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Intraoperative cortical stimulation in brain tumor surgery

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

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Table of content

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 ⊕⊕◯◯). 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 ⊕⊕◯◯). 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 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**

Daniel Nilsson, MD, PhD, Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg, Sweden.

1b **The question was posed by**

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1d **Other participants, from the HTA centre and external reviewers**

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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.

2f **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_1: Craniotomy under general anesthesia.
C_2: Two-step procedure with 'cortical grid'.
C_3: 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 moths 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 ⊕⊕◯◯).

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 ⊕⊕◯◯).

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 ⊕◯◯◯).

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)

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I = Awake craniotomy with intraoperative cortical/subcortical mapping.
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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 case-series, and a closely 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 ⊕◯◯◯).

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.
HTA was accomplished during the period of 2012-04-16 – 2012-10-31.
Last search updated in April 2012

On behalf of the HTA quality assurance group, in Region Västra Götaland, Sweden.
Göteborg, Sweden, 2012-10-31

Christina Bergh, Professor, MD
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Lennart Jivegård MD, Senior university lecturer	Henrik Sjövall MD, Professor	Margareta Warrén Stomberg Senior university lecturer
Peter Johansson MD, PhD	Petteri Sjögren DDS, PhD	Kjell-Arne Ung MD, PhD

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 tvåstegsförfarande 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 = Tvåstegsförfarande 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
Kraniotomi på vaken patient med peroperativ kortikal/subkortikal kartläggning kan resultera i färre kvarstående postoperativa neurologiska bortfall än kraniotomi under narkos, med 11-18 % absolut riskreduktion (ARR). Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯). Kraniotomi på vaken patient med peroperativ kartläggning kan resultera i en högre frekvens av total tumör resektion än kraniotomi under narkos (ARR 19-23%). Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯). Kraniotomi på vaken patient med peroperativ kartläggning kan leda till lägre tumörrelaterad mortalitet än kraniotomi under narkos (ARR 15-34%). Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯). 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 ⊕◯◯◯). Det fanns inga relevanta studier avseende utfallet livskvalitet.

C2: Tvåstegsförfarande med "cortical grid"
Inga relevanta artiklar lokaliserades avseende denna intervention.

C3: Biopsi följt av strålbehandling/expektans
Inga relevanta artiklar lokaliserades 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 jämförbar 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 sjukhusvistelse 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 tumörrelaterad mortalitet än kraniotomi under narkos. Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯). 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 ⊕◯◯◯).

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat 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

HTA-kvalitetssäkringsgruppen:

Christina Bergh	Anders Larsson	Maria Skogby
Professor, överläkare	Med dr, överläkare	Med dr, vårdenhetschef
Thomas Franzén	Christian Rylander	Annika Strandell
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Magnus Hakeberg	Ola Samuelson	Therese Svanberg
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Lennart Jivegård	Petteri Sjögren	Kjell-Arne Ung
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Peter Johansson	Henrik Sjövall	Margareta Warrén Stomberg
Med dr, överläkare	Professor, överläkare	Universitetslektor

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

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Duffau, 2005	France	Cohort study	222	0	Total 8/122 (6.5%) Severe deficits 8/76 within eloquent areas, 0/46 not within eloquent areas n=122	Total 17/100 (17%) p=0.019 Severe deficits 10/35 within eloquent areas, 7/65 not within eloquent areas n=100	Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996) All patients had low-grade gliomas.	Moderate
Sacko, 2011	France	Cohort study	575	0	New deficit 7/214 (3.3%), transient deficit 52/214 (24%), permanent deficit 10/214 (4.6%). n=214	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<0.001 for AC vs GA72	GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n≈27. Prospective, same time period 2002-2007.	Moderate
Bai, 2011	China	Case series	112	0	Permanent deficits 3/112 (2.7%), after 3 months. Transient deficits 51/112 (45.5%).	—	Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75). 5 patients could not fulfil language task due to drowsiness.	
Danks, 2000	USA	Case series	157	0	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.	—	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.	
Duffau, 2008	France	Case series	115	0	115/115 general reduction in language performance (BDAE score) in immediate postoperative period; 2/115 (1.7%) reduction, 6 improvement, after 3 months.	—	Grade II gliomas in left dominant hemisphere.	

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

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Ilmberger, 2008	Germany	Case series	149	0	41/128 new language deficit in cases without pre-operative deficits; 19/25 worsening of pre-operative language deficits.	—	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)	
Kim, 2009	USA	Case series	310	1 (died post op)	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.	—	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<0.001).	
Mehta, 2000	USA	Case series	248	0	Early postoperative deficits 31%.	—	Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23). No follow-up.	
Sanai, 2008	USA	Case series	250	0	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.	—	Patients with gliomas close to speech cortex (low-grade glioma n=124).	
Serletis, 2007	Canada	Case series	511	0	78/511 (15.3%) postoperative neurological worsening in patients who underwent awake surgery and mapping	—	Awake surgery for supratentorial intraaxial tumors (n=610; low-grade glioma n=129, non-tumor n=35). Brain mapping used in 511 cases.	
Taylor, 1999	Canada	Case series	200	0	Transient neurological deficit 17/200 (8.5%), permanent deficit 9/200 (4.5%).	—	Awake surgery for supratentorial intraaxial tumors (low-grade glioma n=24, non-tumor n=12). Brain mapping used in 195 cases.	

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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Duffau, 2005	France	Cohort study	222	0	25.4% (31/122) total, 50.8% (62/122) subtotal, 23.8% (29/122) partial.	6% (6/100) total, 37% (37/100) subtotal, 57% (57/100) partial p<0.001 between groups	MRI. Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996). All patients had low-grade gliomas	Moderate
Sacko, 2011	France	Cohort study	(214 vakna) 575 totalt	0	37% total, 45% subtotal. n=214	GA72 (comparable to AC group): 14% total, 26% subtotal. GA: 52% total, 34% subtotal. n=361 p<0.001 between AC and GA72	MRI. GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n≈27. Prospective, same time period 2002-2007.	Moderate
Bai, 2011	China	Case series	112	0	58.9% total, 30.4% subtotal, 10.7% partial.	—	MRI. Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75).	
Danks, 2000	USA	Case series	157	0	57% total, 23% subtotal, 13% partial, 7% biopsy only.	—	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.	
Duffau, 2008	France	Case series	115	0	32% total, 51% subtotal, 17% partial.	—	MRI. Grade II gliomas in left dominant hemisphere.	
Ilmberger, 2008	Germany	Case series	149	0	48.4% total.	—	MRI. 153 craniotomies in 149 patients with brain lesions in/near language areas (low-grade glioma n=77, non-tumor n=9).	
Kim, 2009	USA	Case series	310	1	64% total, 14% subtotal, 22% partial (39% total in low-grade tumors).	—	MRI. Intracerebral tumors in/near eloquent cortex (low-grade glioma n=58, non-tumor n=5); 10 reoperations.	
Mehta, 2000	USA	Case series	248	0	57% total, 23% subtotal.	—	Imaging method not stated. Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23).	
Sanai, 2008	USA	Case series	250	0	59.6% total (51.6% total in low-grade tumors).	—	MRI. Patients with gliomas close to speech cortex (low-grade glioma n=124).	

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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Duffau, 2005	France	Cohort study	222	0	Partial resections 6/29 (20.6%) died, subtotal resections 5/62 (8%) died, complete resections 0/31 (0%) died. p=0.02 (within group).	Partial resections 30/57 (52.6%) died, subtotal resections 13/37 (35%) died, complete resections 0/6 (0%) died. p=0.04 (within group).	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	Low
Sacko, 2011	France	Cohort study	575	0	Survival after 60 months approx. 0.6*. n= 214 Low-grade glioma only: approx. 0.95*.	Survival after 60 months: GA72: 0.40* (comparable to AC group) GA: 0.5* p<0.001 between groups. n=361 Low-grade glioma only: GA72: 0.5* GA: 0.7* p<0.001 between groups.	GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n≈27.	Moderate

* 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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Duffau, 2005	France	Cohort study	222	0	0/122	2/100 (2%)	Intervention prospective data, control retrospective data; different periods (intervention 1996-2003, control 1985-1996). All patients had low-grade gliomas	Low
Sacko, 2011	France	Cohort study	575	0	0 n=214	0.5% 2 deaths within 90 days in the GA72 group (comparable to AC group) n=361		Low
Bai, 2011	China	Case series	112	0	ns	—	Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75).	
Danks, 2000	USA	Case series	157	0	0	—	Brain lesion in/near eloquent cortex (low-grade glioma n=44, non-tumor n=22). Cortical mapping performed in 122 cases.	
Duffau, 2008	France	Case series	115	0	0	—	Grade II gliomas in left dominant hemisphere.	
Ilmberger, 2008	Germany	Case series	153	0	0	—	153 craniotomies in 149 patients with brain lesions in/near language areas (low-grade glioma n=77, non-tumor n=9).	
Kim, 2009	USA	Case series	310	1	ns	—	Intracerebral tumors in/near eloquent cortex (low-grade glioma n=58, non-tumor n=5); 10 reoperations.	
Mehta, 2000	USA	Case series	248	0	0	—	Craniotomies for tumor resections, various locations (low-grade glioma n=78, non-tumor n=23). No follow-up.	
Sanai, 2008	USA	Case series	250	0	0	—	Patients with gliomas close to speech cortex (low-grade glioma n=124).	
Serletis, 2007	Canada	Case series	610	0	3/610 (0.5%)	—	Awake surgery for supratentorial intraaxial tumors (n=610; low-grade glioma n=129, non-tumor n=35). Brain mapping used in 511 cases.	

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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Taylor, 1999	Canada	Case series	200	0	2/200 (1%) One died 5 days post op (hematoma) One died after 24 days (pulmonary embolism)	—	Awake surgery for supratentorial intraaxial tumors (low-grade glioma n=24, non-tumor n=12). Brain mapping used in 195 cases.	

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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Sacko, 2011	France	Cohort study	575	0	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%	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% GA: Regional complications 12/361 (3.2 %): Wound infection 1.1%; Abscess 0.5%; CSF leak 0.5%; Hematoma 1.1%. Medical complications 24/361 (6.6%): DVT 1.4%; PE 0.5%; Hyponatremia 1.4%; UTI 1.9%; PI 1.4%	GA72=general anesthesia, eloquent cortex. GA=general anesthesia. Low-grade glioma n=72, non-tumor n≈27. Regional complications included: wound infection, abscess/empyema, CFS leak, hematoma. Medical complications included: deep vein thrombosis (DVT), pulmonary embolus (PE), hyponatremia, urinary tract infection (UTI), pulmonary infection (PI).	
Bai, 2011	China	Case series	112	0	Partial seizures 13, acute cephalocele 1, shivering 21. Moderate or severe pain during surgery 0.	—	Neuroepithelial tumors in/close to eloquent areas (low-grade glioma n=75).	
Danks, 2000	USA	Case series	157	0	0 major anesthetic complications; brief seizure 12/157.	—	Brain lesion in/near eloquent cortex (low-grade glioma n=44, non-tumor n=22). Cortical mapping performed in 122 cases.	
Serletis, 2007	Canada	Case series	511	0	Wound complications 4, intraoperative adverse events 5, DVT 7, hyponatremia 3, respiratory failure 3, renal failure 3, arrhythmia 1, postoperative hematoma 7.	—	Awake surgery for supratentorial intraaxial tumors (n=610; low-grade glioma n=129, non-tumor n=35). Brain mapping used in 511 cases.	

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)

Author, year	Country	Study design	Number of patients n=	With drawals-dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention AC	Control GA		
Taylor, 1999	Canada	Case series	200	0	Medical complications 12 (DVT 6, pulmonary ebolus 1), wound complications 2, postoperative hematoma 3.	—	Awake surgery for supratentorial intraaxial tumors (low-grade glioma n=24, non-tumor n=12). Brain mapping used in 195 cases.	

DVT = deep vein thrombosis.

Appendix 2. Excluded articles

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

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 ≥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

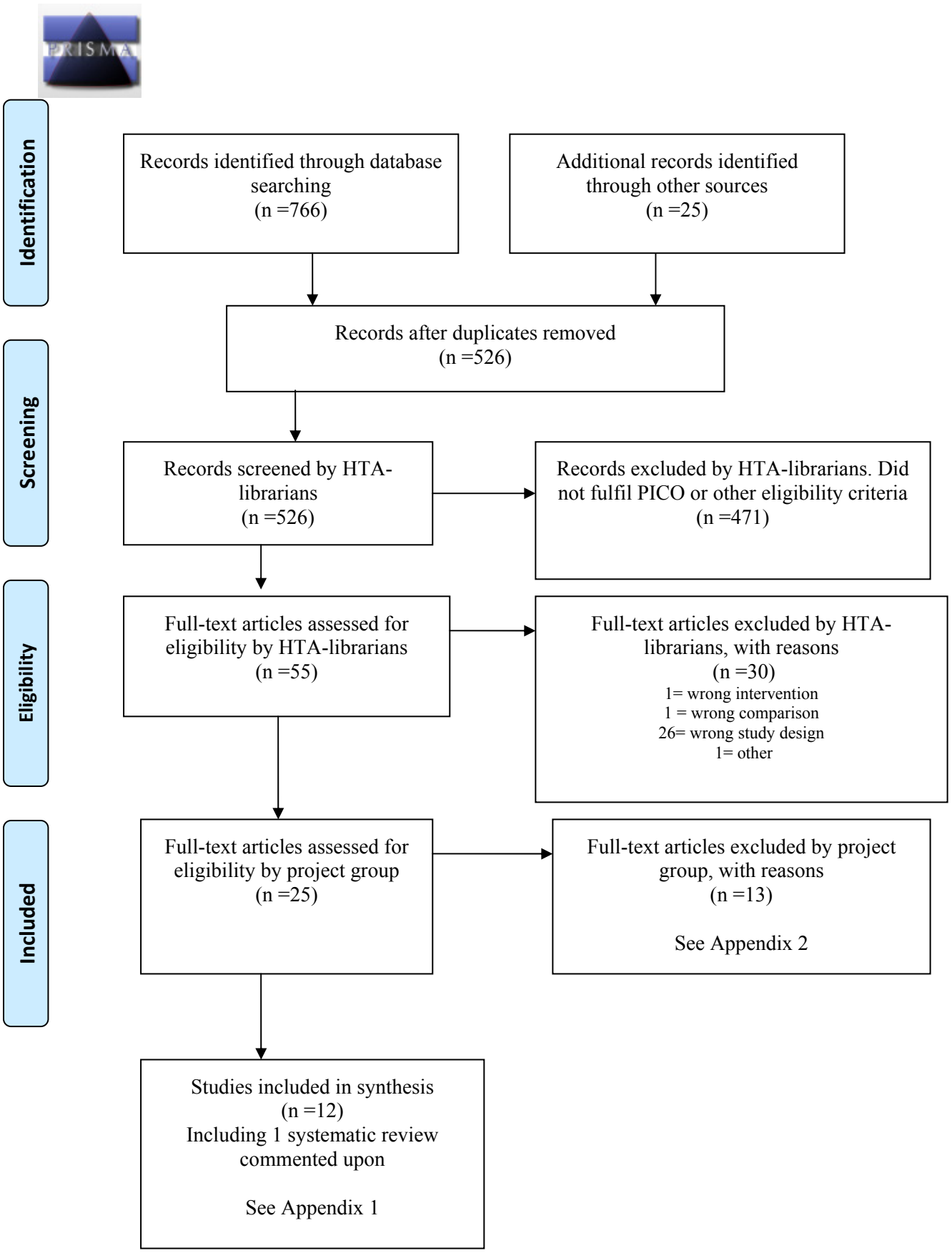
Eligibility criteria

Study design:
Studies with control group
Case series with ≥ 100 patients
Systematic reviews

Language:
English, French, Swedish, Norwegian, Danish

Publication date: 1990-

Selection process – flow diagram



Search strategies

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

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

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

#	Searches	Results
1	exp wakefulness/	15450
2	exp local anesthesia/	25804
3	exp conscious sedation/	3399
4	(awake or local anesthesia).ti,ab.	30022
5	1 or 2 or 3 or 4	63970
6	exp electrostimulation/	67972
7	exp brain mapping/	23518
8	(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.	42701
9	6 or 7 or 8	109258

10	(craniotomy or surgery or neurosurg* or resection).ti,ab.	995313
11	exp neurosurgery/	171453
12	10 or 11	1103634
13	5 and 9 and 12	491
14	**limit 13 to (human and embase and (danish or english or french or norwegian or swedish) and yr="1990 -Current")**	**306**

Database: PsycINFO (ProQuest)
Date: 2012-04-23
No of results: 49

Set	Search	Results
S9	**S3 AND S4 AND S6 Limits applied** **Narrowed by:** **Entered date: 01/ 01/ 1990 - 05/ 01/ 2012;** **Publication frequency: Human**	**49**
S8	S3 AND S4 AND S6 Limits applied Narrowed by: Entered date: 01/ 01/ 1990 - 05/ 01/ 2012	51
S7	S3 AND S4 AND S6	58
S6	SU.EXACT.EXPLODE("Electrical Stimulation") OR ab(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) OR ti(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)	19002
S4	SU.EXACT.EXPLODE("Neurosurgery") OR ab((craniotomy OR neurosurgery)) OR ab((neurosurgical OR surgery)) OR ab(resection) OR ti((craniotomy OR neurosurgery)) OR ti((neurosurgical OR surgery)) OR ti(resection)	19357
S3	SU.EXACT.EXPLODE("Wakefulness") OR SU.EXACT.EXPLODE("Local Anesthetics") OR all((awake OR local anesthesia))	6468

Database: The Cochrane Library
Date: 2012-04-23
No of results: 45
Cochrane reviews 3
Clinical trials 42

ID	Search	Hits
#1	(awake):ti,ab,kw or (local anesthesia):ti,ab,kw or (wakefulness):ti,ab,kw or (conscious sedation):ti,ab,kw	9150
#2	(neurosurgery):ti,ab,kw or (neurosurgical):ti,ab,kw or (craniotomy):ti,ab,kw or (surgery):ti,ab,kw or (resection):ti,ab,kw	79124
#3	(electrical mapping):ti,ab,kw or (electrical stimulation):ti,ab,kw or (cortical stimulation):ti,ab,kw or (subcortical stimulation):ti,ab,kw or (cortical mapping):ti,ab,kw	3085

#4	(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	1826
#5	(#3 OR #4)	4536
#6	**(#1 AND #2 AND #5)**	**45**

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

Line	Search	Hits
1	(local anesthesia) OR (awake) FROM 1990 TO 2012	68
2	(craniotomy) OR (surgery) OR (neurosurg*) OR (resection) FROM 1990 TO 2012	9135
3	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	215
4	**#1 AND #2 AND #3**	**0**

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:

Bai HM, Wang WM, Li TD, He H, Shi C, Guo XF, et al. Three core techniques in surgery of neuroepithelial tumors in eloquent areas: awake anaesthesia, intraoperative direct electrical stimulation and ultrasonography. Chin Med J (Engl). 2011;124(19):3035-41.

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Excluded studies:

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

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

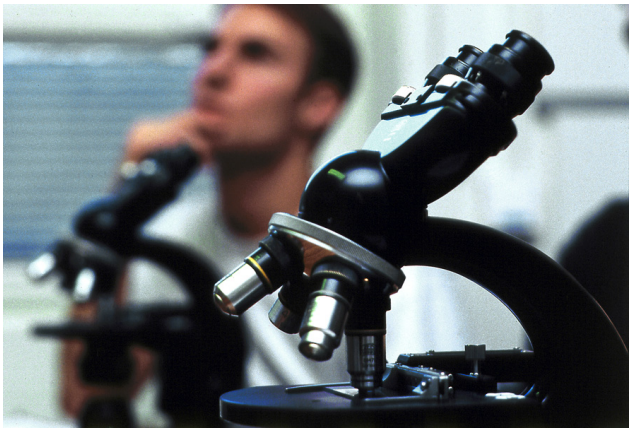
GTR = Gross total resection. NNT = Number needed to treat.

[*] = 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.

Västra Götalandsregionen
HTA-centrum



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.

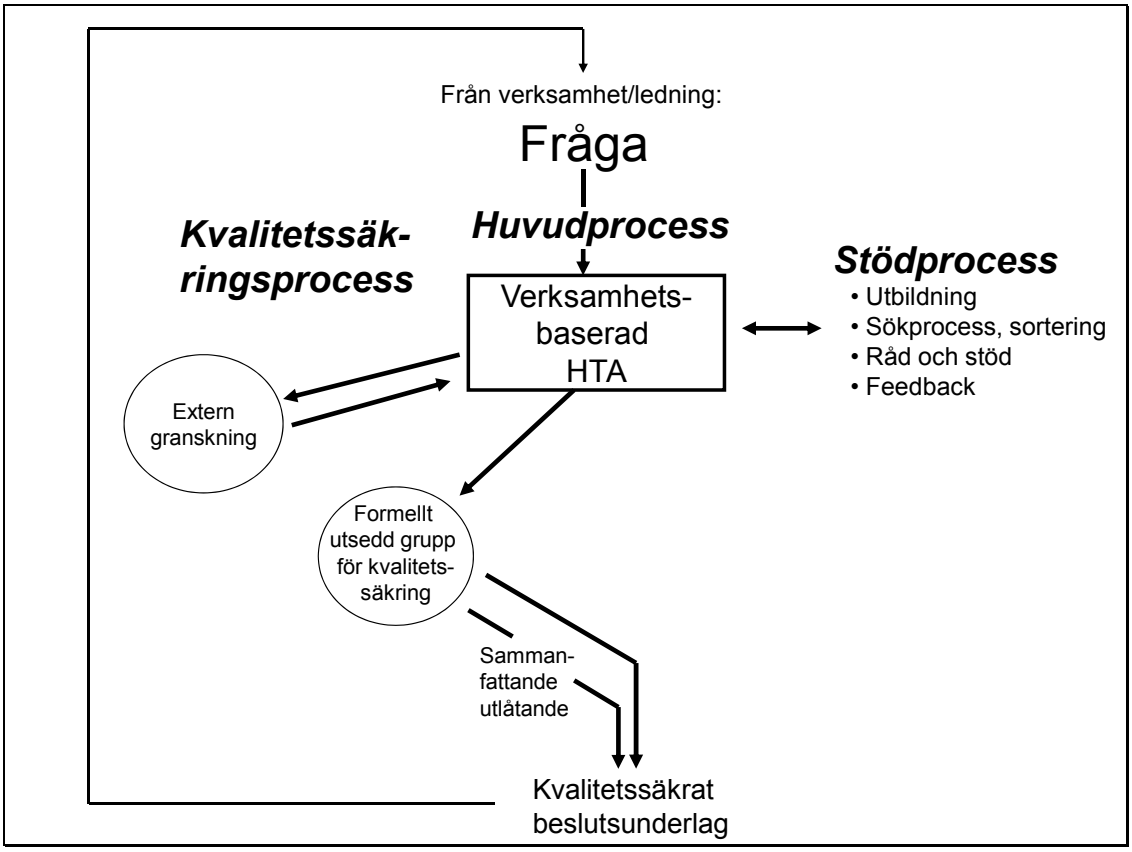
- **Måttligt starkt vetenskapligt underlag** ⊕⊕⊕
  Framtida forskning kommer sannolikt att ha betydelse för vår tilltro till skattningen av effekten. Skattningen kan eventuellt komma att ändras.

- **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)

I GRADE-systemet finns också en rekommendationsdel som inte används av HTA-centrum. Utvärderingen ger ändå vägledning för hälso- och sjukvården. Vid hög och måttlig evidensstyrka för slutsatsen att det finns en positiv effekt är underlaget gott och motiverar sannolikt att metoden tillämpas i hälso- och sjukvårdens kliniska vardag. Begränsad evidensstyrka för samma slutsats visar på att det finns ett visst vetenskapligt underlag som kan motivera att metoden används under förutsättning att andra krav på en acceptabel balans mellan nytta och risk, kostnadseffektivitet och etiska aspekter är uppfyllda. Om evidensstyrkan är otillräcklig indikerar det behov av mer forskning innan metoden börjar tillämpas i klinisk vardag.(GRADE 2004, GRADE List of publications)

Christina Bergh, professor, HTA-chef
HTA-centrum



Figuren visar schematisk HTA-centrums organisation uppdelat på huvudprocess, stödprocess och kvalitetssäkringsprocess.

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