Intraoperative cortical stimulation in brain tumor surgery

Intraoperative cortical stimulation in brain tumor surgery
[Peroperativ kortikal stimulering vid operation för hjärntumör]

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HTA-centrum of Region Västra Götaland - presentation
### Summary of the Health Technology Assessment:

**Method and patient group**
Awake craniotomy to map functional brain areas in patients with brain tumor adjacent to a region with motor and/or speech function.

**Question at issue, PICO:**
Is awake craniotomy with intraoperative cortical/subcortical mapping of functional brain areas better than craniotomy under general anesthesia, or two-step procedure with ‘cortical grid’ (another method for cortical mapping), or biopsy followed by radiation therapy/expectancy, regarding mortality, postoperative neurological deficits, gross total resection of tumor, or quality of life, in adults and adolescents with brain tumor adjacent to a region with motor and/or speech function?

P: Patients ≥13 years with brain tumor

I: Awake craniotomy with intraoperative cortical/subcortical mapping

C1: Craniotomy under general anesthesia
C2: Two-step procedure with ‘cortical grid’
C3: Biopsy followed by radiation therapy/expectancy

O: Postoperative neurological deficits
   Extent of resection/gross total resection
   Mortality (intra or postoperative/tumor-related)
   Quality of life
   Complications and risks

**Studied risks and benefits for patients of the new health technology**
Twelve papers fulfilled the PICO criteria and were included: two cohort studies, nine case-series, and one closely related systematic review (which included studies with ≥20 patients, age ≥20 years, with supratentorial intraparenchymal gliomas, WHO grade 2-4).

C1: Craniotomy under general anesthesia
Awake craniotomy with intraoperative cortical/subcortical mapping may result in less permanent postoperative neurological deficits than craniotomy under general anesthesia, with 11-18% absolute risk reduction (ARR). Low quality of evidence (GRADE ⊕⊕ΟΟ). Awake craniotomy with intraoperative mapping may result in a higher frequency of gross total resection than surgery under general anesthesia (ARR 19-23%). Low quality of evidence (GRADE ⊕⊕ΟΟ). Awake craniotomy with intraoperative mapping may result in lower tumor-related mortality than craniotomy under general anesthesia (ARR 15-34%). Low quality of evidence (GRADE ⊕⊕ΟΟ). It is uncertain if awake craniotomy with intraoperative mapping results in any difference in intra and postoperative mortality as compared to craniotomy under general anesthesia. Very low quality of evidence for (GRADE ⊕ΟΟΟ). There were no relevant studies for the outcome quality of life.
C2: Two-step procedure with ‘cortical grid’
No relevant articles were identified for this intervention.

C3: Biopsy followed by radiation therapy/expectancy
No relevant articles were identified for this intervention.

Complications (other than postoperative neurological deficits)
Intraoperative seizures occur relatively frequently in awake craniotomy, and a small proportion of the patients need conversion to general anesthesia. It seems that the risk of other complications than neurological deficits is comparable between awake craniotomy with intraoperative mapping and craniotomy under general anesthesia.

Ethical questions
Awake craniotomy with intraoperative mapping may be an advantageous method for the studied patient groups, but is still supported by limited evidence.

Economical aspects
Several studies have shown shorter length of hospital stay for awake craniotomy and thus cost reduction. On the other hand longer duration of surgery and involvement of other professions in the operating room (neuropsychologist, neurophysiologist) may increase the costs. The present mean cost for a craniotomy procedure for glioma is 113,621 SEK (range: 60,570-226,260 SEK). An initial one-time investment of 750,000 to 900,000 SEK is needed, for education, equipment, and hardware, in order to be able to perform the intraoperative mappings. Decreased rate of neurological deficits will result in significantly reduced health care costs for care of disabled patients.

Concluding remarks
Awake craniotomy with intraoperative cortical/subcortical mapping may result in reduced rate of permanent postoperative neurological deficits, a higher frequency of gross total resections, and lower tumor-related mortality than craniotomy under general anesthesia (low quality of evidence, GRADE ⊕⊕). It is uncertain if awake craniotomy with intraoperative mapping results in any difference in intra and postoperative mortality as compared to surgery under general anesthesia (very low quality of evidence, GRADE ⊕⊙⊙⊗).
Which health technology or method will be assessed?

1a **Project leader**
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1e **Conflicts of interest for the proposer or any of the work group participants**
No
### Disease/disorder of Interest and Present Treatment

**2a Disease/disorder of interest and its degree of severity**

The disease/disorder of interest regarding the new technology at issue: Intrinsic brain tumor adjacent to a region with motor and/or speech function.

Degree of severity:
- ✔ Risk of premature death
- ✔ Risk of permanent illness or damage, or reduced quality of life
- ✔ Risk of disability and health-related quality of life

**2b Prevalence and incidence of the disease/disorder**

The prevalence of the disease/disorder to be treated is very difficult to assess, but the incidence of low-grade glioma is estimated to be around 1-2/100,000 inhabitants per year (derived from the records of the Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg, Sweden). Permanent or severe neurological deficits following brain surgery in eloquent areas under general anesthesia occurs in 16-29% (Duffau et al., 2005; Sacko et al., 2011).

**2c Present treatment of the disease/disorder in the outpatient setting/inpatient setting**

The present treatment is mainly one of the following three choices:

a) Craniotomy with tumor resection under general anesthesia
b) Two-step procedure with 'cortical grid' (i.e. another method for cortical mapping).
c) Tumor biopsy with subsequent radiation therapy or expectancy.

The treatment is given on an inpatient basis at a Neurosurgical Department/ward, and the hospital stay is between two days (for method c) and ten days (for method b).

**2d Number of patients per year who undergo the current treatment regimen**

The number of patients who undergo the current treatment regimen is around 20-30 per year. Based on a population of approximately two million inhabitants (Region Västra Götaland, Region Halland, and Värmland County), the incidence of low-grade glioma is approximately 1-2/100,000/year, and the majority of patients undergo some neurosurgical procedure, either a biopsy or a resection.

**2e The normal pathway of a patient through the health care system**

Patients diagnosed with intrinsic brain tumors adjacent to motor or speech areas are normally assessed on an outpatient basis where the disease and possible treatment are discussed. If possible, non-invasive preoperative mapping of motor and/or speech areas is done using functional magnetic resonance imaging or navigated transcranial magnetic stimulation. The spatial resolutions of these techniques are approximately 5-10 mm. If the tumor is very close, or even within the functional brain area, higher spatial resolution is needed. Mapping of speech areas using non-invasive techniques is not validated, why invasive mapping is necessary to get robust data on the location of speech centers. Treatment is provided on an inpatient basis at a Neurosurgical Clinic/Department, with surgical biopsy or resective surgery, and subsequent radiation therapy that is provided on an outpatient basis.
Actual wait time in days for medical assessment /treatment
The actual waiting time for medical assessment for patients with a low-grade glioma that are potential candidates for awake craniotomy with intraoperative cortical/subcortical mapping is up to 60 days, and the waiting time from assessment to treatment is up to 90 days. However the majority of patients are seen within four weeks in the outpatient clinic, and are treated within six weeks from the first assessment.
Present Health Technology

3a Name/description of the health technology at issue
Awake craniotomy with cortical/subcortical stimulation is a method to identify brain regions essential to motor function and/or speech in patients with brain tumors. The purpose is to minimize the risk of postoperative neurological deficits and to maximize the extent of resection of brain tumors.

3b The work group’s understanding of the potential value of the health technology
The work group’s primary interest is to use awake craniotomy with cortical/subcortical stimulation in patients with a low-grade glioma adjacent to motor and/or speech areas. As publications using awake craniotomy often include other types of tumors, and there are few papers which includes only low-grade gliomas, we decided to extend the HTA to include all kinds of brain tumors.

In patients with low-grade glioma affecting brain areas essential for motor function and/or speech, awake craniotomy with intraoperative mapping may result in a greater extent of resection, with reduced morbidity. A recent, extensive review of management of low-grade glioma, suggests that a more extensive tumor resection may increase survival and thus, a maximized extent of tumor resection should be the aim of the surgical treatment (Sanai et al., 2011).

Several studies have shown a decreased length of hospital stay in patients treated with awake craniotomy, compared to craniotomy under general anesthesia, and some hospitals even treat these patients in an outpatient setting. (Danks et al., 2000; Serletis et al., 2007; Taylor and Bernstein, 1999). Cost per patient has also been shown to be lower in awake craniotomy (Perruzzi et al., 2011).

The mean age at diagnosis of low-grade glioma is approximately 30 years. Decreased morbidity and increased survival of these patients may result in decreased costs by reducing sick leave and care of disabled patients, as well as in an increase in expected working years.

The primary use of awake craniotomy with intraoperative mapping is in adult patients with a low-grade glioma (C 71.X) adjacent to brain areas with motor/sensory and/or speech areas. There are currently approximately 20-30 patients per year in Region Västra Götaland, Sweden, who would be considered for this treatment. The method could also be applied in selected patients with a high-grade glioma or brain metastasis adjacent to brain areas with motor/sensory and/or speech areas. In this patient group, another 10-20 patients may be eligible for awake craniotomy.

3c The central question for the current HTA project
Is awake craniotomy with intraoperative cortical/subcortical mapping of functional brain areas better than craniotomy under general anesthesia, or two-step procedure with ‘cortical grid’ (another method for cortical mapping), or biopsy followed by radiation therapy/expectancy, regarding mortality, postoperative neurological deficits, gross total resection of tumor, or quality of life, in adults and adolescents with brain tumor adjacent to a region with motor and/or speech function?
3d  **PICO**

P= Patients, I= Intervention, C= Comparison, O=Outcome

**P:** Patients ≥13 years with brain tumor.

**I:** Awake craniotomy with intraoperative cortical/subcortical mapping.

**C**<sub>1</sub>: Craniotomy under general anesthesia.

**C**<sub>2</sub>: Two-step procedure with ‘cortical grid’.

**C**<sub>3</sub>: Biopsy followed by radiation therapy/expectancy.

**O:** Postoperative neurological deficits.
- Extent of resection/gross total resection.
- Mortality (intra and postoperative/tumor-related).
- Quality of life.
- Complications and risks.

**Study design:** Systematic reviews; Controlled studies; Case-series with at least 100 cases.

**Limits:** Publication date from 1990, Danish, English, French, Norwegian, Swedish.

3e  **Keywords**

Brain neoplasms; Craniotomy; Electric stimulation

Hjärntumörer; Kraniotomi; Elektrostimulering
Review of the Quality of Evidence

4  Search strategy, study selection and references – Appendix 3
(Search strategy, Eligibility criteria, Selection process – flow diagram, References)
During April 2012, two librarians performed searches in PubMed, EMBASE (Ovid SP), the Cochrane Library and a number of HTA-databases. Reference lists of relevant articles were also scrutinized for additional references. A total of 526 articles were identified after removal of duplicates, of which 471 abstracts were excluded. Another 30 articles were excluded after having been read in full text. Twenty-five articles were sent to the work group for assessment. Twelve of these articles were included in the report; two were controlled studies and were critically appraised. The appraisal of articles was based on checklists from SBU regarding cohort studies (SBU, 2010). In addition, nine case series and a systematic review were included. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 3. Two librarians (TS, UWA) did the literature searches and exclusion of abstracts, in consultation with the HTA-centre and the work group.

5a Describe briefly the present knowledge of the health technology
Twelve papers were included: two cohort studies that fulfilled the PICO criteria, nine case-series, and one closely related systematic review, which included studies with ≥20 patients, age ≥20 years, with supratentorial intraparenchymal gliomas, WHO grade 2-4 (DeWitt Hamer et al., 2012).

Permanent postoperative neurological deficits – Appendix 1:1
Two cohort studies, of moderate quality, were identified comparing awake craniotomy with intraoperative mapping, with craniotomy under general anesthesia, reporting permanent neurological deficits (not resolved within three months) in 4.6%-6.5% in the awake craniotomy group, and 16-17% in the general anesthesia group (Duffau et al., 2005; Sacko et al., 2011).
One systematic review was identified, reporting permanent neurological deficits (not resolved within three months) in 3.4% (95% CI, 2.3-4.8%) in the awake craniotomy group and 8.2% (95% CI, 5.7-11.4%) in the general anesthesia group (De Witt Hamer et al., 2012).
Nine case-series reported neurological deficits after awake craniotomy (Bai et al., 2011; Danks et al., 2000; Duffau et al., 2008; Ilmberger et al., 2008; Kim et al., 2009; Mehta et al., 2000; Sanai et al., 2008; Serletis and Bernstein, 2007; Taylor and Bernstein, 1999). Persistent neurological deficits, between one to six months after surgery, were reported for 2-17% of the awake craniotomy cases (Bai et al., 2011; Duffau et al., 2008; Kim et al., 2009; Sanai et al., 2008).
Awake craniotomy with intraoperative mapping may reduce the occurrence of postoperative neurological deficits as compared to craniotomy under general anesthesia. Low quality of evidence (GRADE ⊕⊕⊕○○).

Gross total resection – Appendix 1:2
Two cohort studies, of moderate quality, were identified comparing gross total resection rates in awake craniotomy with intraoperative mapping, with those in craniotomy under general anesthesia (Duffau et al., 2005; Sacko et al., 2011). Sacko et al. (2005) reported 37% gross total resections in the awake craniotomy group, and 14% in the general anesthesia group. Duffau et al. (2005) found 25.4 % gross total resections after awake craniotomy with intraoperative mapping, and 6% after
craniotomy under general anesthesia.

In the systematic review by De Witt Hamer et al. (2012) the gross total resection rates were higher, with 75% (95% CI, 66–82%) for awake craniotomy, and 58% (95% CI, 48–69%) for craniotomy under general anesthesia.

In seven case-series the gross total resection rates varied from 32-64% for the awake craniotomy cases, and were 32-52% when only low-grade gliomas were considered (Bai et al., 2011; Danks et al., 2000; Duffau et al., 2008; Ilmberger et al., 2008; Kim et al., 2009; Mehta et al., 2000; Sanai et al., 2008). The definition of gross total resection was inconsistent between studies, which makes data from different studies difficult to compare.

Awake craniotomy with intraoperative mapping may result in higher frequency of gross total resections than craniotomy under general anesthesia. Low quality of evidence (GRADE ⊕⊕ΟΟΟ).

**Tumor-related mortality – Appendix 1:3**

Tumor-related mortality following awake craniotomy with intraoperative mapping, and craniotomy under general anesthesia was compared in two cohort studies (one moderate, and one low quality) with significantly lower mortality in the awake craniotomy groups than in the general anesthesia groups (Duffau et al., 2005; Sacko et al., 2011). Five-year survival for patients with low-grade gliomas was approximately 95% in the awake craniotomy group, and approximately 40% in the general anesthesia group (Sacko et al., 2011).

Awake craniotomy with intraoperative mapping may result in lower tumor-related mortality than craniotomy under general anesthesia. Low quality of evidence (GRADE ⊕⊕ΟΟΟ).

**Intra and postoperative mortality – Appendix 1:4**

Intra and postoperative mortality for awake craniotomy with intraoperative mapping (0%), and for craniotomy under general anesthesia (0.5-2%) was compared in two cohort studies, of low quality (Duffau et al., 2005; Sacko et al., 2011).

It is uncertain if awake craniotomy with intraoperative mapping results in any difference in intra and postoperative mortality compared to craniotomy under general anesthesia. Very low quality of evidence for (GRADE ⊕ΟΟΟΟ).

**Quality of life**

There were no studies on this outcome.

**Complications and side effects – Appendix 1:5**

Complications other than postoperative neurological deficits were reported in one cohort study (Sacko et al., 2011). For awake craniotomy with intraoperative mapping there were: 1.4% wound infections (general anesthesia: 1.1%); 0.4% abscesses (general anesthesia: 0.5%); CSF leaks 0% (general anesthesia: 0.5%); Postoperative hematomas 1.8% (general anesthesia: 1.1%); deep vein thromboses 0.4% (general anesthesia: 1.4%); pulmonary emboli 0% (general anesthesia: 0.5%); hyponatremia 0.4% (general anesthesia: 1.4%); urinary tract infections 0% (general anesthesia: 1.9%); and pulmonary infections 0% (general anesthesia: 1.4%).

In awake craniotomy, intraoperative seizures occurred in 5.7-11.6% of the cases (Bai et al., 2011; Danks et al., 2000; Sacko et al., 2011). Most seizures were brief and focal, resolving with cold-water irrigation and/or administration of anticonvulsants. Conversion to general anesthesia was required in 0-1% of the cases (Danks et al., 2000; Sacko et al., 2011).

Drowsiness or agitation, which made mapping impossible, occurred in 4-5% of the
cases (Bai et al., 2011; Danks et al., 2000).
In conclusion, intraoperative seizures occur relatively frequently in awake craniotomy, and a small proportion needs conversion to general anesthesia. It seems that the risk for complications other than neurological deficits is relatively similar between awake craniotomy with intraoperative mapping and craniotomy under general anesthesia.

PICO 2: Two-step procedure with ‘cortical grid’
No relevant articles were identified for this intervention.

PICO 3: Biopsy followed by radiation therapy/expectancy
No relevant articles were identified for this intervention.

5b  Outcome tables – Appendix 1
5c  Excluded articles – Appendix 2
5d  Ongoing research
A search in the Clinical Trials database (clinicaltrials.gov), 2012-06-15, with the search terms (local anesthesia OR awake) AND (craniotomy OR surgery OR neurosurg* OR resection) AND ((electrical OR cortical OR subcortical OR electrocortical OR function OR brain) AND (mapping OR stimulation)) OR electrostimulation) gave 25 hits. None of these were relevant for this HTA-report.

6  Medical societies or health authorities that recommend the new health technology
No health authority in Sweden has recommended awake craniotomy for low-grade gliomas.
Ethical aspects

7 Ethical consequences
Awake craniotomy with intraoperative cortical/subcortical mapping may be an advantageous method for the studied patient groups, but is still supported by limited evidence.

Organization

8a When the new health technology can be put into practice
Awake craniotomy with intraoperative cortical/subcortical mapping can be implemented at the Neurosurgical Section, Sahlgrenska University Hospital (Göteborg, Sweden) by the beginning of year 2013. Investment in neurophysiological stimulating apparatus has to be made, as well as education of involved personnel in the operating room.

8b Use of the technology in other hospitals in Region Västra Götaland of Sweden
Sahlgrenska University Hospital in Göteborg is the only hospital in Region Västra Götaland where neurosurgery is performed, and thus the technology at issue has not been implemented in other hospitals in Region Västra Götaland.

8c Consequences of the new health technology for personnel, according to the work group
Implementation of this new technology does primarily involve personnel in the operating room, anesthetic personnel, scrub nurses, and surgical assistants, who need to be adequately informed and educated. The work group has not been able to detect any other possible consequences or needs regarding involved personnel.

8d Consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden
The new technology will involve the use of personnel and neurostimulating devices from the Neurophysiology Section during operations with awake craniotomy, but otherwise no consequences can be foreseen regarding other clinics at the hospital or other hospitals in the region.
Economy

9a **Present costs of currently used technologies**
The present mean cost for a craniotomy procedure for glioma is 113,621 SEK (range: 60,570-226,260 SEK).

9b **Expected costs of the new health technology**
There are four types of costs involved in starting with intraoperative cortical stimulation in brain tumor patients:
1. Investment in new hardware
2. Education of personnel involved
3. Increased cost of procedure
4. Additional patients, previously regarded inoperable

Regarding hardware, a new cortical stimulator is needed. The investment cost is approximately 500,000-600,000 SEK.

Neurosurgeons, anesthesiologist, anesthesiology nurses and scrub nurses need training for this new procedure. We have cooperation with Ullevål Hospital in Oslo, Norway, where awake craniotomy with intraoperative mapping is performed. Within this cooperation selected personnel from our department have visited Ullevål Hospital, and they are willing to assist in the introduction of the new technology on-site at our department. The costs for this are expected to be approximately 250,000 to 300,000 SEK.

Initially, an increased operating time is expected, since the new type of anesthesia and the stimulation procedure requires more time and more personnel. In centers where awake craniotomy is done frequently, the total costs are lower than for craniotomy under general anesthesia, due to shorter length of hospital stay (Taylor and Bernstein, 1999). A 40% initial cost increase is expected, compared to craniotomy under general anesthesia. However, with an increasing patient volume this cost is expected to diminish, and possibly decrease compared to craniotomy under general anesthesia.

As awake craniotomy allows surgery of previously inoperable tumors, we expect 5-7 additional patients/year.

9c **Total change of cost**
If 1, 2, 3, and 4 above are added, a one-time cost of 750,000 to 900,000 SEK for education and hardware investment is needed. An initial cost increase of 45,500 SEK/procedure/year adds up to 455,000 SEK/year, based on 10 patients/year. Each additional patient will cost 159,000 SEK. Based on seven patients per year the costs for previously inoperable patients will be 1,130,000 SEK/year. The total sum is 2,168,000 to 2,368,000 SEK. However, the total cost for the Region Västra Götaland may well decrease, due to less postoperative neurological deficits, and thus reduced need for long-term hospital stays in rehabilitation clinics.

9d **Possibility to adopt and use the new technology within the present budget (clinic budget/hospital budget)**
Not possible within the present budget.

9e **Available analyses of health economy, cost advantages or disadvantages**
In a recent report, the authors concluded that patients undergoing glioma resection using intraoperative cortical stimulation have a significantly shorter hospital stay with reduced inpatient hospital expenses after postoperative ICU care (Perruzzi et al., 2011).
Unanswered Questions

10a Important gaps in scientific knowledge
Randomized controlled trials to evaluate awake craniotomy with intraoperative mapping may be difficult to conduct since the number of cases is relatively low.

How well do the results from the preoperatively available non-invasive techniques, such as functional magnetic resonance imaging, navigated transcranial magnetic stimulation, and diffusion tensor imaging of functional areas and nervous pathways in different systems of the brain, correlate to those of the intraoperative direct electrical stimulations?

How much can the preoperative planning and postoperative outcome regarding neurological deficits be improved by systematic use of these non-invasive techniques?

What impact would systematic use of the above-mentioned techniques have on morbidity, mortality, and economical aspects of the handling of these patients?

10b Interest in the own clinic/research group/organization to start studies/trials within the research area at issue
Cortical mapping under general anesthesia can currently be considered a reference standard. Thus, cortical stimulation in an (at least temporarily) awaken patient adds the ability to localize functional areas (usually language and sensory areas) where participation from the patient is required. Thereby, cortical mapping under general anesthesia, and cortical mapping in an awaken patient can be compared, and regarded as essentially different. If also possibility is given to preoperatively, and noninvasively, do much of the mapping (at least cortical) with transcranial magnetic stimulation, very likely the duration of operation would be reduced, and the surgical precision would improve.

We see three potential studies within this research area:

1. Validation of noninvasive navigated transcranial magnetic brain stimulation (NBS) against direct cortical stimulation in awake craniotomy. By comparing maps of motor and speech function acquired using noninvasive NBS with results from direct cortical stimulation, the accuracy of NBS could be validated. This would be a necessary step before introducing NBS in clinical practice for preoperative non-invasive mapping of speech areas.

2. Correlation of preoperative magnetic resonance imaging-based tractography of corticospinal tracts (motor function) and arcuate fasciculus (speech function) with mapping through subcortical stimulation in awake craniotomy.

3. The method of awake craniotomy with intraoperative mapping for brain tumor surgery needs to be further evaluated in a clinical setting.
Statement from HTA-centrum of Region Västra Götaland, Sweden

Intraoperative cortical stimulation in brain tumor surgery

Question at issue
Is awake craniotomy with intraoperative cortical/subcortical mapping of functional brain areas better than craniotomy under general anesthesia, or two-step procedure with ‘cortical grid’ (another method for cortical mapping), or biopsy followed by radiation therapy/expectancy, regarding mortality, postoperative neurological deficits, gross total resection of tumor, or quality of life, in adults and adolescents with brain tumor adjacent to a region with motor and/or speech function?

PICO (Patient, Intervention, Comparison, Outcome)

P = Patients ≥13 years with brain tumor.
I = Awake craniotomy with intraoperative cortical/subcortical mapping.
C1 = Craniotomy under general anesthesia.
C2 = Two-step procedure with ‘cortical grid’.
C3 = Biopsy followed by radiation therapy/expectancy.
O = Postoperative neurological deficits.
Extent of resection/gross total resection.
Mortality (intra or postoperative/tumor-related).
Quality of life.
Complications and risks.

Summary of the health technology assessment

Method and patient category
Awake craniotomy to map functional brain areas in patients with brain tumor adjacent to a region with motor and/or speech function.

Level of evidence
Twelve papers were included: two cohort studies that fulfilled the PICO criteria, nine caseseries, and a closely related related systematic review.

C1: Craniotomy under general anesthesia (GA)
Awake craniotomy with intraoperative cortical/subcortical mapping may result in less permanent postoperative neurological deficits than craniotomy under general anesthesia, with 11-18% absolute risk reduction (ARR). Low quality of evidence (GRADE ⊕⊕⋄⋄). Awake craniotomy with intraoperative mapping may result in a higher frequency of gross total resections than surgery under general anesthesia (ARR 19-23%). Low quality of evidence (GRADE ⊕⊕⋄⋄). Awake craniotomy with intraoperative mapping may result in lower tumor-related mortality than craniotomy under general anesthesia (ARR 15-34%). Low quality of evidence (GRADE ⊕⋄⋄⋄). It is uncertain if awake craniotomy with intraoperative mapping results in any difference in intra and postoperative mortality as compared to craniotomy under general anesthesia. Very low quality of evidence for (GRADE ⊕⋄⋄⋄). There were no relevant studies for the outcome quality of life.

C2: Two-step procedure with ‘cortical grid’
No relevant articles were identified for this intervention.

C3: Biopsy followed by radiation therapy/expectancy
No relevant articles were identified for this intervention.
Complications (other than postoperative neurological deficits)
Intraoperative seizures occur relatively frequently in awake craniotomy, and a small proportion of the patients need conversion to general anesthesia. It seems that the risk of other complications than neurological deficits is comparable between awake craniotomy with intraoperative mapping and craniotomy under general anesthesia.

Ethical aspects
Awake craniotomy with intraoperative mapping may be an advantageous method for the studied patient groups, but is still supported by limited evidence.

Economical aspects
Several studies have shown shorter length of hospital stay for awake craniotomy and thus cost reduction. On the other hand longer duration of surgery and involvement of other professions in the operating room (neuropsychologist, neurophysiologist) may increase the costs. The present mean cost for a craniotomy procedure for glioma is 113,621 SEK (range: 60,570-226,260 SEK). An initial one-time investment of 750,000 to 900,000 SEK is needed, for education, equipment, and hardware, in order to be able to perform the intraoperative mappings. Decreased rate of neurological deficits will probably result in significantly reduced health care costs for care of disabled patients.

Concluding remarks
Awake craniotomy with intraoperative cortical/subcortical mapping may result in reduced rate of permanent postoperative neurological deficits, in a higher frequency of gross total resections, and in lower tumor-related mortality than craniotomy under general anesthesia (low quality of evidence, GRADE ⊕⊕). It is uncertain if awake craniotomy with intraoperative mapping results in any difference in intra and postoperative mortality as compared to surgery under general anesthesia (very low quality of evidence, GRADE ⊕).
Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Peroperativ kortikal stimulering vid operation för hjärntumör

Frågeställning:
Är kraniotomi på vaken patient med peroperativ kortikal/subkortikal kartläggning av funktionella områden i hjärnan bättre än kraniotomi under narkos, eller ett tvåstegsförfarrande med "cortical grid" (en annan metod för kortikal kartläggning), eller biopsi följt av strålbehandling/expektans, avseende mortalitet, postoperativt neurologiskt bortfall, resektionsgrad av tumör, eller livskvalitet, hos vuxna och ungdomar med hjärntumör intill ett område med motor- och/eller talfunktion?

PICO: (Patient, Intervention, Comparison, Outcome)

P  =  Patienter ≥13 år med hjärntumör.
I  =  Kraniotomi på vaken patient med peroperativ kortikal/subkortikal kartläggning.
C1 = Kraniotomi under narkos.
C2 = Tvåstegsförfarrande med "cortical grid".
C3 = Biopsi följt av strålbehandling/expektans.
O  =  Postoperativa neurologiska bortfall.
    Resektionsgrad/Total tumör resektion (dvs. avlägsnat väsentligen all synlig tumörvävnad).
    Mortalitet (per- eller postoperativ/tumörrelaterad).
    Livskvalitet.
    Komplikationer och risker.

Resultatet av HTA-processen

Metod och målgrupp:
Kraniotomi på vaken patient för att kartlägga funktionella områden i hjärnan hos patienter med hjärntumör intill ett område med motor- och/eller talfunktion.

Evidensläge för studerad patientnytta
Tolv artiklar inkluderades: Två kohortstudier som uppfyllde PICO kriterierna, nio fallserier, och en närliggande systematisk översikt.

C1: Kraniotomi under narkos

C2: Tvåstegsförfarrande med "cortical grid"
Inga relevanta artiklar lokaliseras avseende denna intervention.

C3: Biopsi följt av strålbehandling/expektans
Inga relevanta artiklar lokaliseras avseende denna intervention.
Komplikationer (utöver postoperativa neurologiska bortfall)
Peroperativa kramper förekommer förhållandevis ofta vid kraniotomi på vaken patient, och för en liten andel av patienterna krävs omställning till narkos. Risken för andra komplikationer än neurologiska bortfall verkar vara jämförlig mellan AC och GA.

Etiska aspekter
Kraniotomi på vaken patient med peroperativ kartläggning kan vara en fördelaktig metod för de studerade patientgrupperna, men det vetenskapliga underlaget är fortfarande begränsat.

Ekonomiska aspekter
Flera studier har påvisat kortare sjukhusrättsvistelse vid kraniotomi på vaken patient och därmed kostnadsreduktion. Däremot kan längre operationstider och behov av samverkan mellan fler yrkeskategorier i operationssalen (neuropsykolog, neurofysiolog) öka kostnaderna. Den nuvarande snittkostnaden för kraniotomi vid gliom är 113 621 kr (60 570-226 260 kr). För att kunna utföra den peroperativa kartläggningen krävs en initial engångsinvestering på 750 000-900 000 kr för utbildning, utrustning, och hårdvara. Minskad förekomst av postoperativa neurologiska bortfall lär dock resultera i kraftigt sänkta kostnader för vård av funktionshindrade patienter.

Sammanfattning och slutsats
Kraniotomi på vaken patient med peroperativ kortikal/subkortikal kartläggning kan resultera i färre kvarstående postoperativa neurologiska bortfall, högre förekomst av total tumör resektion, samt lägre tumörraterad mortalitet än kraniotomi under narkos. Begränsat vetenskapligt underlag (GRADE ⊕⊕ΟΟ). Det är osäkert huruvida kraniotomi på vaken patient med peroperativ kartläggning resulterar i någon skillnad i per- eller postoperativ mortalitet jämfört med kraniotomi under narkos. Otillräckligt vetenskapligt underlag (GRADE ⊕ΟΟΟO).

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlad evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.
Projektet har pågått under perioden 2012-04-16 –2012-10-31
Sista uppdatering av artikelsökning april 2012

För HTA-kvalitetssäkringsgruppen 2012-10-31
Christina Bergh
Ordförande

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Appendix 1: Outcome variable: Postoperative neurological deficits for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals-dropouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffau, 2005</td>
<td>France</td>
<td>Cohort study</td>
<td>222</td>
<td>0</td>
<td>Total 8/122 (6.5%) Severe deficits 8/76 within eloquent areas, 0/46 not within eloquent areas n=122</td>
<td>Total 17/100 (17%) p=0.019 Severe deficits 10/35 within eloquent areas, 7/65 not within eloquent areas n=100</td>
<td>Intervention prospective data, control retrospective data; different periods intervention 1996-2003, control 1985-1996 All patients had low-grade gliomas.</td>
</tr>
<tr>
<td>Sacko, 2011</td>
<td>France</td>
<td>Cohort study</td>
<td>575</td>
<td>0</td>
<td>New deficit 7/214 (3.3%), transient deficit 52/214 (24%), permanent deficit 10/214 (4.6%). n=214</td>
<td>GA72 (comparable to AC group): new deficit 40/70 (57%), transient deficit 59/70 (84%), permanent deficit 11/70 (16%). GA: new deficit 47/359 (13%), transient deficit 81/359 (22.5%), permanent deficit 13/359 (3.6%). n=361 p&lt;0.001 for AC vs GA72</td>
<td>GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n=27. Prospective, same time period 2002-2007.</td>
</tr>
<tr>
<td>Bai, 2011</td>
<td>China</td>
<td>Case series</td>
<td>112</td>
<td>0</td>
<td>Permanent deficits 3/112 (2.7%), after 3 months. Transient deficits 51/112 (45.5%).</td>
<td>—</td>
<td>Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75). 5 patients could not fulfil language task due to drowsiness.</td>
</tr>
<tr>
<td>Danks, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>157</td>
<td>0</td>
<td>1/81 major deficit, 2/81 minor deficit in patients without pre-operative deficits. 33% complete resolution, 32% improvement, 28% no change, 8% permanent worsening in patients with pre-operative deficits.</td>
<td>—</td>
<td>Brain lesion in/near eloquent cortex (low-grade glioma n=44, non-tumor n=22). Cortical mapping performed in 122 cases. Time point for evaluation was not stated.</td>
</tr>
<tr>
<td>Duffau, 2008</td>
<td>France</td>
<td>Case series</td>
<td>115</td>
<td>0</td>
<td>115/115 general reduction in language performance (BDAE score) in immediate postoperative period; 2/115 (1.7%) reduction, 6 improvement, after 3 months.</td>
<td>—</td>
<td>Grade II gliomas in left dominant hemisphere.</td>
</tr>
</tbody>
</table>
Appendix 1: Outcome variable: Postoperative neurological deficits for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals-dropouts</th>
<th>Intervention</th>
<th>Control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilmberger, 2008</td>
<td>Germany</td>
<td>Case series</td>
<td>149</td>
<td>0</td>
<td>41/128 new language deficit in cases without pre-operative deficits; 19/25 worsening of pre-operative language deficits.</td>
<td>—</td>
<td>153 craniotomies in 149 patients with brain lesions in/near language areas (low-grade glioma n=77, non-tumor n=9). Early postoperative deficits (median 7 days after surgery)</td>
</tr>
<tr>
<td>Kim, 2009</td>
<td>USA</td>
<td>Case series</td>
<td>310</td>
<td>1 (died post op)</td>
<td>Worsened deficits 111/309 (36%) in immediate post-operative period, 52/309 (17%) after 1 month. 22/309 (7%) persistent neurological deficits after 3 months.</td>
<td>—</td>
<td>Intracerebral tumors in/near eloquent cortex (low-grade glioma n=58, non-tumor n=5); 10 reoperations. Predictors of neurological outcome were cortical mapping results (p=0.01), extent of resection (p=0.019), and intraoperative neurological changes (p&lt;0.001).</td>
</tr>
<tr>
<td>Mehta, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>248</td>
<td>0</td>
<td>Early postoperative deficits 31%.</td>
<td>—</td>
<td>Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23). No follow-up.</td>
</tr>
<tr>
<td>Sanai, 2008</td>
<td>USA</td>
<td>Case series</td>
<td>250</td>
<td>0</td>
<td>21/250 (8.4%) worsened language deficit, 35/250 (14.0%) new deficit after one week. 4/243 (1.6%) persistent language deficit after 6 months.</td>
<td>—</td>
<td>Patients with gliomas close to speech cortex (low-grade glioma n=124).</td>
</tr>
<tr>
<td>Serletis, 2007</td>
<td>Canada</td>
<td>Case series</td>
<td>511</td>
<td>0</td>
<td>78/511 (15.3%) postoperative neurological worsening in patients who underwent awake surgery and mapping</td>
<td>—</td>
<td>Awake surgery for supratentorial intraaxial tumors (n=610; low-grade glioma n=129, non-tumor n=35). Brain mapping used in 511 cases.</td>
</tr>
<tr>
<td>Taylor, 1999</td>
<td>Canada</td>
<td>Case series</td>
<td>200</td>
<td>0</td>
<td>Transient neurological deficit 17/200 (8.5%), permanent deficit 9/200 (4.5%).</td>
<td>—</td>
<td>Awake surgery for supratentorial intraaxial tumors (low-grade glioma n=24, non-tumor n=12). Brain mapping used in 195 cases.</td>
</tr>
</tbody>
</table>
Appendix 1.2. Outcome variable: Extent of resection for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals-dropouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffau, 2005</td>
<td>France</td>
<td>Cohort study</td>
<td>222</td>
<td>0</td>
<td>25.4% (31/122) total, 50.8% (62/122) subtotal, 23.8% (29/122) partial.</td>
<td>6% (6/100) total, 37% (37/100) subtotal, 57% (57/100) partial p&lt;0.001 between groups</td>
<td>MRI. Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996). All patients had low-grade gliomas</td>
</tr>
<tr>
<td>Sacko, 2011</td>
<td>France</td>
<td>Cohort study</td>
<td>(214 vakna) 575 total</td>
<td>0</td>
<td>37% total, 45% subtotal. n=214</td>
<td>GA72 (comparable to AC group): 14% total, 26% subtotal. GA: 52% total, 34% subtotal. n=361 p&lt;0.001 between AC and GA72</td>
<td>MRI. GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n=27. Prospective, same time period 2002-2007.</td>
</tr>
<tr>
<td>Bai, 2011</td>
<td>China</td>
<td>Case series</td>
<td>112</td>
<td>0</td>
<td>58.9% total, 30.4% subtotal, 10.7% partial.</td>
<td>—</td>
<td>MRI. Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75).</td>
</tr>
<tr>
<td>Dunks, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>157</td>
<td>0</td>
<td>57% total, 23% subtotal, 13% partial, 7% biopsy only.</td>
<td>—</td>
<td>CT and/or MRI. Brain lesion in/near eloquent cortex (low-grade glioma n=44, non-tumor n=22). Cortical mapping performed in 122 cases.</td>
</tr>
<tr>
<td>Duffau, 2008</td>
<td>France</td>
<td>Case series</td>
<td>115</td>
<td>0</td>
<td>52% total, 51% subtotal, 17% partial.</td>
<td>—</td>
<td>MRI. Grade II gliomas in left dominant hemisphere.</td>
</tr>
<tr>
<td>Ilmberger, 2008</td>
<td>Germany</td>
<td>Case series</td>
<td>149</td>
<td>0</td>
<td>48.4% total.</td>
<td>—</td>
<td>MRI. 153 craniotomies in 149 patients with brain lesions in/near language areas (low-grade glioma n=77, non-tumor n=9).</td>
</tr>
<tr>
<td>Kim, 2009</td>
<td>USA</td>
<td>Case series</td>
<td>310</td>
<td>1</td>
<td>64% total, 14% subtotal, 22% partial (39% total in low-grade tumors).</td>
<td>—</td>
<td>MRI. Intracerebral tumors in/near eloquent cortex (low-grade glioma n=58, non-tumor n=51; 10 reoperations.</td>
</tr>
<tr>
<td>Mehta, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>248</td>
<td>0</td>
<td>57% total, 23% subtotal.</td>
<td>—</td>
<td>Imaging method not stated. Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23).</td>
</tr>
<tr>
<td>Sanai, 2008</td>
<td>USA</td>
<td>Case series</td>
<td>250</td>
<td>0</td>
<td>59.6% total (51.6% total in low-grade tumors).</td>
<td>—</td>
<td>MRI. Patients with gliomas close to speech cortex (low-grade glioma n=124).</td>
</tr>
</tbody>
</table>
### Appendix 1.3. Outcome variable: Tumor-related mortality for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients</th>
<th>With withdrawals/dropouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duffau, 2005</td>
<td>France</td>
<td>Cohort study</td>
<td>222</td>
<td>0</td>
<td>Partial resections 6/29 (20.6%) died, subtotal resections 5/62 (8%) died, complete resections 0/31 (0%) died. p=0.02 (within group).</td>
<td>Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996). Shorter follow-up in intervention group. All patients had low-grade gliomas</td>
<td>Low</td>
</tr>
<tr>
<td>Sacko, 2011</td>
<td>France</td>
<td>Cohort study</td>
<td>575</td>
<td>0</td>
<td>Survival after 60 months: GA72: 0.40* (comparable to AC group) GA: 0.5* p&lt;0.001 between groups. n=361 Low-grade glioma only: GA72: 0.5* GA: 0.7* p&lt;0.001 between groups.</td>
<td>GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n≈27.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* Estimated from figures in Sacko et al., 2011.
Appendix 1.4. Outcome variable: Intra and postoperative mortality for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals-droppouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffau, 2005</td>
<td>France</td>
<td>Cohort study</td>
<td>222</td>
<td>0</td>
<td>0/122</td>
<td>2/100 (2%)</td>
<td>Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996). All patients had low-grade gliomas</td>
</tr>
<tr>
<td>Sacko, 2011</td>
<td>France</td>
<td>Cohort study</td>
<td>575</td>
<td>0</td>
<td>0</td>
<td>0.5%</td>
<td>2 deaths within 90 days in the GA72 group (comparable to AC group) n=361</td>
</tr>
<tr>
<td>Bai, 2011</td>
<td>China</td>
<td>Case series</td>
<td>112</td>
<td>0</td>
<td>ns</td>
<td>—</td>
<td>Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75).</td>
</tr>
<tr>
<td>Danks, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>157</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>Brain lesion in/near eloquent cortex (low-grade glioma n=44, non-tumor n=22).</td>
</tr>
<tr>
<td>Duffau, 2008</td>
<td>France</td>
<td>Case series</td>
<td>115</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>Grade II gliomas in left dominant hemisphere.</td>
</tr>
<tr>
<td>Ilmberger, 2008</td>
<td>Germany</td>
<td>Case series</td>
<td>153</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>153 craniotomies in 149 patients with brain lesions in/near language areas (low-grade glioma n=77, non-tumor n=9).</td>
</tr>
<tr>
<td>Kim, 2009</td>
<td>USA</td>
<td>Case series</td>
<td>310</td>
<td>1</td>
<td>ns</td>
<td>—</td>
<td>Intracerebral tumors in/near eloquent cortex (low-grade glioma n=58, non-tumor n=5); 10 reoperations.</td>
</tr>
<tr>
<td>Mehta, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>248</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23). No follow-up.</td>
</tr>
<tr>
<td>Sanai, 2008</td>
<td>USA</td>
<td>Case series</td>
<td>250</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>Patients with gliomas close to speech cortex (low-grade glioma n=124).</td>
</tr>
<tr>
<td>Serletis, 2007</td>
<td>Canada</td>
<td>Case series</td>
<td>610</td>
<td>0</td>
<td>3/610 (0.5%)</td>
<td>—</td>
<td>Awake surgery for supratentorial intraaxial tumors (n=610; low-grade glioma n=129, non-tumor n=35). Brain mapping used in 511 cases.</td>
</tr>
</tbody>
</table>
Appendix 1.4. Outcome variable: Intra and postoperative mortality for awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With dropouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 1999</td>
<td>Canada</td>
<td>Case series</td>
<td>200</td>
<td>0</td>
<td></td>
<td></td>
<td>Awake surgery for supratentorial intraaxial tumors (low-grade glioma n=24, non-tumor n=12). Brain mapping used in 195 cases.</td>
</tr>
</tbody>
</table>
Appendix 1:5. Outcome variable: Complications (other than neurological deficits) for brain tumor surgery with awake craniotomy (AC) with intraoperative cortical stimulation and craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals/dropouts</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention AC</td>
<td>Control GA</td>
</tr>
<tr>
<td>Sacko, 2011</td>
<td>France</td>
<td>Cohort study</td>
<td>575</td>
<td>0</td>
<td>Regional complications 8/214 (3.7%): Wound infection 1.4%; Abscess 0.4%; CSF leak 0%; Hematoma 1.8%. Medical complications 2/214 (0.9%): DVT 0.4%; PE 0%; Hyponatremia 0.4%; UTI 0%; PI 0%</td>
<td>GA72: Regional complications 5/72 (6.9%): Wound infection 1.3%; Abscess 1.3%; CSF leak 1.3%; Hematoma 2.7%. Medical complications 10/72 (14%): DVT 2.7%; PE 1.3%; Hyponatremia 2.7%; UTI 4.1%; PI 2.7%</td>
</tr>
<tr>
<td>Bai, 2011</td>
<td>China</td>
<td>Case series</td>
<td>112</td>
<td>0</td>
<td>Partial seizures 13, acute cephalocele 1, shivering 21. Moderate or severe pain during surgery 0.</td>
<td>—</td>
</tr>
<tr>
<td>Danks, 2000</td>
<td>USA</td>
<td>Case series</td>
<td>157</td>
<td>0</td>
<td>0 major anesthetic complications; brief seizure 12/157.</td>
<td>—</td>
</tr>
<tr>
<td>Serletis, 2007</td>
<td>Canada</td>
<td>Case series</td>
<td>511</td>
<td>0</td>
<td>Wound complications 4, intraoperative adverse events 5, DVT 7, hyponatremia 3, respiratory failure 3, renal failure 3, arrhythmia 1, postoperative hematoma 7.</td>
<td>—</td>
</tr>
</tbody>
</table>
Appendix 1.5. Outcome variable: Complications (other than neurological deficits) for brain tumor surgery with awake craniotomy (AC) with intraoperative cortical stimulation and craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients n=</th>
<th>With withdrawals-dropouts</th>
<th>Result</th>
<th>Comments</th>
<th>Quality (may vary according to outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 1999</td>
<td>Canada</td>
<td>Case series</td>
<td>200</td>
<td>0</td>
<td>AC 12</td>
<td>Medical complications 12 (DVT 6, pulmonary embolus 1), wound complications 2, postoperative hematoma 3.</td>
<td>—</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis.
### Appendix 2. Excluded articles

<table>
<thead>
<tr>
<th>Study (author, publication year)</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekar et al., 2009</td>
<td>No cortical mapping during surgery, did not fulfil PICO criteria</td>
</tr>
<tr>
<td>Bertani et al., 2009</td>
<td>Paper on technical issues regarding cortical stimulation, without data on relevant outcomes.</td>
</tr>
<tr>
<td>Carrabba et al., 2007</td>
<td>Not clear how many patients were awake during surgery, did not fulfil PICO criteria</td>
</tr>
<tr>
<td>Chang et al., 2011</td>
<td>Does not state how many patients were awake during surgery, did not fulfil PICO criteria</td>
</tr>
<tr>
<td>Conte et al., 2010</td>
<td>Paper considers intraoperative anesthesiological complications only. No data on relevant outcomes.</td>
</tr>
<tr>
<td>Conte et al., 2006</td>
<td>Paper considers intraoperative anesthesiological complications only. No data on relevant outcomes.</td>
</tr>
<tr>
<td>Danks et al., 1998</td>
<td>&lt;100 cases.</td>
</tr>
<tr>
<td>Gupta et al., 2007</td>
<td>No cortical stimulation was performed in awaken patient group, did not fulfil PICO criteria.</td>
</tr>
<tr>
<td>Keles et al., 2004</td>
<td>Patients were asleep during procedure/stimulation.</td>
</tr>
<tr>
<td>Palese et al., 2008</td>
<td>Qualitative study on patients’ experiences, did not fulfil PICO.</td>
</tr>
<tr>
<td>Peruzzi et al., 2011</td>
<td>&lt;100 cases.</td>
</tr>
<tr>
<td>Pinsker et al., 2007</td>
<td>&lt;100 cases.</td>
</tr>
<tr>
<td>Vitaz et al., 2003</td>
<td>Paper on technical issues regarding cortical stimulation, without data on relevant outcomes.</td>
</tr>
</tbody>
</table>
Appendix 3, Search strategy, study selection and references

Question(s) at issue:
Is awake craniotomy with intraoperative cortical/subcortical mapping of functional brain areas better than craniotomy under general anesthesia, or two-step procedure with ‘cortical grid’ (another method for cortical mapping), or biopsy followed by radiation therapy/expectancy, regarding mortality, postoperative neurological deficits, gross total resection of tumor, or quality of life, in adults and adolescents with brain tumor adjacent to a region with motor and/or speech function?

P: Patients \( \geq \)13 years with brain tumor

I: Awake craniotomy with intraoperative cortical/subcortical mapping.

C1: Craniotomy under general anesthesia.
C2: Two-step procedure with ‘cortical grid’.
C3: Biopsy followed by radiation/expectancy.

O: Postoperative neurological deficits
Extent of resection/gross total resection.
Mortality (intra and postoperative/tumor-related)
Quality of life
Complications and risks

Eligibility criteria

Study design:
Studies with control group
Case series with \( \geq \) 100 patients
Systematic reviews

Language:
English, French, Swedish, Norwegian, Danish

Publication date: 1990-
Selection process – flow diagram

Identification

Records identified through database searching (n = 766)
Additional records identified through other sources (n = 25)

Records after duplicates removed (n = 526)

Screening

Records screened by HTA-librarians (n = 526)
Records excluded by HTA-librarians. Did not fulfil PICO or other eligibility criteria (n = 471)

Eligibility

Full-text articles assessed for eligibility by HTA-librarians (n = 55)
Full-text articles excluded by HTA-librarians, with reasons (n = 30)
1 = wrong intervention
1 = wrong comparison
26 = wrong study design
1 = other

Full-text articles assessed for eligibility by project group (n = 25)

Full-text articles excluded by project group, with reasons (n = 13)

Included

Studies included in synthesis (n = 12)
Including 1 systematic review commented upon

See Appendix 1
Search strategies

**Database:** PubMed  
**Date:** 2012-04-23  
**No of results:** 366

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
<th>Items found</th>
</tr>
</thead>
<tbody>
<tr>
<td>#30</td>
<td>Search (#28) NOT #17 Limits: English, French, Danish, Norwegian, Swedish, Publication Date from 1990/01/01</td>
<td>366</td>
</tr>
<tr>
<td>#29</td>
<td>Search (#28) NOT #17</td>
<td>458</td>
</tr>
<tr>
<td>#28</td>
<td>Search (#27) NOT #16</td>
<td>559</td>
</tr>
<tr>
<td>#27</td>
<td>Search ((#7) AND #14) AND #26</td>
<td>569</td>
</tr>
<tr>
<td>#26</td>
<td>Search #25 OR #9</td>
<td>918677</td>
</tr>
<tr>
<td>#25</td>
<td>Search ((craniotomy[Title/Abstract]) OR surgery[Title/Abstract]) OR neurosurg*[Title/Abstract] OR resection[Title/Abstract]</td>
<td>811992</td>
</tr>
<tr>
<td>#17</td>
<td>Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))</td>
<td>3663550</td>
</tr>
<tr>
<td>#16</td>
<td>Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])</td>
<td>1163605</td>
</tr>
<tr>
<td>#14</td>
<td>Search ((#11) OR #12) OR #13</td>
<td>264604</td>
</tr>
<tr>
<td>#13</td>
<td>Search brain mapping[Title/Abstract]</td>
<td>1096</td>
</tr>
<tr>
<td>#12</td>
<td>Search brain mapping[MeSH Terms]</td>
<td>57658</td>
</tr>
<tr>
<td>#11</td>
<td>Search (((((((electrical mapping) OR electrical stimulation) OR cortical stimulation) OR subcortical stimulation) OR cortical mapping) OR subcortical mapping) OR electrostimulation) OR electrocortical stimulation) OR functional mapping</td>
<td>248765</td>
</tr>
<tr>
<td>#9</td>
<td>Search (neurosurgery[MeSH Terms]) OR neurosurgical procedures[MeSH Terms]</td>
<td>144833</td>
</tr>
<tr>
<td>#7</td>
<td>Search (#5) OR #6</td>
<td>51492</td>
</tr>
<tr>
<td>#6</td>
<td>Search ((local anesthesia[MeSH Terms]) OR wakefulness[MeSH Terms]) OR conscious sedation[MeSH Terms]</td>
<td>31591</td>
</tr>
<tr>
<td>#5</td>
<td>Search (awake[Title/Abstract]) OR local anesthesia[Title/Abstract]</td>
<td>26030</td>
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</tbody>
</table>

**Database:** EMBASE (OVID SP)  
**Date:** 2012-04-23  
**No of results:** 306

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
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<tbody>
<tr>
<td>1</td>
<td>exp wakefulness/</td>
<td>15450</td>
</tr>
<tr>
<td>2</td>
<td>exp local anesthesia/</td>
<td>25804</td>
</tr>
<tr>
<td>3</td>
<td>exp conscious sedation/</td>
<td>3399</td>
</tr>
<tr>
<td>4</td>
<td>(awake or local anesthesia).ti,ab.</td>
<td>30022</td>
</tr>
<tr>
<td>5</td>
<td>1 or 2 or 3 or 4</td>
<td>63970</td>
</tr>
<tr>
<td>6</td>
<td>exp electrostimulation/</td>
<td>67972</td>
</tr>
<tr>
<td>7</td>
<td>exp brain mapping/</td>
<td>23518</td>
</tr>
<tr>
<td>8</td>
<td>(electrical mapping or electrical stimulation or cortical stimulation or subcortical stimulation or cortical mapping or subcortical mapping or electrostimulation or electrocortical stimulation or functional mapping or brain mapping).ti,ab.</td>
<td>42701</td>
</tr>
<tr>
<td>9</td>
<td>6 or 7 or 8</td>
<td>109258</td>
</tr>
<tr>
<td>ID</td>
<td>Search</td>
<td>Hits</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>#1</td>
<td>(awake):ti,ab,kw or (local anesthesia):ti,ab,kw or (wakefulness):ti,ab,kw or (conscious sedation):ti,ab,kw</td>
<td>9150</td>
</tr>
<tr>
<td>#2</td>
<td>(neurosurgery):ti,ab,kw or (neurosurgical):ti,ab,kw or (craniotomy):ti,ab,kw or (surgery):ti,ab,kw or (resection):ti,ab,kw</td>
<td>79124</td>
</tr>
<tr>
<td>#3</td>
<td>(electrical mapping):ti,ab,kw or (electrical stimulation):ti,ab,kw or (cortical stimulation):ti,ab,kw or (subcortical stimulation):ti,ab,kw</td>
<td>3085</td>
</tr>
</tbody>
</table>

**Database:** The Cochrane Library  
**Date:** 2012-04-23  
**No of results:** 45  
*Cochrane reviews 3*  
*Clinical trials 42*
(subcortical mapping):ti,ab,kw or (electrostimulation):ti,ab,kw or (electrocortical stimulation):ti,ab,kw or (functional mapping):ti,ab,kw or (brain mapping):ti,ab,kw

(#3 OR #4)

(#1 AND #2 AND #5)

**Database:** CRD  
**Date:** 2012-04-23  
**No of results:** 0

<table>
<thead>
<tr>
<th>Line</th>
<th>Search</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(local anesthesia) OR (awake) FROM 1990 TO 2012</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>(craniotomy) OR (surgery) OR (neurosurg*) OR (resection) FROM 1990 TO 2012</td>
<td>9135</td>
</tr>
<tr>
<td>3</td>
<td>electrical mapping or electrical stimulation or cortical stimulation or subcortical stimulation or cortical mapping or subcortical mapping or electrostimulation or electrocortical stimulation or functional mapping or brain mapping</td>
<td>215</td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2 AND #3</td>
<td>0</td>
</tr>
</tbody>
</table>

The web-sites of SBU, Kunnskapssenteret and Sundhedsstyrelsen were visited  
Nothing relevant to the question at issue was found

**Reference lists**  
25 results
Reference lists

Included studies:


Systematic reviews, no appraisal done, only commented on:
Excluded studies:


Other references:
Available from:
http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%3a4ltmedel%20under%20projektet/B03_Granskningsmall%20f%20b%20kontrollgrupper.doc


GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2012 Mar 8]. Available from:
http://www.gradeworkinggroup.org/publications/index.htm


Appendix 4. Summary of Findings. Awake craniotomy (AC) with intraoperative cortical/subcortical mapping of functional brain areas versus craniotomy under general anesthesia (GA)

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Number of studies</th>
<th>Design</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication bias</th>
<th>Magnitude of effect</th>
<th>Relative risk reduction</th>
<th>Absolute risk reduction (NNT)</th>
<th>Quality of evidence GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological deficits, AC vs. GA</td>
<td>2 (11*)</td>
<td>2 cohort*</td>
<td>Some limitations (?)</td>
<td>No serious inconsistency</td>
<td>Some uncertainty (?)</td>
<td>No imprecision</td>
<td>Unlikely</td>
<td>Large effect (+1)</td>
<td>0.63-0.70</td>
<td>0.11-0.18 (5.5-9.1)</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>Extent of resection GTR, AC vs. GA</td>
<td>2 (9*)</td>
<td>2 cohort*</td>
<td>Some limitations (?)</td>
<td>No serious inconsistency</td>
<td>Some uncertainty (?)</td>
<td>No imprecision</td>
<td>Unlikely</td>
<td>Large effect (+1)</td>
<td>0.62-0.76†</td>
<td>0.19-0.23† (4.3-5.2)</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>Tumor-related mortality, AC vs. GA</td>
<td>2</td>
<td>2 cohort*</td>
<td>Some limitations (?)</td>
<td>No serious inconsistency</td>
<td>Some uncertainty (?)</td>
<td>No imprecision</td>
<td>Unlikely</td>
<td>Not relevant</td>
<td>0.27-0.79‡</td>
<td>0.15-0.34‡ (2.9-6.7)</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>Intra and postoperative mortality, AC vs. GA</td>
<td>2 (11*)</td>
<td>2 cohort*</td>
<td>Some limitations (?)</td>
<td>No serious inconsistency</td>
<td>Some uncertainty (?)</td>
<td>Serious imprecision (-1)</td>
<td>Unlikely</td>
<td>Not relevant</td>
<td>1.0</td>
<td>0.01-0.02 (50-200)</td>
<td>⊕⊕⊕⊕</td>
</tr>
</tbody>
</table>

GTR = Gross total resection. NNT = Number needed to treat.
* = The quality of evidence (GRADE) and effect size calculations are based on the two cohort studies.
† = Calculated only for data on total resection.
‡ = Data for Sacko et al., 2011 estimated from figures.
HTA står för Health Technology Assessment

En systematisk granskning av den vetenskapliga dokumentationen för en metod eller teknologi inom hälso- och sjukvården. Avsikten med ett HTA-projekt är att värdera en viss teknik eller metod avseende:

- Effekten i form av patientnytta och risker
- Etiska aspekter
- Organisatoriska aspekter
- Kostnader

HTA-centrum använder sig av det internationellt utarbetade GRADE-systemet för att gradera evidensstyrkan i det sammanlagda vetenskapliga underlaget för slutsatsen avseende en viss fråga. Evidensstyrkan graderas i fyra olika nivåer:

- **Starkt vetenskapligt underlag** ⊕⊕⊕⊕
  Det är osannolikt att framtida forskning kommer att ha betydelse för vår tilltro till skattningen av effekten.

- **Måttligt starkt vetenskapligt underlag** ⊕⊕⊕
  Framtida forskning kommer sannolikt att ha betydelse för vår tilltro till skattningen av effekten. Skattningen kan eventuellt komma att ändras.

- **Begränsat vetenskapligt underlag** ⊕⊕
  Det är högst sannolikt att framtida forskning har betydelse för vår tilltro till skattningen av effekten. Det är mycket möjligt att skattningen kommer att ändras.

- **Otillräckligt vetenskapligt underlag** ⊕
  Varje skattning av effekten är mycket osäker (inget uttalande om effekt)


Christina Bergh, professor, HTA-chef
HTA-centrum
Figuren visar schematisk HTA-centrums organisation uppdelat på huvudprocess, stödprocess och kvalitetssäkringsprocess.