Patient rated QoL may be an interesting adjunct to the typical outcome parameters in surgical case series
- Modern glioma operations per se do not have a detrimental overall effect on QoL in the average patient – however it is of paramount importance to avoid new deficits as this has a major undesirable effect on QoL. WHO grade, extent of resection, and primary versus subsequent resection are not predictive factors of surgically related change in QoL

11 References

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TECHNIQUE APPLICATIONS

Navigated resection of giant intracranial meningiomas based on intraoperative 3D ultrasound

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Abstract
Background Surgical resection of giant meningiomas may pose different challenges. Normal brain tissue is often compressed to the limit and is vulnerable to further traction. In addition, severe intraoperative bleeding may be a problem as many giant meningiomas are vascularised with deep feeding vessels entering from the skull base. Neuronavigation based on preoperative imaging can be of limited use as there may be extensive brain shifts during surgery.
Method We have retrospectively evaluated navigated resection based on intraoperative 3D ultrasound in a series of 15 giant meningiomas with a diameter of more than 5 cm. A pre- and postoperative MRI was preformed in all patients. Preoperative and postoperative neurological function was assessed.
Findings We were able to safely perform ultrasound-guided intracapsular gross total resection of tumour tissue in all patients. Twelve out of 15 patients were radically operated (Simpson grade I and II). Major feeding arteries and adjacent normal arteries could be identified by ultrasound power Doppler angiography. In one patient we were not able to indentify important venous structures. All patients experienced postoperative improvement of their symptoms. Postoperative MRIs did not reveal significant ischemic changes in adjacent normal brain tissue. The mean duration of hospitalisation after surgery was 4.9 days.
Conclusion We present a method of ultrasound-guided resection of giant meningiomas. The method enables image-guided resection through narrow approaches that minimise traction. Power Doppler angiography allows the identification of feeding vessels that may be coagulated to limit bleeding. Likewise, normal arteries can be avoided during surgery. The tumour capsule is often surprisingly easy to remove from the arachnoid membrane after gross intracapsular tumour reduction.

Keywords Meningioma · Ultrasound · Neuronavigation

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Introduction

Surgical excision is the primary goal in management of giant symptomatic intracranial meningiomas. The recurrence rates are lower for complete resections that include the dural base [10, 20]. However, many meningiomas are not easily excised or simply should not be operated on radically due to excess risk of damage to enveloped cranial nerves or vital vessels or sinuses. In large meningiomas the mortality and morbidity associated with surgery can be considerable [1, 2, 21]. The technical challenges and risks vary with location, the vascularisation of the tumour and the degree of involvement of vital structures.

Neuronavigation with 3D visualisation of preoperative imaging modalities has been suggested useful to facilitate the surgical approach, to identify important neurovascular structures and to guide the resection of the dural tail in operations for skull base meningiomas [8, 11, 17]. However, guided surgery based on preoperative imaging modalities has limitations because of registration inaccuracy and brain shift following the resection of tumour tissue. In giant meningiomas, such brain shifts may be particularly great due to the enormous tumour volumes.

In our department we have for years assessed image-guided tumour resection based on neuronavigation with integrated intra-operative ultrasound [9, 19, 23, 24]. Based on a series of 15 patients we evaluate and describe the possible utility of intraoperative 3D ultrasound in giant intracranial meningiomas.

Patients and methods

In the 6-year period between July 2002 and June 2008, 22 meningiomas with a diameter of at least 5 cm were operated in the Department of Neurosurgery, St.Olav's University Hospital, Trondheim, Norway. In 15 cases, the surgeon chose to use intra-operative 3D ultrasound during surgery. We have reviewed these operations and patients to evaluate the potential benefit of 3D ultrasound neuronavigation in this patient group. The study was approved by the local ethics committee.

All patients underwent a pre- and postoperative MRI. In suspected highly vascularised tumours, supplementary preoperative MR angiograms or digital subtraction angiography (DSA) was carried out. None of the patients underwent endovascular embolisation of feeding vessels. Surgical resection grades were reviewed studying the patients' operation journals and contrast-enhanced postoperative MRIs. MRIs with diffusion-weighted sequences were performed within 72 h after surgery in 12 of the 15 patients, enabling identification of possible circulatory changes in normal brain tissue due to the surgical trauma, a method described elsewhere [12]. The operative procedures were performed by three surgeons, and most of the procedures were performed by the senior author (GU). Conventional operative approaches were chosen. The patient positioning was typically adjusted to enable the surgical approach at the highest point. This was done to facilitate recording of intraoperative ultrasound images through a saline-filled tumour cavity during resection. In most cases, a preoperative 3D MRI scan was used for navigation to facilitate optimal placement of the craniotomy. In one patient with a tumour located adjacent to the rolandic cortex, navigated functional MRI (fMRI) was assessed during the operation, a method previously described [16].

An ultrasound-based neuronavigation system was utilised (SonoWand, Trondheim, Norway). A 4- to 8-MHz flat phased array probe with optimal focusing properties at 3 to 6 cm was used for image acquisition. The probe could also be used for recording power Doppler (ultrasound angiography) images. Three-dimensional ultrasound image volumes for neuronavigation are based on a reconstruction of recorded 2D images. Images were acquired from the intact dura during the initial phase of the operations or from the tumour cavity filled with saline as the operations progressed. The acquisition and the display are done in the same reference system. Therefore, the registration inaccuracy is eliminated with 3D ultrasound [Figs. 1, 2 and 3 (top)]. A tracked pointer device or CUSA (Valleylab, Boulder, CO) with an attached tracking frame was used for neuronavigation. The surgeon was able to alternate between microscopic-guided resection and watching the position of the CUSA tip or the tracked pointer in the 3D ultrasound volumes. The position of the instrument used for tracking, i.e., the CUSA or pointer, could be displayed in axial, coronal and sagittal planes (ACS) on the screen or in a plane defined by the direction and rotation of the instrument used (anyplane). So-called "dual anyplane" was often assessed, presenting a second plane 90 degrees perpendicular to the first plane defined by the surgical instrument.

The tumour capsule was exposed in the operation field and opened to enable intra-capsular resection to start at the highest point of the tumour with minimal traction of normal tissue. Positioning is significant in ultrasound-guided surgery as the cup-shaped cavity has to be filled with saline before updated 3D ultrasound volumes can be recorded during surgery. When required because of suspected brain shift or for progression control, updated ultrasound image data were acquired after some resection. Neuronavigation in 3D

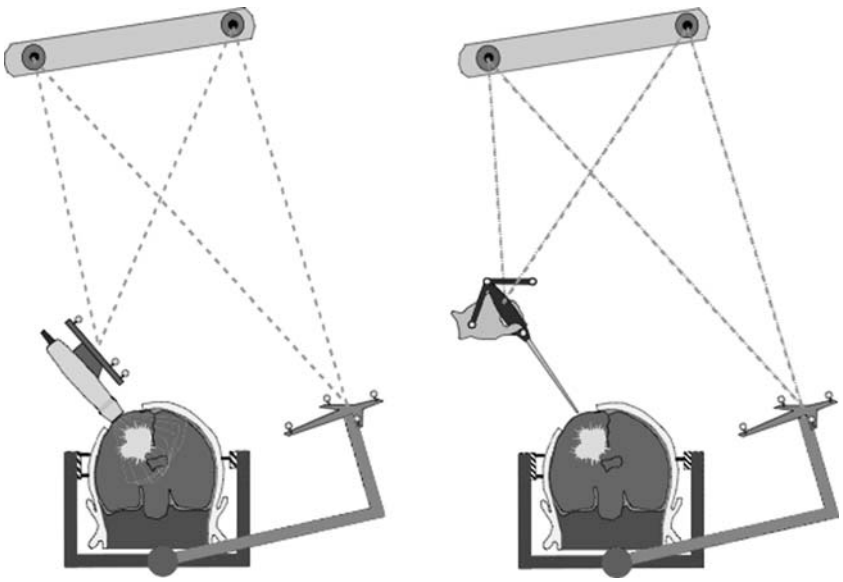

Fig. 1 The acquisition and the display of 3D ultrasound are done in the same reference system, thus minimising registration inaccuracy

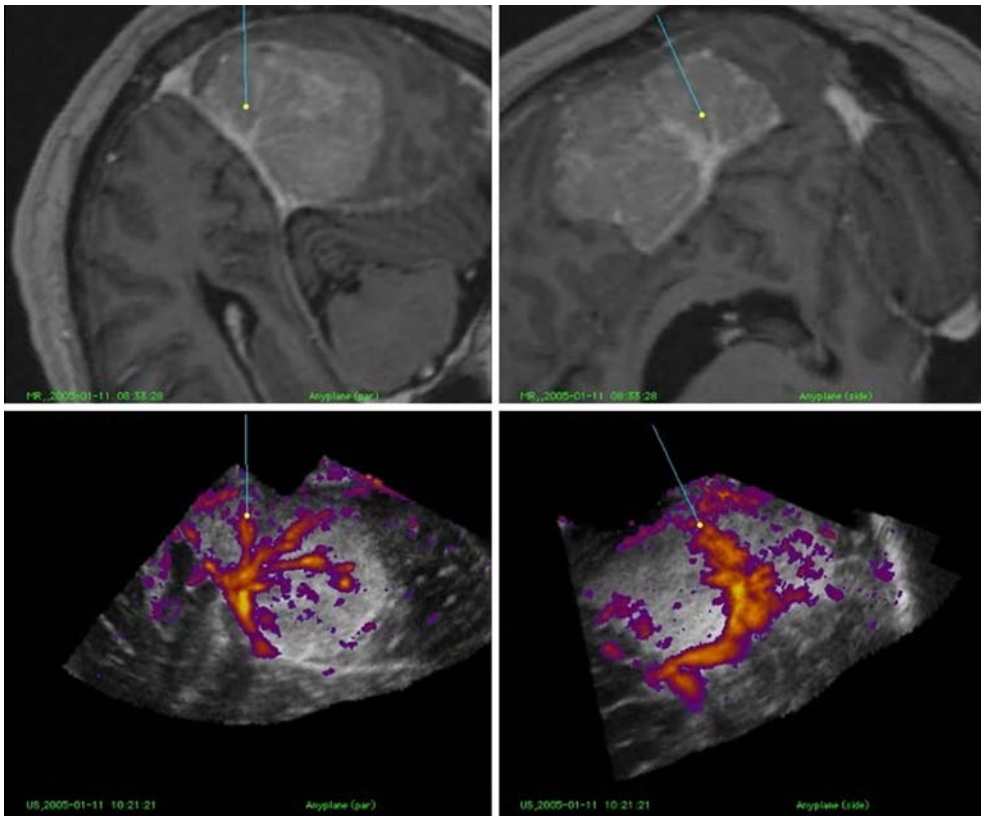

Fig. 2 Patient E: Navigated 3D MRI and 3D US in the same volume. Power Doppler angiography displays feeding vessels from the falx

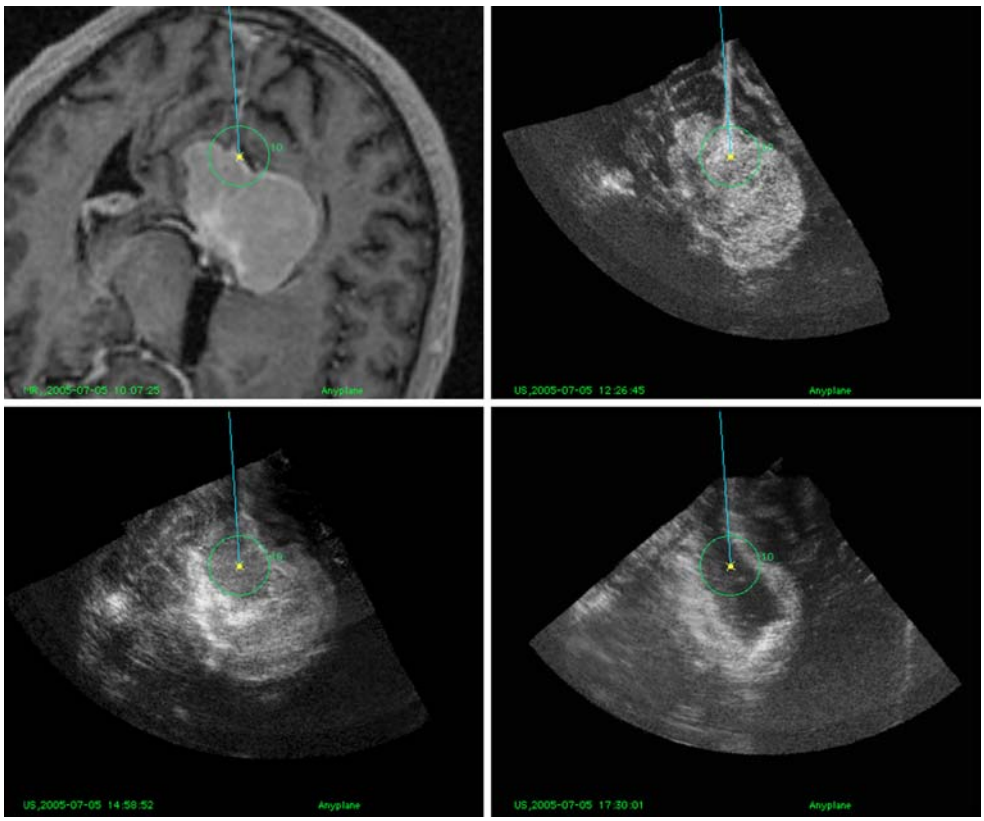

Fig. 3 Patient A: Top: A navigated preoperative MRI and corresponding ultrasound view before resection. Notice the significant registration inaccuracy seen in the navigated MRI. Bottom: Updated 3D US images have been recorded during resection, displaying resection at two different stages

ultrasound volumes, with or without a tracked CUSA, was carried out as the surgeon performed a rapid intra-capsular gross tumour reduction, first leaving 2–3 mm of tumour tissue along the inner borders of the tumour capsule. In patients where vital structures, such as cranial nerves or vessels, were engulfed in the tumour, the gross resection was done more carefully. Ultrasound power Doppler angiography was assessed for visualising vessels. As only the peripheral circumference of the tumours was left, the surgeon could progress without neuronavigation. Microsurgical separation of the tumour capsule from the arachnoid membrane was carefully carried out. The large cavity enabled mobilisation of the remaining tumour border and capsule without traction of adjacent normal tissue.

Results

3D ultrasound imaging and guided resection

The image quality was good in all cases, enabling a clear visualisation of tumour borders. The meningiomas are hyperechoic compared to normal brain tissue. Phased array probes record image data in sectors that are narrow close to the probe. Thus, covering the entire tumour volume of such large tumours may be challenging, especially for tissue adjacent to the probe. A phased probe will only produce optimal images beyond its nearest focal point, requiring a certain distance between the footprint of the probe and the tumour surface. Gelatin stand-off pads were therefore used on the brain surface or on the dura in some cases to increase the distance from the probe to the tumour during ultrasound recordings.

In an early stage of resection, a gross reduction of the intra-capsular tumour volume could be done fairly quickly and safely due to neuronavigation in updated 3D ultrasound volumes. Guided resection with a navigated CUSA was carried out in 14 out of 15 operations (Tables 1, 2, 3). When required due to suspected brain shift or for progression control, new ultrasound image data were acquired (Figs. 3, 4, 5).

Intraoperative bleeding

Even in very vascularised tumours, only heavy bleeding impeded ultrasound-guided gross resection significantly, since the surgeon could rely on updated intra-operative images. As the tumour volumes were reduced, the bleeding typically ebbed, and the feeding vessels of the dural base were reached, exposed and coagulated. In cases with very heavy bleeding, haemostasis was regained through cottonoid packing, bipolar electro-coagulation, irrigation, pausing or applying haemostatic agents. As seen in Table 2, the blood loss was considerable in several patients. In one patient with a particularly vascularised tumour, the bleeding was 3,600 ml. The blood loss was due to profuse intratumoural bleeding before the supplying arteries of the dural base could be reached and coagulated.

Table 1 Preoperative patient data

Patient	Age	Sex (M/F)	Tumour origin, location	Tumour size (mm)	Preoperative symptoms
A	59	M	Midline cerebral tenorium, supra- and infra-tentorial	51×51×46	Headache, diplopia, homonymous hemi-anopsia, cognitive dysfunction
B	37	M	Sphenoid ridge, right frontal	76×72×68	Morning headache, nausea, vomiting
C	52	F	Olfactory groove, right/midline frontal	70×60×55	Headache, cognitive dysfunction, personality change, nausea, incontinence, anosmia
D	34	M	Anterior clinoid process, right frontal	56×55×48	Generalised epileptic seizures
E	62	M	Falx, left occipital	70×50×40	Headache, right homonymous hemi-anopsia.
F	67	M	Convexity, right parieto-occipital	55×46×45	Mild left hemiparesis, reduced vision, unsteadiness
G	47	F	Falx, right fronto-parietal	65×62×60	Generalised epileptic seizures
H	70	M	Sphenoid ridge, right frontal	65×54×40	Headache. Focal epileptic seizures. Mild left hemiparesis, incontinence
I	69	F	Sphenoid ridge, right sylvian fissure	53×42×39	Headache, fatigue, cognitive dysfunction, generalised epileptic seizures, weight loss
J	65	F	Lateral sphenoid ridge, left frontal	68×57×55	Dysphasia, generalised epileptic seizures
K	42	M	Falx, right fronto-parietal	61×59×51	Headache, cognitive dysfunction
L	42	F	Olfactory groove, midline, frontal	55×49×43	Generalised epileptic seizues, cognitive dysfunction, anosmia
M	75	F	Olfactory groove, midline, frontal	53×45×32	Anosmia. Personality change. Cognitive dysfunction
N	28	M	Convexity, right fontal	53×51×46	Focal epileptic seizures
O	62	K	Lateral Sphenoid ridge, left frontal	51×46×43	Generalised epileptic seizures

Table 2 Peroperative patient data

Patient	MRI neuro-navgiation	fMRI neuro-navigation	3D-US navigated CUSA	3D-US angio	Peroperative bleeding (ml)
A	+	–	+	+	500
B	+	–	+	+	3,600
C	–	–	+	+	1,500
D	+	–	+	+	1,600
E	+	–	+	+	800
F	+	–	+	+	600
G	–	–	+	+	1,400
H	+	–	–	+	200
I	+	–	+	+	1,900
J	+	–	+	+	1,700
K	+	+	+	+	2,500
L	+	–	+	–	300
M	+	–	+	+	2,000
N	+	–	+	–	400
O	+	–	+	+	600

Ultrasound angiography

Ultrasound angiography was assessed for visualising normal vessels engulfed by the tumour or in the neighbouring tissue (Fig. 5). Also major branches from feeding vessels were visualised in the tumours (Fig. 2). In patient K, the pericallosal artery was engulfed in the tumour located close to the rolandic cortex. The ultrasound angiography was found

Table 3 Postoperative patient data

Patient	Histo-pathology	Simpson scale	Significant new postop DWI MRI changes in adjacent brain	Surgical complications	Hospital- isation after surgery (days)	Postoperative function
A	Atypical	IV	–	–	5	Good recovery. Still left lower quadrant anopsia and mild memory dysfunction
B	Atypical	II	Missing data	–	9	Good recovery
C	Benign	IV	Missing data	Haematoma in the cavity	6	Good recovery. Still anosmia
D	Benign	I	–	–	4	Good recovery. No seizures
E	Benign	I	–	Peripheral, partial facial nerve lesion	3	Good recovery. Improvement of visual field defects
F	Benign	I	–	–	3	Good recovery. Improvement of balance. Still mild left arm paresis
G	Benign	I	–	Deep vein thrombosis	5	Good recovery. Still seizures at follow-up
H	Benign	I	–	–	3	Good recovery.
I	Benign	I	–	Peripheral, partial facial nerve lesion	4	Good recovery
J	Benign	I	–	Pulmonary embolism	4	Good recovery
K	Atypical	V	–	Transient generalised epileptic seizures	4	Good recovery. Improvement of cognition
L	Benign	I	–	–	8	No seizures at follow-up. Anosmia. Still mild memory dysfunction
M	Benign	I	–	Pneumonia	6	Some recovery. Anosmia. Still moderate cognitive deficits
N	Atypical	I	Missing data	Pyelonephritis	4	Good recovery
O	Benign	II	–	–	6	Good recovery

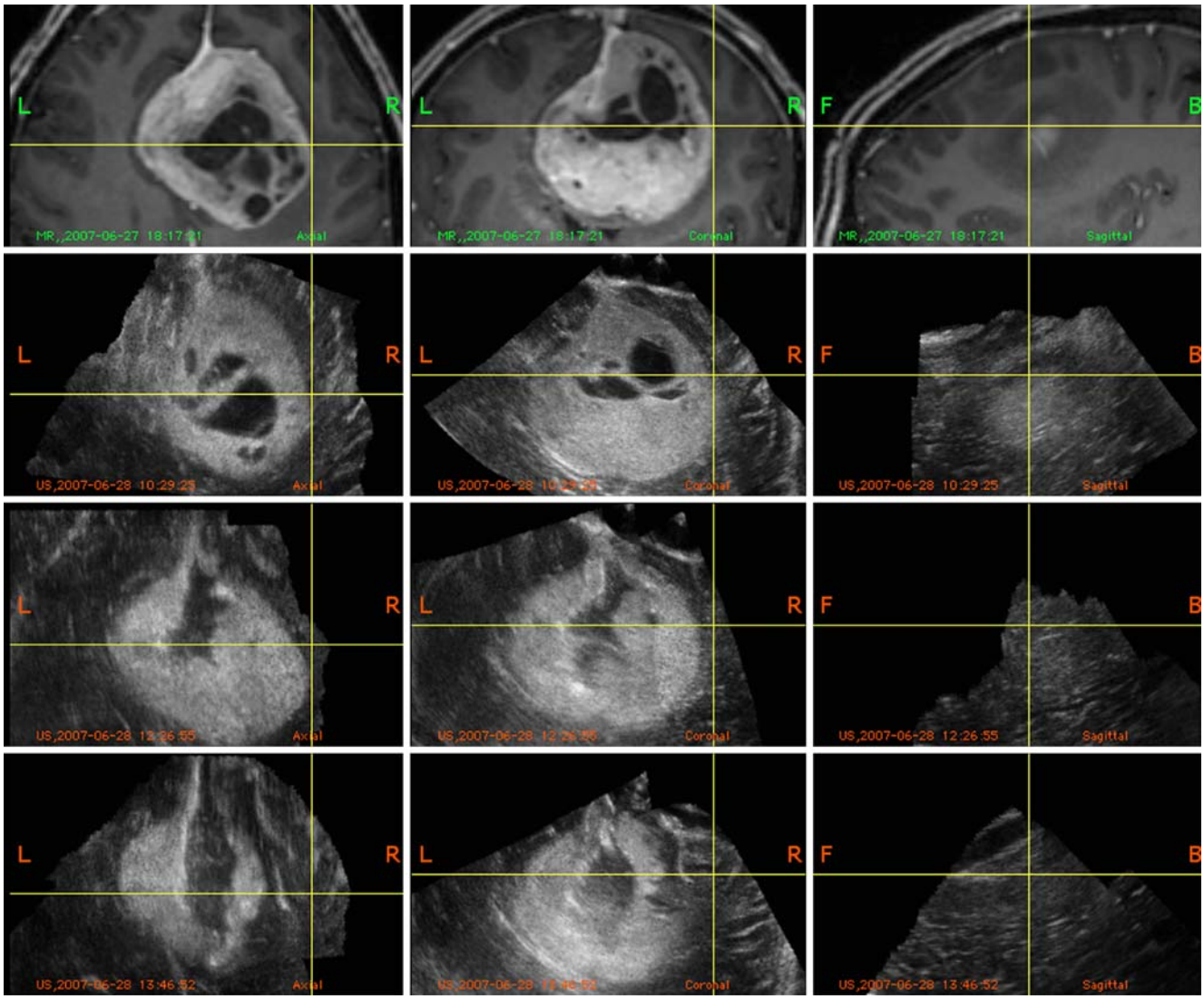

Fig. 4 Patient K: Preoperative MRI (top row) shown together with intraoperative navigated ultrasound images before tumour resection (second row) and at two stages during resection (two bottom rows). The image views are axial, coronal and sagittal from left to right. Notice the considerable brain shift of the lateral tumour border indicated by the cross

useful for identifying the vessel (Fig. 5). In patient C, the very large olfactory groove meningioma had a capsule that was adherent to the parenchyma. The angiography was found useful for the identification of the pericallosal arteries adherent to the capsule. In patient A the venous flow in the vein of Galen could not be visualised by ultrasound angiograms, and the surgeon had to rely on navigation based on preoperative MRI angiograms to avoid this vessel.

Surgical outcome and complications

A complete removal of the tumour (Simpson grade I and II) was possible in 12 of the 15 operations, and postoperative MRIs showed no sign of residual tumour tissue. In two operations (patients A and K), a residual tumour was left deliberately because of involvement of the important venous structures, such as the vein of Galen, the vein of Rosenthal and the posterior part of the superior sagittal sinus. In patient C with a giant benign olfactory groove meningioma, the capsule was adherent to the cribiform plate, and a small remnant was seen in the olfactory groove on the postoperative MRI. Early postoperative MRIs with diffusion-weighted imaging were conducted in 12 of the 15 patients within 72 h. Comparing to preoperative MRIs, no new significant diffusion changes that could indicate circulatory changes because of traction or trauma to the adjacent parenchyma were seen after surgery.

The mean hospital stay after surgery was 4.9 days. None of the patients died, and all patient experienced postoperative improvement of their symptoms. There were no re-operations due to complications. One patient (C) was, however, diagnosed with a haematoma in the tumour cavity.

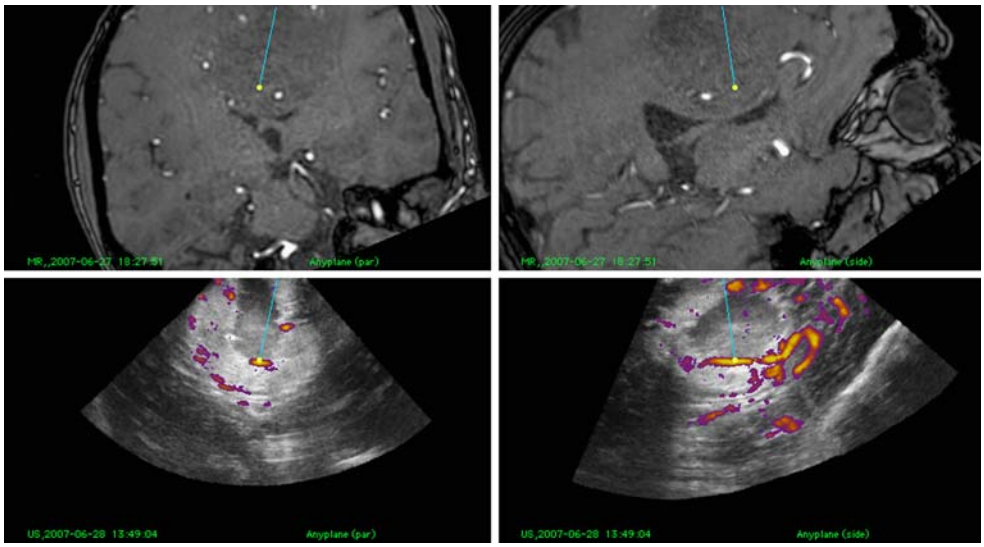

Fig. 5 Patient K: Preoperative navigated MR angiography (top) together with peroperative ultrasound 3D recordings (bottom) displayed in the same volume. The central parts of the tumour are resected. The pericallosal artery was found engulfed in the hyperechoic tumour, as expected from the ultrasound images

The haematoma resorbed, and the patient experienced good recovery.

Two patients suffered a partial loss of function in the temporal branch of the facial nerve because of the low fronto-temporal surgical approach. One patient had a postoperative lower extremity deep vein thrombosis, and one patient was treated for pulmonary embolism after surgery. One patient had epileptic seizures during the first weeks after surgery but has since been seizure free.

Discussion

In operations for large meningiomas, one common conventional operative strategy is to work around the tumour. The surgeon alternates between subcapsular tumour resection and careful removal of the often thin tumour capsule from the arachnoid membrane. In such large lesions, dissecting along the arachnoid membrane may be difficult without traumatising the often oedematous adjacent brain tissue. Another strategy is to follow the inner border of the tumour capsule in order to carry out an intra-capsular gross tumour resection. When operating within such a large tumour mass, attempting to judge the distance to neighbouring and perhaps vital structures is a challenge. Our solution to this challenge is the navigated 3D ultrasound-based resection.

The tumour size inclusion criteria chosen for this evaluation were somewhat arbitrary. There is no accepted definition of "giant meningioma", and various size definitions are used in different publications [2, 7, 15, 22]. We have reviewed 15 ultrasound-guided operations for giant meningiomas measuring more than 5 cm in diameter. In our department, the surgeons chose to operate on seven additional giant meningiomas with conventional methods during the same time period. These cases were however not reviewed for comparison since an unbalanced case control study with only 15 cases would be lacking power and of limited value. Instead, we merely present our subjective evaluation of 3D ultrasound in giant meningiomas to illustrate the technical aspects of this method. Our main point is that guided resection in updated image volumes can facilitate safe tumour removal with minimal traction.

In giant meningiomas the intracranial reserve volume capacity is stretched to its limits, and only minimal traction during surgery can increase the risk of new neurological deficits. To avoid hazardous traction on the normal brain, large skull base tumours and feeding vessels may be reached through extensive bone removal or large craniotomies [4, 5, 7]. Still, most approaches often remain quite narrow during the initial phase of resection in large skull base tumours. Surgery through narrow approaches can be facilitated by image-guided resection since the surgeon can rely on a navigated CUSA when the field of view in the microscope is limited. In the presented cases we found that a gross reduction of the intra-capsular tumour volumes could be carried out at an early stage due to neuronavigation in 3D ultrasound volumes. When required because of suspected shift of the tumour border or for progression control, new ultrasound image datasets could be acquired. In a sphere-shaped tumour with a diameter of 6 cm, leaving 2 mm of margin along the inner border means that 81% of the tumour is removed. Similarly, a quick resection of approximately 80% of the tumour volume was possible in many of our cases, and the haemostasis could be regained as the residual tumour mass shrunk and the feeding vessels of the dural base were exposed and coagulated. We found that with only minimal intracapsular tumour tissue left, the tumour capsule was often surprisingly easy to dissect from the arachnoid membrane of the adjacent brain tissue.

The blood supply of large meningiomas may arise from several vessels, in many cases entering from the dural base and terminating in clouds of minute vessels that may cause profuse bleeding during resection. A common surgical strategy is attempting to isolate and seal off major feeding vessels as the initial step. Early intraoperative interruption of feeding arteries often requires major traction when the feeders are located at the scull base. In selected cases, endovascular embolisation may be an attractive alternative [13]. However, embolisation may be associated with ischemic events and haemorrhages. In a selected series of 167 cranial base meningiomas, neurological deficits occurred in 21.6% with permanent deficits in 9% after preoperative embolisation [18]. In an unselected series of 185 consecutive meningiomas, the overall neurological complication rate after endovascular embolisation was 6.5% [3]. Retrospective studies of embolisation in meningiomas have nonetheless indicated benefits in terms of blood loss during surgery [6, 14]. We chose to operate without preoperative endovascular embolisation in our patients. A considerable peroperative bleeding of more than 2,000 ml was seen in three of our patients. This was due to profuse bleeding from the exposed and highly vascularised tumour tissue before the feeding arteries of the dural base could be reached and coagulated. Approaching such large tumours from the top may be a disadvantage when it comes to bleeding, but is otherwise a gentle technique as traction on normal brain tissue is minimal.

We found that 3D ultrasound angiograms based on power Doppler images were helpful in identifying both major feeding vessels and normal vessels. However, as demonstrated in case A, the visualisation of low-flow veins may be limited. Another problem with angiography based on the power-Doppler technique is that smaller vessels may be overestimated and may cause unnecessary caution due to blooming artefacts that smear colour signals outside vessel boundaries. Still, high-flow major arteries and major normal arteries are usually easily identified during ultrasound-guided tumour surgery [19]. Neuronavigation based on preoperative MR angiograms displayed together with intraoperative 3D ultrasound makes the interpretation of ultrasound angiograms easier.

In our small series of giant meningiomas the clinical outcome was generally very good with quick recovery and reqiring quite short postoperative hospitalisation. In 12 of the 15 cases, a complete removal of the tumour (Simpson grade I or II) was possible. Early postoperative MRIs that were conducted in 12 of our patients showed no significant new diffusion changes that could indicate ischemic complications or traumatic injury to adjacent brain tissue when compared to preoperative MRI. We believe that the lack of new diffusion changes was due to minimal traction and safe and controlled removal of the tumour capsule after gross tumour resection.

Ultrasound-guided resection with a tracked CUSA has a few challenges. The tracking system with cameras needs to localise the CUSA under the microscope at all times. To avoid a possible “navigation shadow” from the microscope, we found it useful to place the cameras low and the microscope a bit higher than usual. In order to easily alternate between looking through the microscope and looking at the ultrasound screens, positioning of the screen is important to avoid unnecessary head movement for the surgeon. As phased array probes were utilised, image sectors are narrow close to the probe with limited near field resolution. When the tumour is close to the probe, covering the entire tumour volume may in some cases be challenging while recording 3D data sets. Gelatin stand-off pads may be used on the brain surface or on the dura to increase the distance from the probe to the tumour during acquisition of ultrasound volumes. To avoid the problem with narrow sectors and limited near field resolution, linear probes with larger apertures will be assessed in the near future.

Conclusion

Giant meningiomas frequently involve normal vessels and may adhere to eloquent structures. Navigation in updated 3D ultrasound volumes with power Doppler-angiography enables a quick and safe intra-capsular tumour resection with minimal traction. It facilitates the identification of important neurovascular structures and a safe removal of the tumour.

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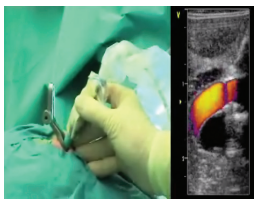

ONLINE DIGITAL VIDEO

Intrasellar Ultrasound in Transsphenoidal Surgery: A Novel Technique

OBJECTIVE: Residual tumor masses are common after transsphenoidal surgery. The risk of a residual mass increases with tumor size and parasellar or suprasellar growth. Transsphenoidal surgery is usually performed without image guidance. We aimed to investigate a new technical solution developed for intraoperative ultrasound imaging during transsphenoidal surgery, with respect to potential clinical use and the ability to identify neuroanatomy and tumor.

METHODS: In 9 patients with pituitary macroadenomas, intrasphenoidal and intrasellar ultrasound was assessed during transsphenoidal operations. Ultrasound B-mode, power-Doppler and color-Doppler images were acquired using a small prototype linear array, side-looking probe. The long probe tip measures only 3 × 4 mm. We present images and discuss the potential of intrasphenoidal and intrasellar and ultrasound in transsphenoidal surgery.

RESULTS: We present 2-dimensional, high-resolution ultrasound images. A small side-looking, high-frequency ultrasound probe can be used to ensure orientation in the midline for the surgical approach to identify important neurovascular structures to be avoided during surgery and for resection control and identification of normal pituitary tissue. The image resolution is far better than what can be achieved with current clinical magnetic resonance imaging technology.

CONCLUSION: We believe that the concept of intrasellar ultrasound can be further developed to become a flexible and useful tool in transsphenoidal surgery.

KEY WORDS: Pituitary tumor, Surgery, Ultrasound

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Unfortunately, residual tumor masses are quite common after transsphenoidal surgery. The risk of a residual mass increases with tumor size and parasellar or suprasellar growth.[1–4] In a large consecutive series of 361 nonfunctional pituitary adenomas, a residual tumor was present in 35.2% of patients after microsurgical transsphenoidal resection.[5] In another consecutive series, transsphenoidal endoscopic tumor removal of 87 pituitary adenomas was total in only 51 (59%) patients.[6] Most residual tumor masses are found in the lateral or suprasellar regions, areas not visualized by direct microscopy or 0-degree endoscopy.

There are several reports on the use of peroperative ultrasound technology for resection control during transsphenoidal surgery. Perioperative transcranial Doppler sonography has been suggested to be helpful for resection control in large macroadenomas.[7] Transcranial Doppler sonography enabled the detection of a shift in A1 signals from the anterior cerebral arteries to a normal position as resection progressed. An inversion of the pituitary diaphragm was suggested an indicator of complete tumor removal. Furthermore, intraoperative B-mode ultrasound through a separate frontal trephination hole has been used for image-guided transsphenoidal resection of large pituitary macroadenomas.[8] However feasible, resolution and quality of ultrasound imaging may be poor at such depths because of the attenuation of ultrasound energy. Moreover, the bony cranial

ABBREVIATIONS: MR, magnetic resonance; **MRI**, magnetic resonance imaging

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base will produce artifacts and shadows in ultrasound images. The advantage of more close-up image recording was explored introducing a pediatric 7.5-MHz phased array transesophageal echo probe with a 9.8-mm tip into the sphenoid sinus during transsphenoidal tumor operations.[9] Transdural color Doppler ultrasonography could visualize major cerebral arteries and residual tumor masses. Transdural high-frequency ultrasound imaging may be a highly sensitive image modality in pituitary microadenomas. In patients with Cushing's disease, using 12- and 15-MHz mechanically oscillating, forward-looking transducers with 11-mm probe tips, extrasellar transdural intraoperative ultrasound was able to visualize 47 of 68 (69%) microadenomas where preoperative 1.5 contrast-enhanced magnetic resonance imaging (MRI) scans were negative or equivocal.[10]

Despite these initial enthusiastic reports, there have not been articles on intraoperative ultrasound in pituitary surgery the past 10 years. A review article from 2006 states that poor image resolution is a major limitation of ultrasound in image-guided pituitary surgery.[11] There has been a conflict between probe sizes and narrow surgical approaches. Looking into the sella from the sphenoid sinus with forward-looking, phased array probes will not ensure clear visualization of perhaps the most interesting regions in surgery for macroadenomas: the suprasellar and parasellar regions. This is because of artifacts from the sphenoid bone and limited near-field resolution.

Ultrasound technology is improving, and element sizes can be made smaller, enabling the construction of smaller probes with much better resolution. We assessed a prototype 6.2- to 14.3-MHz side-looking, linear array, catheter-shaped probe that allows visualization of the supra- and parasellar regions during transsphenoidal surgery. The probe is small enough to be used in the sella during conventional transsphenoidal approaches guided by endoscopy or direct microscopy.

To our knowledge, we are presenting the first report on intrasellar ultrasound. To date, transsphenoidal operations have been assisted by intraoperative 2-dimensional ultrasound in 9 patients with pituitary macroadenomas. We present our initial experience with this potential tool.

PATIENTS AND METHODS

Selection of Patients and Surgical Technique

The study was approved by the Regional Ethics Committee and the Norwegian Data Inspectorate. All patients were included after signing informed consent. Patients included were scheduled for transsphenoidal surgery for pituitary macroadenomas in our department. Endonasal transsphenoidal microsurgical surgery was performed in all cases with the patients positioned in a conventional supine position.

Prototype Probe

Ultrasound images were acquired using a prototype linear array, side-looking probe with a 3 × 4-mm tip diameter and a 4-mm thick distal probe shaft (Figure 1). The transducer array consists of 64 elements with 205-μm pitch and 1.5-mm elevation aperture, covering 12.8 mm of the most distal part of the probe. The center frequency is 10.3 MHz (bandwidth 6.2–14.3 MHz). The probe was produced by Vermon (Tours, France) and equipped with a connector for a commercial system (Vivid 7; GE Vingmed, Horten, Norway), and a specialized application for the probe was developed on this scanner. Acoustic measurements in the ultrasound laboratory of the Norwegian University of Science and Technology verified that thermal and mechanical indexes were within established safety regulations. The ultrasound probe was further electronically tested and approved by the technical department of St. Olavs University Hospital before being used in patients.

Image Acquisition

The probe was covered with sterile drape filled with gel or saline. The probe was introduced into the saline-filled sella turcica after opening the dura. Fluoroscopy was assessed to control positioning of the probe (Figure 2). By rotating the side-looking probe, we could visualize the difficult supra- and parasellar regions not seen through the microscope or a 0-degree endoscope. By electronic tilting of the ultrasound image view as much as 20 degrees forward or backward, the area of visualization could be further extended (Figure 3).

Follow-up

Patients were seen by the surgeon as outpatients approximately 1 month after surgery. All patients underwent routine postoperative MRI 3 months after surgery, except for patient 9, who underwent early postoperative MRI the day after surgery. All patients were admitted for hormone status with stimulation tests 3 months after the operations.

RESULTS

Brief Patient Characteristics, Image Findings, and Clinical Outcome

As seen in Table 1, all 3 patients with functional adenomas were biochemically healed after surgery. No patients in this small series had postoperative hypopituitarism. The patients with preoperative visual field defects improved after surgery. There were no major complications.

When studying the figures in this article, one should bear in mind that ultrasound is a dynamic image modality. Much information is lost when only looking at frozen images. Ultrasound images are best interpreted when holding the probe in 1 hand, enabling manipulation with different image planes to sort out artifacts from other signals. To appreciate the flexibility and dynamics of this imaging technique, we strongly encourage the reader to view the short accompanying video (See Video, Supplemental Digital Content 1, http://links.lww.com/NEU/A248, which demonstrates the ultrasound probe being rotated inside the sella in a patient with a macroadenoma.). If comparing the ultrasound image quality with the presented magnetic resonance (MR) images, it is essential to remember that the areas seen in the ultrasound images are much smaller than the larger MR images presented. Thus, ultrasound images may appear coarse if compared directly to the presented MR images without attention to the difference in image size. An example of such a comparison is seen in Figures 4 and 5.

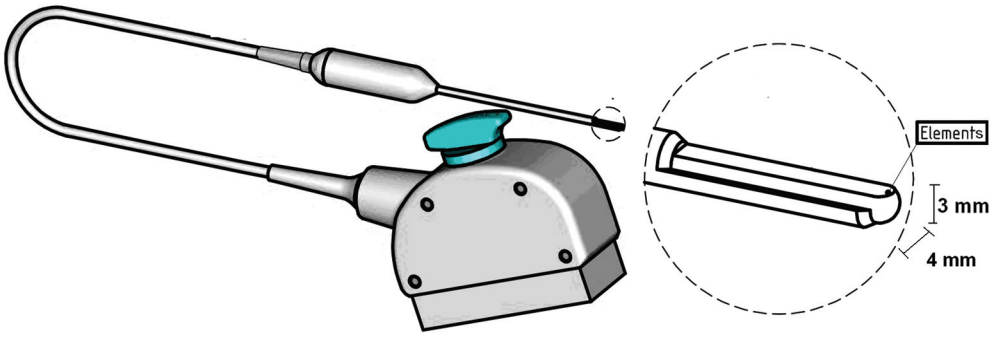

FIGURE 1. *Prototype flat linear array ultrasound probe with the side-looking elements at the distal end magnified.*

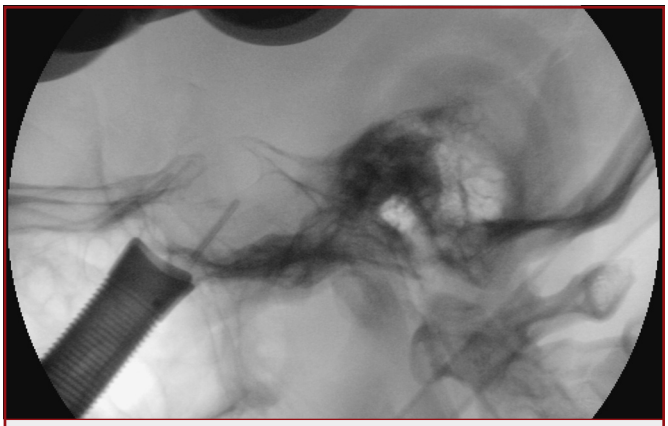

FIGURE 2. *Fluoroscopic image of the tip of the probe introduced in the sphenoid sinus.*

Illustrative Cases

Patient 1

A 44-year-old man underwent repeated surgery for a growing residual nonfunctioning macroadenoma. Because of the limited experience with image interpretation at that stage, the remnant tumor (Figure 6) was not identified or removed, but is easily seen when comparing postoperative MR images with ultrasound images from the operation.

Patient 3

A 74-year-old man had visual field defects caused by compression of the optic chiasm from a nonfunctioning macroadenoma. Because of limited experience with image interpretation at that early stage, the remnant tumor was not seen. However, when reviewing intraoperative ultrasound recordings retrospectively, the tumor remnant was easily identified (Figure 7).

Patient 4

A 35-year-old woman underwent surgery for acromegaly caused by a macroadenoma. Orientation in the sella was eased by ultrasound as the distance to the suprasellar cistern was easily determined (Figure 8).

Patient 5

A 58-year-old woman had a growing nonsecreting macroadenoma approaching the optic chiasm. Orientation in the sella was eased by ultrasound as the midline and normal tissue was localized (Figure 4). The distance to the optic chiasm was easily determined (Figure 9).

Patient 6

A 67-year-old man with severe acromegaly had a large macroadenoma (Figures 10–12). The sphenoid sinus was obliterated with tumor masses. Intraoperative ultrasound enabled orientation and resection control in the sphenoid sinus (Figure 11). After microscopy-guided resection was complete, intrasellar ultrasound imaging demonstrated a tumor remnant by the right carotid artery (Figure 12). The remnant tumor was found and removed. Growth hormone levels fell from 150 mIE/L before to 0.8 mIE/L after surgery. At the time of follow-up, there was no abnormal

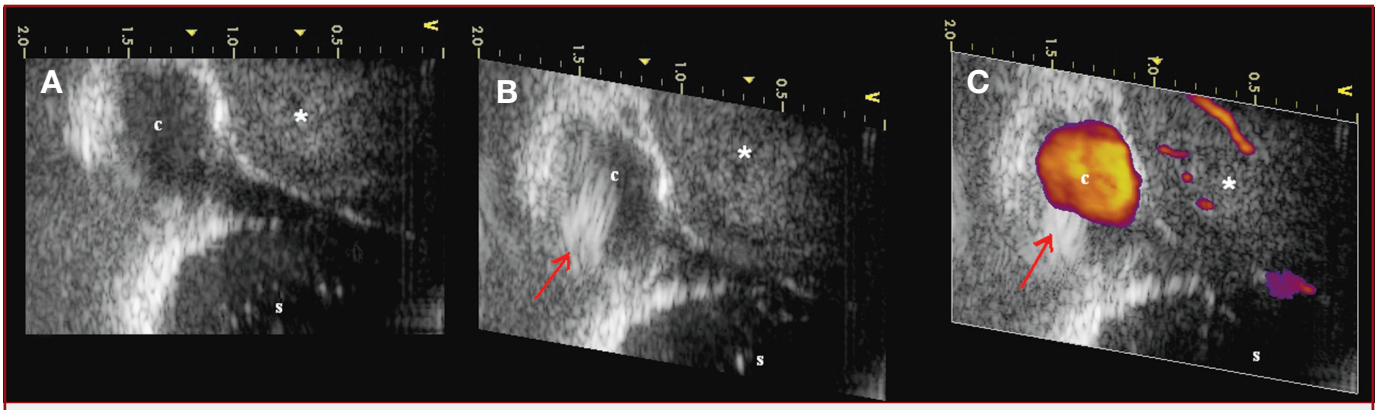

FIGURE 3. **A**, *side view with the probe partially introduced into the sella turcica, displaying tumor tissue (*), the carotid artery (c), and the saline-filled sphenoid sinus (s).* **B** *and* **C**, *side view tilted 20 degrees forward to enable visualization of the dorsolateral parts of the cavernous sinus.* **C**, *power Doppler sonography demonstrates the carotid artery and a vessel within the pituitary gland. Note so-called grating lobe artifacts (red arrows).*

TABLE 1. Patient characteristics, MR image findings, and clinical outcomes

Patient no.	Previous pituitary surgery	Tumor size (mm)	Preoperative hypersecretion	Postoperative hypersecretion	Postoperative hypopituitarism	Preoperative visual field defects	Postoperative visual field defects	Extended resection because of intraoperative ultrasound	Remnant tumor on postoperative magnetic resonance imaging
1	Yes	17 × 16 × 11			No	Quadrant anopsia	No	No	Yes
2	No	19 × 11 × 13			No			No	No
3	No	21 × 21 × 16			No	Bitemporal hemianopsia	No	No	Yes
4	No	18 × 17 × 12	Acromegaly	No	No			No	No
5	No	21 × 15 × 14			No			No	No
6	No	33 × 32 × 31	Acromegaly	No	No			Yes	No
7	No	20 × 19 × 19	Acromegaly	No	No			Yes	No
8	No	28 × 26 × 13			No	Bitemporal quadrant anopsia	No	No	No
9	No	26 × 22 × 19			No	No	No	Yes	No

FIGURE 4. **A**, *contrast-enhanced T1-weighted magnetic resonance imaging (MRI) showing a border between normal tissue and tumor tissue in the right part of the sella turcica.* **B**, *contrast-enhanced T1-weighted MRI. Enlarged view of the area within the red box seen in* **A** *enables comparison of image quality between MRI and ultrasound.* **C**, *combined coronal/axial ultrasound view in the same area showing the tumor border. The tumor was hypoechoic compared with the normal tissue (n). Note the image shadow (sh) produced by bone in the lateral part of the sphenoid sinus.*

increase in growth hormone after a glucose tolerance test. No remnant tumor was seen on postoperative MRI (Figure 10).

Patient 7

A 74-year-old man with acromegaly caused by a macroadenoma. Orientation in the sella was ensured by intraoperative ultrasound displaying the tumor and the normal tissue in relation to the carotid arteries (Figure 5). No remnant tumor was seen on postoperative MRI. His acromegaly was biochemically healed.

Patient 9

A 50-year-old man had a growing nonsecreting adenoma compressing the optic chiasm. Orientation within the sella was ensured by intraoperative ultrasound (Figure 13). The distance to the sella diaphragm and the optic chiasm could be determined. Resection was extended by intraoperative ultrasound as a remnant tumor mass was found and removed from the inferoposterior part of the sella (Figure 14). Normal tissue could be seen by the right carotid artery. Postoperative MRI revealed no visible tumor remnant (Figure 14).

Visualization of Vessels

The carotid artery was easily seen on both sides in all patients (Figures 3–7, 12, 14, and 15). In some patients, the carotid arteries could also be visualized through the lateral wall of the sphenoid bone (Figure 15) before opening the sella floor. By directing the probe elements upward inside the sella, a sagittal view enabled the visualization of the A1 and A2 branches from anterior cerebral arteries, the anterior communicating artery, and the ophthalmic arteries (Figures 8, 9 and 13). In several patients, such as in Figure 5, branches from the superior or inferior hypophyseal arteries were also seen.

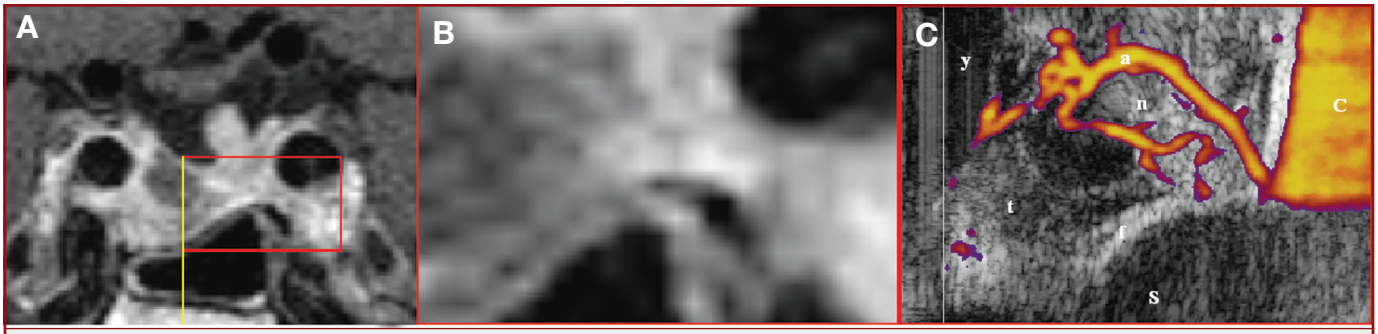

FIGURE 5. **A**, *preoperative coronal T1-weighted contrast-enhanced magnetic resonance (MR) image of the partly necrotic growth hormone–secreting adenoma. The normal tissue is located to the patient's left side. The red box indicates the region visualized in a more axial view in the ultrasound image.* **B**, *the area in the red box in the MR image is magnified to enable a better comparison of image quality between magnetic resonance imaging and ultrasound.* **C**, *ultrasound B-mode and power Doppler image of the left side of the pituitary in a coronal/axial view. Note the carotid artery (c) in the cavernous sinus, the saline-filled sphenoid sinus (s), the sella floor (f), the necrotic/cystic part of the tumor (y), the more solid tumor tissue (t), and the inferior hypophyseal artery (a) supplying the normal pituitary tissue (n).*

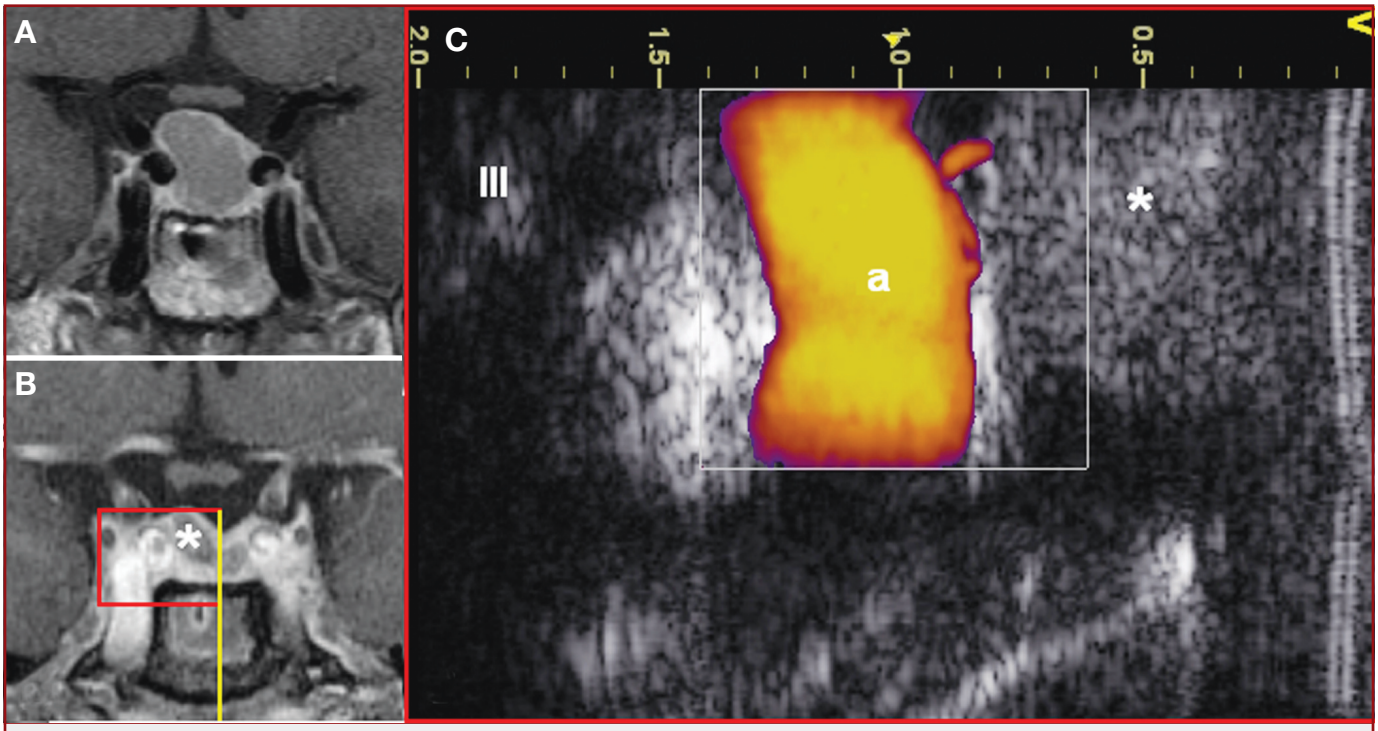

FIGURE 6. **A**, *preoperative magnetic resonance imaging showing the growing residual tumor approximating the optic chiasm.* **B**, *postoperative T1-weighted contrast-enhanced MRI showing a remnant tumor mass (*) on the right side of the sella turcica. The red square indicates the area displayed in the ultrasound image, but in a more axial view.* **C**, *intraoperative ultrasound image displaying the carotid artery with power Doppler angiography (a). Notice the sella floor in the lower right corner and the oculomotor nerve in the upper left corner (III). Ultrasound imaging was done after microsurgical tumor resection. Because of the limited experience with image interpretation at that stage, the remnant tumor (*) was not identified or removed, but is easily seen in retrospect when comparing postoperative magnetic resonance images with ultrasound images from the operation. The scale above the image scale is in centimeters.*

Visualization of Tumor and the Normal Pituitary Gland

Tumor masses were easily visualized in all patients (Figures 3–8, 11–13). Normal pituitary tissue was visualized in B-mode images in 7 of the 9 patients (Figures 4, 5, 8, 13, and 14). For comparison, enhancing normal tissue was also only seen on preoperative MRI scans in 7 of the 9 patients. Normal tissue was somewhat more hyperechoic than the tumor tissue. However, image contrast between normal tissue and tumor tissue varied among the patients, making the interpretation difficult at times. As seen in Figure 5, the vessel supply from the hypophyseal artery termi-

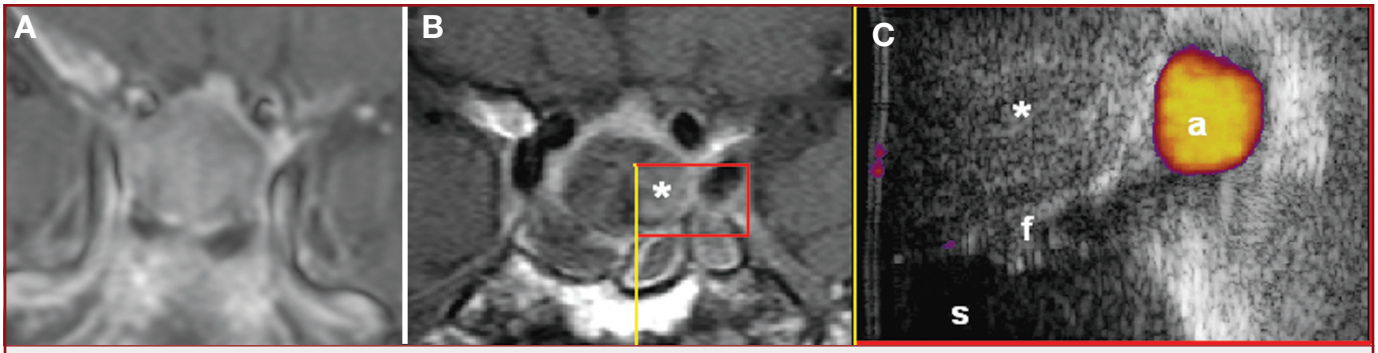

FIGURE 7. **A**, *preoperative contrast-enhanced coronal magnetic resonance imaging (MRI) showing the macroadenoma.* **B**, *early postoperative contrast-enhanced coronal MRI showing a tumor remnant (*) by the left carotid artery.* **C**, *intraoperative ultrasound images reviewed in retrospect clearly display the tumor remnant (*) close to the left carotid artery (a). The sphenoid sinus (s) is separated from the sella by the sella floor (f).*

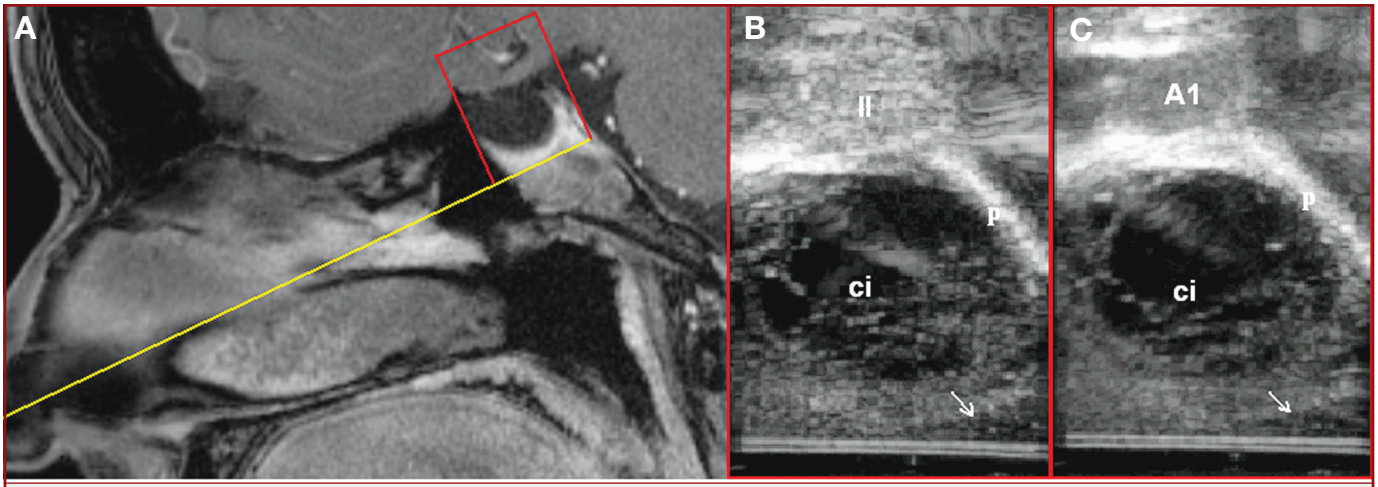

FIGURE 8. **A**, *preoperative sagittal magnetic resonance imaging displaying the trajectory of the catheter ultrasound probe (yellow) and the approximate area displayed in the ultrasound images.* **B**, *after tumor resection; the ultrasound probe angled directly upward toward the suprasellar cistern (ci) displaying the optic chiasm (II) and the pituitary stalk (p). Note the arachnoid membranes within the cistern.* **C**, *ultrasound probe angled upward but slightly rotated to the side enabling visualization of the anterior cerebral artery (A1). The arrows point to the interface between saline in the cavity and normal pituitary tissue.*

nated in the normal part of the gland, aiding the image interpretation and identification of normal tissue.

Visualization of Nervous Tissue

The optic chiasm could easily be seen in sagittal ultrasound views, as demonstrated in Figures 8, 9, and 13. In Figure 7, the pituitary stalk is also seen. However, because of the 90-degree side-looking probe design, the neurohypophysis and pituitary stalk often remain outside the possible image sectors. The oculomotor nerve is seen in Figures 6 and 14. As seen in Figures 9 and 13, the visualization of the suprasellar cistern can help to separate the tumor tissue from the optic chiasm in the ultrasound images.

Visualization in the Sphenoid Sinus

As seen in Figures 11 and 15, lateral views of the sphenoid sinus can ensure orientation in the midline during the surgical approach and enable resection control if tumor tissue extends into the sphenoid sinus. Septations in the sinus can also be visualized.

Image Artifacts

The use of sterile drapes to cover the probe was a common source of image artifacts as small bubbles of air sometimes got trapped in the ultrasound gel in the tip of the narrow drape. Solid bone will produce shadows in the ultrasound images, as demonstrated in Figures 4, 9, and 13. As seen in Figure 3, electronically tilting the ultrasound image may enable an extended visualization; however, so-called grating lobe artifacts may limit the usefulness of this feature.

Blood Clots

Blood clots in the surgical cavity made image interpretation more difficult in several cases. An example of a blood clot in the

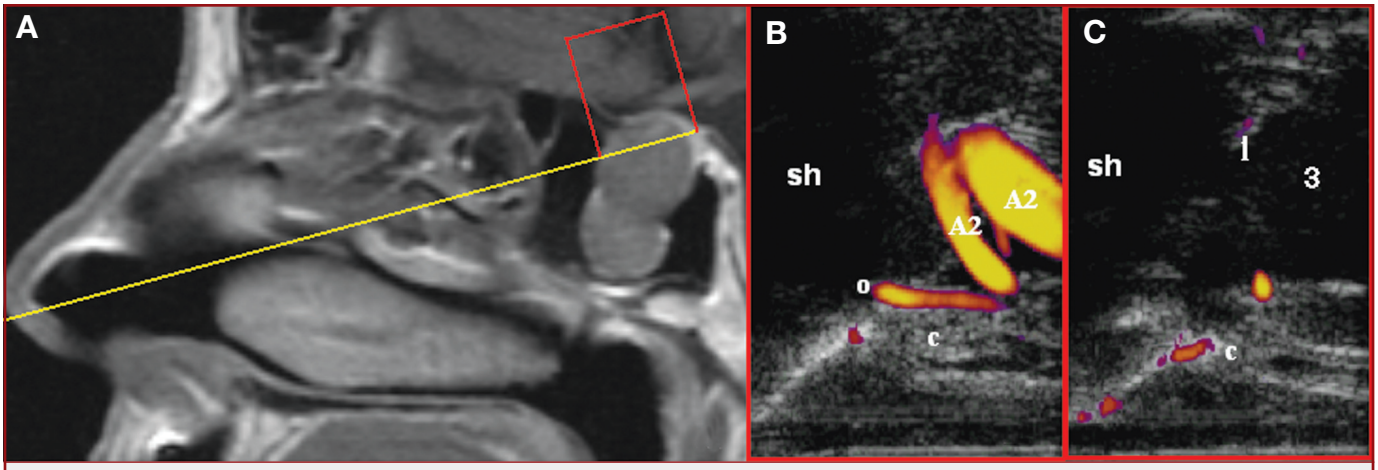

FIGURE 9. **A**, *sagittal magnetic resonance imaging demonstrating the trajectory of the ultrasound probe with the ultrasound elements directed upward.* **B**, *corresponding slightly rotated sagittal ultrasound view displaying the optic chiasm (c), ophthalmic artery (o), and anterior cerebral arteries (A2 and A2). Note the shadow (sh) in the image produced by bone in the cranial base (anterior clinoid ridge).* **C**, *straighter sagittal view compared with that in* **B** *showing the terminal lamina (l) and the third ventricle (3).*

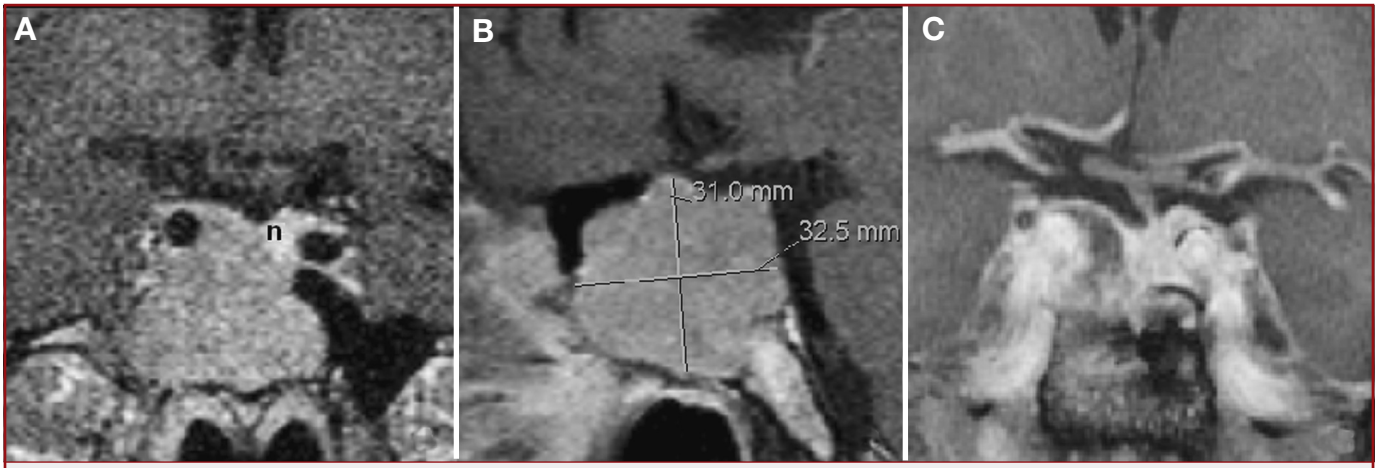

FIGURE 10. **A**, *coronal T1-weighted contrast-enhanced coronal magnetic resonance imaging (MRI) demonstrating the macroadenoma filling the sphenoid sinus and extending to the right cavernous sinus. Normal tissue (n) is seen by the left carotid artery.* **B**, *MRI sagittal view of the tumor showing that the entire sphenoid sinus is obliterated.* **C**, *coronal T1-weighted MRI displaying the contrast-enhanced pituitary gland 3 months after surgery. No remnant tumor is seen.*

posterior part of the sella is seen in Figure 17. The echogenicity of blood can be in the range of hypo- to hyperechoic, depending on the extent of dilution from saline in the surgical cavity. Thus, blood clots may be mistaken for tumor remnants or normal tissue.

Decision Making Based on Peroperative Ultrasound

In the first patients, the interpretation of ultrasound images from unfamiliar projections was difficult, and because of an initial lack of confidence in interpretation, ultrasound did not alter our surgical decisions. The more oblique views may be especially difficult (Figure 16). However, after gaining experience, remnant tumor masses were found and removed after ultrasound imaging. Resection was extended because of ultrasound findings in 3 of our last 4 patients (patients 6, 7, and 9). Postoperative MRI revealed no remnant tumor tissue in these patients. When reviewing the intraoperative ultrasound recordings retrospectively, remnant tumor tissue was also quite clearly seen in the ultrasound images from patients 1 and 3 (Figures 6 and 7).

DISCUSSION

We assessed intrasphenoidal and intrasellar ultrasound in 9 patients undergoing transsphenoidal surgery for pituitary macroadenomas. This novel technology can produce high-resolution images for guidance during surgery. Intraoperative ultrasound can be used to ease anatomic orientation, ensure the identification of important neurovascular structures, and enable detection of residual tumor tissue.

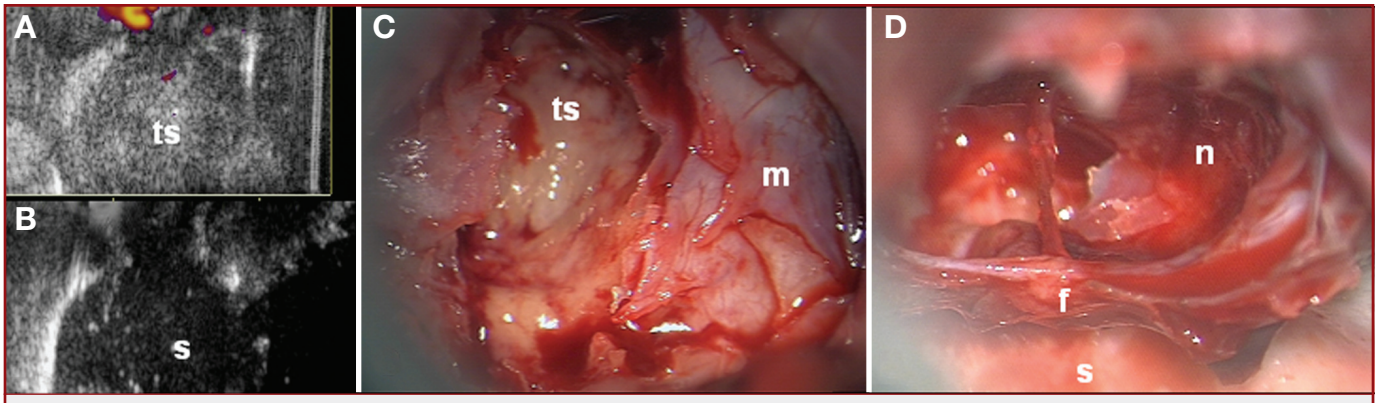

FIGURE 11. **A**, *right lateral ultrasound view of the sphenoid sinus obliterated with tumor tissue (ts).* **B**, *right lateral ultrasound view displaying the saline-filled sphenoid sinus (s) after tumor resection.* **C**, *microscope view of the sphenoid sinus before resection of tumor (ts) and the mucous membrane (m).* **D**, *microscope view of the sella turcica, sella floor (f), and cranial part of the sphenoid sinus (s) after tumor resection. The large opening of the anterior wall of the sella was eroded by the tumor. Normal tissue (n) was seen by the left cavernous sinus.*

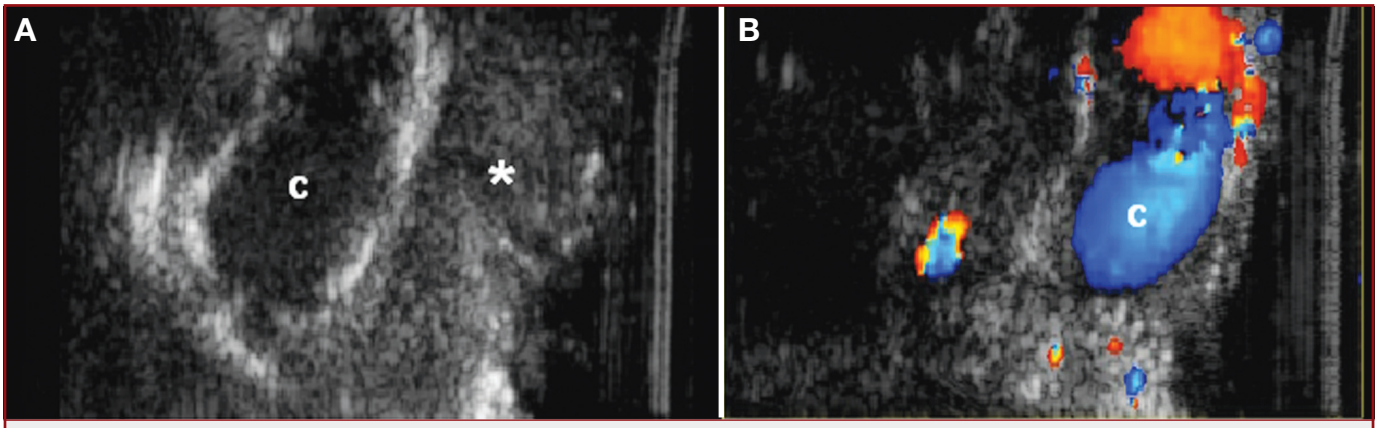

FIGURE 12. **A**, *after microscopy-guided resection was complete; right lateral ultrasound view demonstrated a tumor remnant (*) close to the right carotid artery (c).* **B**, *remnant tumor was found and removed. The carotid artery is demonstrated with color Doppler signals.*

Today, the transsphenoidal approach is the surgical route of choice for almost all pituitary tumors. Major surgical complications are fortunately rare. Operative mortality reaches just more than 1%.[12] Major surgical complications include vascular injuries, injury to optic or oculomotor nerves, hypothalamic injury, and cerebrospinal fluid fistulas, adding up to overall morbidity rates of approximately 5%.[13,14] In addition to strict surgical complications, various percentages of patients experience postoperative hypopituitarism because of damage to the pituitary gland.

Several of the mentioned complications may occur as a consequence of the wrong trajectory during surgery or losing the orientation within the surgical cavity. Anatomic landmarks such as the vomer and the posterior wall of the sphenoid are important for maintaining the operative approach in the midline. In reoperations or operations for large tumors extending outside the sella, these anatomic landmarks may be missing. Anatomic variations such as unusual septations within the sphenoid sinus can increase the chance of missing the trajectory. Such trajectory errors may be avoided by fluoroscopic frameless stereotaxy or navigation systems,[15,16] but neuronavigation is not in wide use, presumably because of practical reasons. A recent article reports that localization of the carotid arteries with a blind Doppler probe may help to avoid carotid artery injuries.[17]

Residual tumor masses may lead to recurrences or lack of remission. Remission rates after surgery depend on tumor size, growth patterns, hormone secretion, the biochemical definition of remission, and the surgeons' experience. Most residual tumor masses are found in the lateral region or in the suprasellar region, areas not visualized through direct microscopy or 0-degree endoscopy.

Endoscopes can provide panoramic close-up views of the anatomy, and angled lens endoscopes enable visualization of the parasellar and suprasellar regions that are not seen with direct microscopy. However, because both microscopy and endoscopy

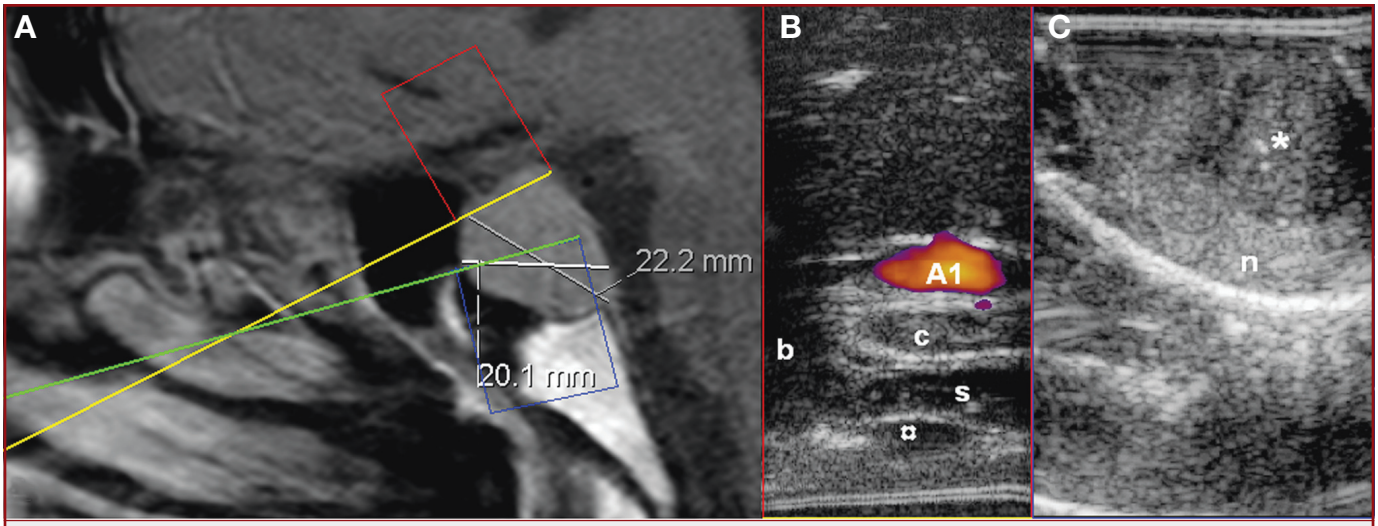

FIGURE 13. **A**, *preoperative T1-weighted magnetic resonance imaging (MRI) demonstrating the trajectory of the ultrasound probe with the ultrasound elements directed cranially (yellow) and caudally (green).* **B**, *corresponding sagittal ultrasound view of the suprasellar region displaying the anterior cerebral artery close to the anterior communicating artery (A1), optic chiasm (c), and suprasellar cistern (s). Note the small cyst just below the sellar diaphragm (€) also visible on MRI. The anterior clinoid bone produced a shadow artifact (b).* **C**, *sagittal ultrasound view produced when directing the elements caudally toward the sella floor and clivus. Note the remnant tumor tissue (*) and the 2-mm thin rim of slightly more echoic normal tissue (n).*

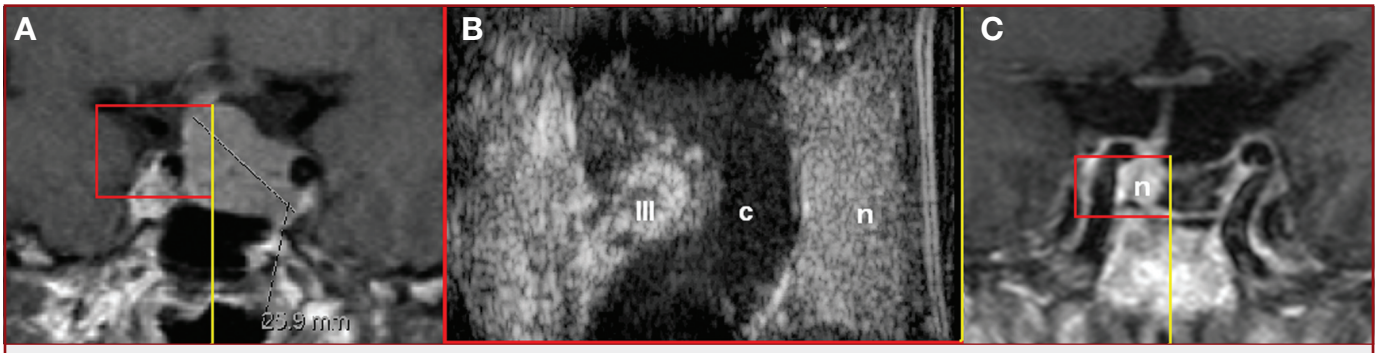

FIGURE 14. *Patient 9.* **A**, *preoperative coronal T1 contrast-enhanced MRI view of the macroadenoma. The red box indicates the region visualized in a more axial view in the ultrasound image.* **B**, *ultrasound view of the right parasellar region showing the optic nerve (III), the carotid siphon (c) and the normal pituitary tissue (n).* **C**, *postoperative coronal MRI view showing the contrast-enhancing normal tissue (n) located by the right carotid artery. There was no visible tumor remnant.*

are limited to the inspection of surfaces, only the surgical cavity can be seen. "Buried" residual tumor masses may easily be missed, especially as bleeding may often diminish the visual gain from the angled endoscope. In repeated surgery, scar tissue may conceal tumor remnants. In terms of frequency of residual tumors, symptom relief, or complication rates, outcome after endoscopic pituitary surgery seems similar to that after transsphenoidal surgery with direct microscopy.[18,19]

Intraoperative MRI is assessed in several centers. In a study of 85 patients with macroadenomas, high-field 3-T intraoperative MRI was assessed and led to extended resection in 34%. This increased the rate of complete tumor removal from 58% to 82% in the reported series.[20] Low-field magnets may also be used,[21] however, with reduced image quality.[22,23] Because pituitary adenomas are nonenhancing in contrast series, early postoperative MR images are not easily interpreted because of hemorrhage and fluid collection in the surgical cavity.[24] It has been suggested that contrast-soaked cottonoid packing in the tumor resection cavity during intraoperative MRI may be of use.[25]

Intrasellar Ultrasound: Probe Considerations

Earlier reports on transsphenoidal ultrasound in pituitary surgery have all assessed forward-looking probes that are used to look into the sella turcica from the sphenoid sinus. Introducing a pediatric 7. 5-MHz phased array transesophageal echo probe with a 9.8-mm tip into the sphenoid sinus during microsurgical transsphenoidal tumor operations, transdural color Doppler ultrasound visualizes major cerebral arteries and residual tumor masses.[9] Using 12- and

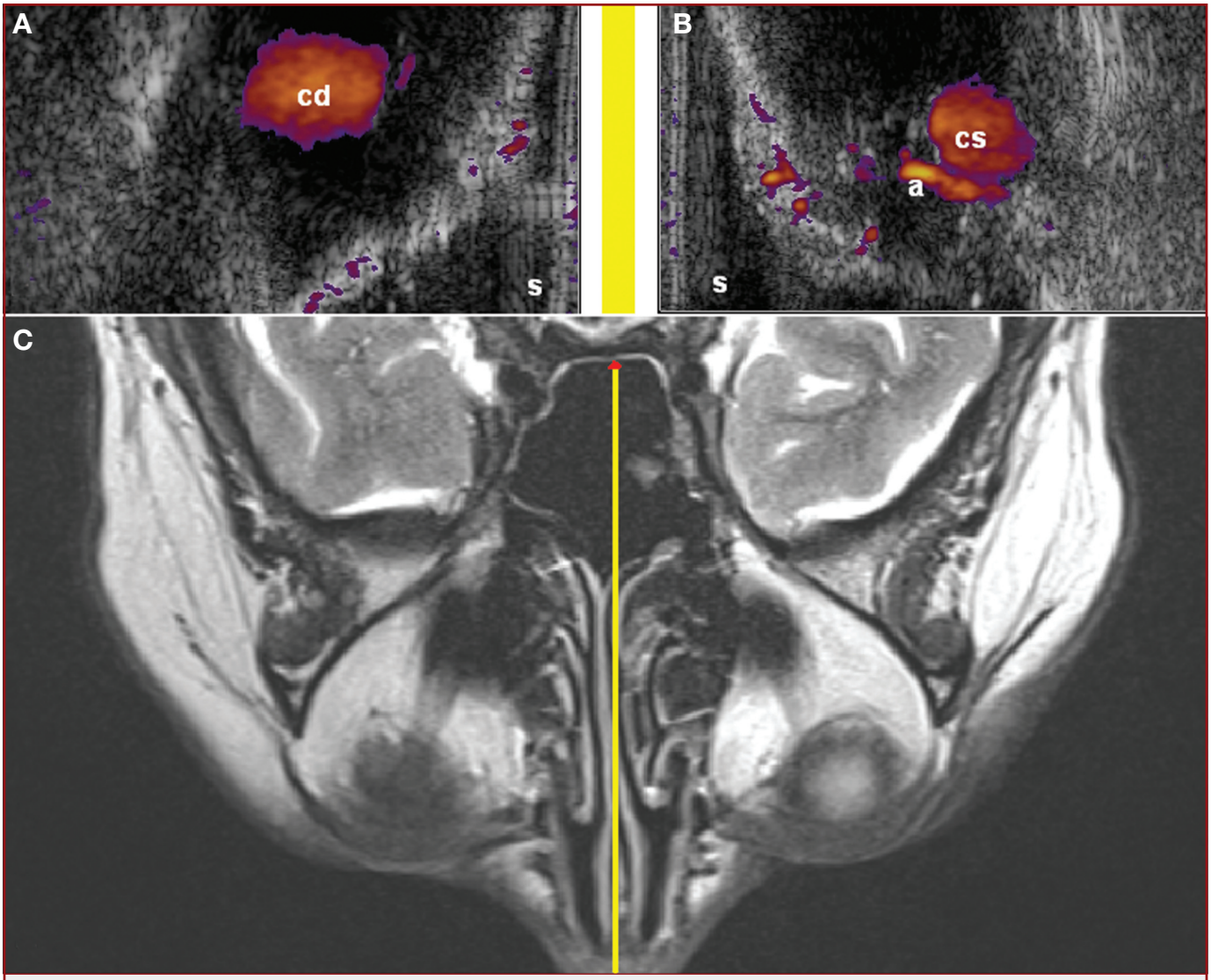

FIGURE 15. *Right- (**A**) and left- (**B**) side ultrasound view of the saline-filled sphenoid sinus (s) before opening of the sella floor displaying the power Doppler signal from the right (cd) and the left (cs) carotid artery behind the lateral wall of the sphenoid sinus. Based on these 2 images, the midline in the sella can easily be found. A smaller artery is also seen (a). **C**, preoperative axial T2-weighted magnetic resonance imaging (MRI) displaying the sphenoid sinus and the carotid arteries laterally. The probe is represented by the yellow line with the red distal tip. The image projections are not exactly similar in the ultrasound and MRI views because the probe is pointed cranially toward the sella and the MRI view is axial.*

15-MHz mechanically oscillating, forward-looking transducers with a 11-mm probe,[7,10,26] presellar transdural image acquisition was more sensitive than 1.5-T MRI for the identification of microadenomas. However, because of image shadows produced by bone, such as the sphenoid bone around the sella turcica, along with limited image sectors and resolution close to the probe in phased array technology, ultrasound acquisition from outside the sella turcica will often not enable clear visualization of the lateral or suprasellar regions. These regions are most important in macroadenomas because both complications and remnant tumor masses are associated with these areas. Forward-looking probes are also often limited by probe size because image resolution is closely dependent on the aperture or footprint of the probe.

Placing the linear array probe elements on the side of the probe reduces the probe size significantly. The diameter of the tip of our catheter-shaped probe is only 3 × 4 mm (Figure 1). There was no need to remove excess bone to fit the tip of the probe into the sella. The technique is also suitable for pure endoscopic approaches because the probe is as slim as most endoscopes. Unfortunately, the connector of our prototype probe cannot be sterilized, so we had to cover the probe in sterile drapes. The draped probe was therefore somewhat bulkier than desired.

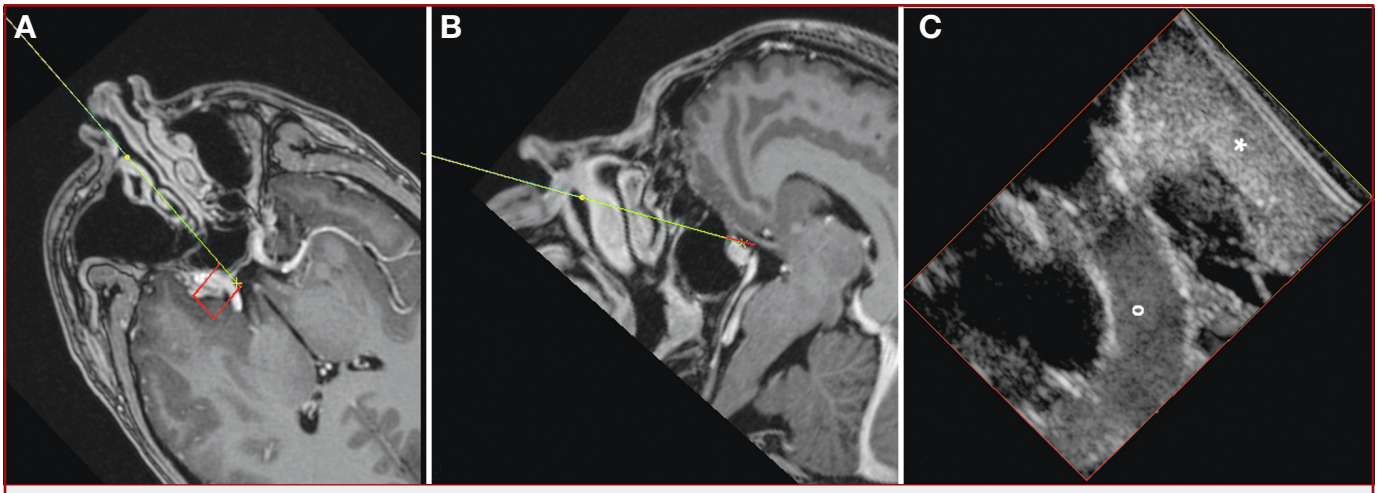

FIGURE 16. **A**, *to ensure the right interpretation of unfamiliar image projections, simulated neuronavigation-based preoperative 3-dimensional magnetic resonance imaging (in a nontumor patient) was used to demonstrate the trajectory of the ultrasound probe. The view is a combined axial/coronal view. The red box indicates the region seen in* **C**. **B**, *corresponding sagittal view.* **C**, *patient 9: a slightly oblique combined axial/coronal ultrasound view of the carotid artery top (o) and the adjacent tumor tissue (*).*

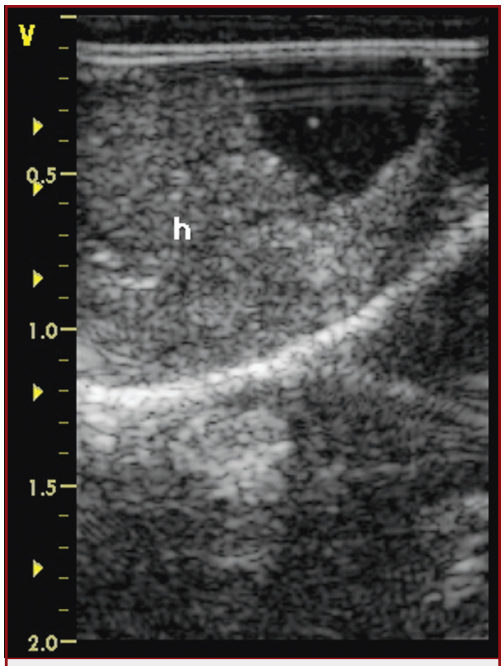

FIGURE 17. *Ultrasound view of the lower part of the sella showing a blood clot (h) that resembled a tumor remnant.*

To further develop the probe technology, some modifications can be made. Our next intrasellar probe will most likely be constructed for sustaining sterilization procedures, thus diminishing need of the sterile drape. This will also remove some image artifacts and ease the practical handling as the somewhat bulky drape adds to the mass to be fitted in the already narrow surgical approach.

Image Quality and Artifacts

Because of frequency-dependent attenuation of ultrasound waves, there is a trade-off between high-resolution images close to the probe and the ability to produce images at a distance when designing ultrasound probes. Our focus has been to produce high-resolution images in the difficult parasellar and suprasellar regions at a distance up to 3 to 4 cm from the probe. Linear array technology will produce excellent resolution from the first millimeters. The resolution in high-frequency ultrasound with our probe is up to 0.19 × 0.22 mm (radial × lateral resolution), enabling the visualization of small structures that are invisible on MRI. For comparison, the pixel size in 3-T MRI is approximately 1.0 × 1.0 mm. As seen in Figures 4 and 5, a comparison of image quality between a corresponding area from preoperative MRI and our intraoperative ultrasound is not necessarily in favor of MRI. Although image contrast may be superior in contrast-enhanced T1-weighted MRI, resolution is inferior.

As demonstrated in Figure 3, the ultrasound image may be electronically tilted to enable views forward or backward from the default 90-degree image plane. As with angled-lens endoscopes, changing the angle can be useful for visualization of distant corners in the surgical field. However versatile, tilting the image from our prototype catheter probe produced so-called grating lobe artifacts, which reduce image contrast. A probe with smaller element widths (pitch) would not be as susceptible to producing grating lobes, a consideration to take into account when designing our next intrasellar ultrasound probe.

As seen in Figures 4, 9, and 13, bone will produce ultrasound image shadows. However, once the probe elements are sending and receiving from within the sella, such bone artifacts are only a minor problem. In larger tumors extending beyond the limits of

the sella turcica (Figures 10 and 11), bone destruction by the tumor itself will often improve the ultrasound environment.

Air artifacts may be a problem in ultrasound imaging; however, filling the cavity with saline solves this problem. The sterile drape covering the probe was also the source of image artifacts as small bubbles of air easily got trapped in the ultrasound gel in the tip of the drape.

Blood clots in the surgical cavity can be mistaken for a remnant tumor mass (Figure 17). Careful recovery of hemostasis before or continuous irrigation during image acquisition will lessen this problem. However, confronted with an unknown mass in the ultrasound images, gently using a curet in the same region can usually sort out the nature of the mass.

Detection of Normal Pituitary Tissue

Earlier publications have reported both hyperechoic and hypoechoic tumors compared with the normal pituitary tissue.[9,26] In our series, the tumors were hypoechoic compared with normal tissue, but with varying echo intensity in different tumors. In ultrasound, the echo depends on the acoustic impedance of the object, a product of mass density and tissue velocity of sound. Stiffer, denser tumors will usually be seen as hyperechoic, and more soggy tumors are most likely hypoechoic. Because most macroadenomas are usually less solid than the normal pituitary gland, we deduce that larger tumors are most often relatively hypoechoic, a deduction supported by our image findings.

Tumor Resection Control

Resection grades were not a main focus in our small initial series. Maximal resection was only strongly pursued in younger patients and in patients with functional adenomas to reduce the chance of unnecessary postoperative hypopituitarism. The interpretation of images and technical tuning of the ultrasound equipment also varied from patient to patient. In patients 1 (Figure 6) and 3 (Figure 7), there was an unknown echo in the ultrasound images corresponding with the remnant tumor seen on postoperative MRI. However, as we gained experience, image interpretation became easier. In 3 of the last 4 patients, ultrasound imaging revealed residual tumor masses when resection was thought to be complete. Thus, resection was extended because of intrasellar ultrasound. Our learning curve is still pointing upward. Based on our experience from this small patient series, we believe that resection grades can be increased by assessing high-resolution intrasellar ultrasound. As we have learned to make use of this new technology, resection grades will be the subject of a future study.

The Learning Curve

To aid the readers' understanding of the images in this article, the orientation of the images is reversed to resemble familiar MRI projections. Interpreting ultrasound images displayed by our catheter probe takes some practice because many image planes are different from the axial, sagittal, and coronal views of the sella region seen in familiar preoperative images. The learning curve is, however, steep because there are several anatomic landmarks in most ultrasound views. The ultrasound images produced by our catheter probe are 90 degrees to the side of the probe shaft. Directing the probe elements directly downward will produce a sagittal view of the sella floor, as seen in Figure 13. Directing the probe upward enables an upward sagittal view, as seen in Figures 8, 9, and 13. To the surgeon, this view is, however, displayed upside-down compared with preoperative sagittal MRI scans. Directing the elements of the probe laterally will produce a view into the lateral part of the sella and the cavernous sinus. Because of the straight shaft of the probe, this view is a combined coronal and axial view. Other more oblique views are displayed when rotating the probe between the sagittal view and the lateral view. As illustrated in Figure 16, neuronavigation based on preoperative 3-dimensional MRI scans may aid in the understanding of more unconventional image projections. A 3-dimensional reconstruction of the 2-dimensional images can perhaps enable ultrasound-based neuronavigation in transsphenoidal surgery.

Intrasphenoidal Ultrasound

Using our side-looking ultrasound probe, orientation in the midline to avoid injury to the carotid arteries is easier. As seen in Figure 15, the distance to the lateral wall of the sphenoid sinus could be judged, ensuring that the sella and dura was opened in the midline. Intrasphenoidal side-looking ultrasound probes may also be helpful to ensure orientation within the sphenoid sinus and may ensure radical resection of tumor masses in this region, as demonstrated in Figure 11.

Time Consumption

Ultrasound imaging prolongs surgery only a few minutes and can easily be repeated multiple times during surgery. In comparison, the mean total imaging for intraoperative MRI is 20 to 35 minutes per surgical procedure.[20,27] In a feasibility study, implementation of the PoleStar low-field intraoperative MRI led to an approximately 50% increase in both anesthesia and operation times in pituitary surgery.[28]

CONCLUSION

As demonstrated in our small case series, a small linear, phased array, side-looking, high-frequency ultrasound probe can be used to ensure anatomic orientation to identify normal pituitary tissue and important neurovascular structures to be avoided during surgery. This novel technology enables resection control in macroadenomas. The image resolution is superior to what can be achieved with current clinical MRI technology. We believe that a technical solution based on small intrasellar ultrasound probes can be further improved to become a flexible tool in transsphenoidal surgery.

Disclosure

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COMMENTS

This article deals with a tool that has not gained widespread use in the neurosurgical community. The technology that permits real-time recognition of the amount of tumor removed in transsphenoidal surgery is widely and well represented by neuronavigation devices intraoperative magnetic resonance imaging (MRI) and, above all, the endoscope, in both standard and extended approaches to the cranial base.

The effort of the authors to implement the technique during transsphenoidal surgery deserves recognition, and their device can complement the existing ones in achieving the best tumor removal possible, compatibly with the biology of the lesion and the strategy of the surgeon.

Paolo Cappabianca
Naples, Italy

This is an interesting technique with significant advantages over previously reported ultrasound techniques in the sella. However, as the authors note, there is a significant learning curve for interpretation of the ultrasound images. The images are still relatively crude for the soft-tissue components compared with the arterial structures.

Nine patients is a relatively small number, but the main point of the report is to demonstrate the technique and to stimulate further research in the ultrasound arena for this surgery. The linear array side-looking probe may offer significant advances over the previously available probes. The authors point out that the technique needs refinement, but that there is a strong potential for its adjunctive use.

I find it relatively easy to see the arterial structures with this system, but differentiating the tumor tissue from other normal tissue is difficult. Although the authors are very enthusiastic and believe that they can see more with this technique than with intraoperative MRI, I do not agree with that yet. Intraoperative MRI quality is clearly related to the strength of the magnet and sophistication of the equipment and users, but I believe it is superior at the current time.

All in all, this is an interesting addition to the literature and one that I hope will stimulate further work. It is much easier to bring an ultrasound machine into the operating room than it is to build an MRI-equipped operating room.

Kalmon D. Post
New York, New York

Any attempt to improve outcomes of transsphenoidal surgery is welcome. The authors describe a novel application of the ultrasound technique in assessing completeness of pituitary tumor removal and in distinguishing tumor tissue from residual anterior pituitary. Attempting to do this is not only novel but also commendable. However, the limited experience with only 9 cases throws a serious shadow of doubt on the veracity of the authors' conclusions, especially the statement that this technique is superior to imaging with intraoperative MRI. Perhaps this may be so after all. However, I am absolutely convinced that direct visualization through either the microscope or endoscope is more reliable. I believe that anybody claiming otherwise could be accused of having no sense.

Ivan Ciric
Evanston, Illinois

Visualized here is Coatlique, the earth mother and creator god from the Aztec narrative. "The Lady of the Skirt of Snakes" as she was also known, gave birth to the goddess of the moon and to a group of male offspring, who became the stars. After giving birth to Huitzilopochtli, the fiery God of war, Coatlique and all of her offspring were killed. After death, she fell from heaven and was fertilized, and her children, the gods of life, spring, sun, night and sorcery, were scattered and disjointed throughout the universe. To stop Coatlique from eating all of creation, two serpents pulled her apart, and her head and shoulders became the earth and the lower part of her body the sky. From her hair was created trees, grass, and flowers; caves, fountains, and wells from her eyes; rivers from her mouth; hills and valleys from her nose; and mountains from her shoulders. Credit istockphoto.com.