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Gamma Knife

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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Objective

The objective of this technology review was to assess the efficacy of gamma knife SRS in the treatment of arteriovenous malformations, acoustic neuroma, cerebral metastases and trigeminal neuralgia, the latter representing a non-invasive approach to precision ablation for benign conditions. The efficacy of gamma knife relative to microsurgery and LINAC-based SRS was a particular focus of this review for all conditions excluding the treatment of trigeminal neuralgia.

Background

Stereotactic radiosurgery [SRS] is used to define a form of radiation treatment that allows the treatment of small lesions with pinpoint accuracy using 3-dimensional "strereotactic" imaging and the delivery of multiple thin radiation beams through an arc or sphere with the target lesion as the focal point.

Currently, linear accelerators [LINAC] are employed across the province for the purposes of stereotactic radiosurgery. SRS using Cobalt as the radiation source is the basis for the *gamma knife*.

To date, SRS has been used almost exclusively in the treatment of inoperable intracranial lesions, all of which, with the exception of cerebral metastases, are benign. These include the following common indications:

- Acoustic neuroma – a benign tumour involving the eighth cranial nerve
- Arteriovenous malformations – a mass of tangled arteries and veins linked by fistulas
- One or more cerebral metastases

In addition, SRS has been used less commonly in the treatment of:

- Pituitary tumours [benign]
- Pineal tumours [benign]
- Trigeminal neuralgia
- Focal epilepsy
- Meningioma

SRS Services In Ontario

While Ontario has LINAC-based SRS capacity in several Ontario radiation treatment facilities , there is no operational *gamma knife* capacity in Ontario.

The Princess Margaret Hospital has a dedicated LINAC for SRS ["X-Knife"], which has been fully modernized. Ottawa and London Regional Cancer Centres and the Toronto-Sunnybrook Regional Cancer Centres all possess LINAC-based SRS capability.

Description of SRS Technologies

It should be noted that radiosurgery does not involve surgery at all, apart from fixing the stereotactic frame to the head and that the *gamma knife* is not a “knife”.

As stated above, the two SRS technologies employed are the *gamma knife* and LINAC-based radiation.

Gamma Knife

The *gamma knife* uses 201 fixed CO sources arranged in a sphere. A stereotactic frame is attached to the patient’s head with 4 screws and radiation is delivered according to a treatment plan based on 3-dimensional CT or MRI imaging that centres the lesion at the focal point of the convergent beams. A typical treatment takes 40-60 minutes.

LINAC-based SRS

The LINAC-based SRS uses a linear accelerator with modifications and sophisticated software to rotate the gantry through 360° so that the radiation beams are directed to the focal point in a dose distribution that maximizes the dose of radiation to the lesion under consideration. The application of a fixed stereotactic frame and treatment planning employing 3-dimensional imaging is conducted as per the *gamma knife* described above.

Whereas *gamma knife* treatment requires only one treatment, LINAC-based SRS may be delivered either as a single treatment or through multiple treatments [multi fractionated] to increase safety and effectiveness. The decision to use single or multiple treatments using LINAC-based SRS is based on the type and location of the lesion being treated.

Technology applied to *gamma knife* has been relatively constant, whereas modifications to LINAC technology have continued to provide refinements to SRS applications including micro-multileaf collimators and non - fixed stereotactic frame.

In April 2002, the Ministry’s Medical Advisory Secretariat was requested to provide advice regarding the purchase and operation of a *gamma knife* in Ontario based on a review of the existing scientific literature on effectiveness of the technology and other relevant considerations.

Methodology Of The Technology Review

The objective of this technology review was to assess the efficacy of gamma knife SRS in the treatment of arteriovenous malformations, acoustic neuroma, cerebral metastases and trigeminal neuralgia, the latter representing a non-invasive approach to precision ablation for benign conditions. The efficacy of gamma knife relative to microsurgery and LINAC-based SRS was a particular focus of this review for all conditions excluding the treatment of trigeminal neuralgia.

Search terms were *gamma knife*, efficacy, cost -effectiveness.

Levels of evidence were assigned to publications accepted for review according to the schema in appendix 1

In conducting technology assessments, the first priority of the Ministry is to search for current HTAs performed by other national or international jurisdictions. If a credible HTA is identified, the Ministry conducts a synthesis review of the HTA to identify issues of relevance to application in Ontario and policy recommendations are informed by the modified HTA. If no applicable HTA exists in another jurisdiction, the Ministry conducts a rapid response HTA.
A search of Health Technology Assessment Organizations affiliated to the International Network of Agencies for Health Technology Assessment [INAHTA] was conducted.

Further literature searches were employed to update any existing HTA. For this purpose, the Cochrane database was searched and included databases for systematic reviews, DARE, Controlled Trials Register, HTA and NHS Economic Evaluation Databases. MEDLINE was searched, without language restrictions, between January 1998 and April 2002.

1. Results

Database Analysis

Cochrane Database of Systematic Reviews (Protocols)	3
Database of Abstracts of Reviews of Effectiveness (DARE)	2
Cochrane Controlled Trials Register	14
Cochrane Health Technology Assessment Database	10
NHS Economic Evaluation Database (NHS EED)	5
MEDLINE	70
Total number of abstracts found	104

Of the 104 abstracts, only 11 were found to be relevant to the search. Abstracts excluded were reviews, the use of SRS for conditions not included in this analysis, insufficient data reported in an abstract or the report had been analyzed as part of the Medicare Services Advisory Committee [MSAC] study [See below].

2. Summary of Existing HTA Reports on SRS

A detailed HTA on SRS performed by the MSAC of the Department of Health and Aged Care, Australia was produced in October 2000 [1]. The quality of this HTA was considered to be rigorous and credible and forms the basis for this review, supplemented with HTAs from other international jurisdictions. The MSAC HTA concentrated on three main indications for SRS:

- cerebral arteriovenous malformations [AVMs],
- cerebral metastases and
- acoustic neuroma.

The findings of the MSAC HTA are summarized below

Summary of MSAC HTA findings

Out of 720 abstracts identified in the literature search, only 33 were considered eligible for analysis. These studies included a total of 3,635 patients treated with *gamma knife* and 1,661 patients treated with LINAC-based SRS.

There were no studies comparing *gamma knife* with LINAC-based SRS and the quality of studies analyzed was considered to be poor methodologically.

The report concluded that for the subset of patients with small, surgically-accessible AVMs, microsurgery is the most appropriate treatment with total resection rates of 94-100% and neurological complication rates of <5%.

Using SRS, obliteration rates at 2 years was 44-68% for LINAC-based SRS and 26-45% for *gamma knife* with neurological complication rates of 2-10%.

The MSAC report concluded that:

"there is insufficient information to determine whether one method of radiosurgery is superior to another. Two-year obliteration rates for LINAC and gamma knife radiosurgery appear similar, as do complication rates."

The MSAC report also cited a HTA conducted by Agencia de Evaluacion de Tecnologias Sanitarias, 1997 [AETS], [2] on SRS which stated that:

"***although thousands of patients have been treated , due to the 1)small clinical differences observed, 2) small number of studies which evaluated clinical effectiveness and 3) the effect of patient selection, it was not possible to establish differences in the effectiveness of linear accelerator and gamma knife radiosurgery techniques."***

Updated Literature Analysis

Analysis from updated literature search resulted in three additional studies on SRS in the treatment of AVM. These studies are summarized in Table 1. This included two retrospective and one prospective case studies. All three studies involved the exclusive use of *gamma knife* SRS.

An important study was the consecutive series of 240 patients reported by Pan et al [3]. The obliteration rate was dependent on the AVM size with a 32% rate for AVMs larger than 10cm3 and 55% for AVMs less than 10cm3. This is consistent with the MSAC HTA obliteration rate for *gamma knife* reported as 26-45%. The study by Pan et al [3] projected a much higher obliteration rate using a Kaplan-Meir analysis. Since this analysis was not carried out for reported LINAC-based SRS studies, it has no relevance for the purposes of comparison between these technologies.
The retrospective studies by Regis et al [4] of 45 patients and Massager et al [5] of 87 patients reported obliteration rates of 82% and 73% respectively. The mean AVM volume in the study by Regis et al was 5.5cm3 and in the study by Massager et al, it was 1.3cm3. These obliteration rates are higher than those reported by Pan et al [3] and by the MSAC HTA [1].

The re-bleeding rates reported by these three studies ranged from 3.4-9.2%, the highest re-bleeding rate attributed to the largest lesions treated.

Acoustic Neuroma

Summary of MSAC HTA Findings

Of the 292 abstracts identified in the literature, only 19 were considered eligible for analysis. Outcomes evaluated in the review were local control, hearing, cranial nerve abnormality and other complications such as edema or haemorrhage. There were 4 studies on microsurgical resection [total number of patients 1,817], 9 studies on *gamma knife* SRS [total number of patients 870] and 8 studies on LINAC-based SRS, 5 of which were fractionated SRS [total number of patients 269]. No meta-analysis was attempted due to inter-study heterogeneity.

The MSAC report concluded that:

- Microsurgical resection is the treatment of choice in patients fit for surgery, especially for small unilateral tumours. Microsurgical resection offers almost 100% complete resection rates, facial nerve complication rates of up to 20% and hearing preservation of 30-90%. Overall performance is dependent on surgical experience.
- SRS produces 100% tumour control rates and complication rates are similar to microsurgery.
- For SRS, there appears to be little difference between *gamma knife* and LINAC radiosurgery, although fractionated LINAC approach may reduce facial cranial

nerve complications. Outcomes for either technology may be more dependent on expertise, quality of imaging and treatment planning capability than on the technology itself.
- Changes in methods over time make longitudinal comparisons difficult.
- SRS may be especially useful for patients with contraindications for surgery.
- The quality and quantity of evidence on the effectiveness and safety of SRS and microsurgery are limited.
- The MSAC HTA concluded

"***The current information does not allow reliable comparison of treatments and it is therefore not possible to determine whether one method is superior to any other. It is likely that the outcomes will depend more on the treatment team expertise, quality of imaging and treatment planning, than on the method used to deliver the radiation or the surgical approach.***"

The MSAC report also cited five other HTA's on surgical resection and SRS in the treatment of acoustic neuroma and these are summarized later in this report. These five HTA's were produced by:

- The Health Council of the Netherlands [1994] [6];
- Minnesota Health Care Commission, Health Technology Advisory Committee [1995] [7]
- University Health Consortium Technology Assessment Program of the Clinical Practice Advancement Center [1995] [8];
- ECRI, US [1996]; formerly the "Emergency Care Research Institute" [9];
- Alberta Heritage Foundation for Medical Research [1999] [10]

Each of the above HTAs failed to demonstrate any benefit for *gamma knife* over LINAC-based SRS in the treatment of acoustic neuroma, though there are no published RCTs in which these two technologies were compared head to head.

Updated Literature Analysis

Analysis from an updated literature search resulted in one additional study in the treatment of acoustic neuroma. [See Table 1 for summary] This abstract [11] reported on the use of fractionated LINAC-based SRS in 68 patients with a median follow up of 32 months. A decrease in tumour size was seen in 38% of patients with tumour size less than 3 cm and in 59% of patients with tumour size greater than 3 cm. The remaining patients all experienced cessation of growth. One patient experience transient facial weakness.

Brain Metastases

Summary of MSAC HTA Findings

The MSAC HTA on brain metastases was based on an updated Veteran's Affairs MDRC Technology Assessment Program [TAP], published by Anderson and Flynn [1997]. The

MDRC TAP included 13 case series. The MSAC HTA identified 17 eligible studies for analysis out of 131 references on brain metastases from 1990 to March 2000, including one RCT reported by Kondziolka with a sample size of 27 patients in which SRS plus whole brain radiation therapy [WBRT] was compared to WBRT plus SRS.

Due to significant heterogeneity between studies and lack of RCT evidence, only conclusions from the HTA are presented.

The median survival from SRS ranged from 6-11 months which, according to the HTA is comparable to surgery plus WBRT. There also did not appear to be any difference between SRS alone or in combination with WBRT. However, only a small number of patients received SRS alone. The fact that most studies assessed the combination of WBRT plus SRS makes it difficult to determine the merits of SRS.

While local control appeared better for patients treated with SRS, this did not translate into significant survival benefits for these patients.

Complications associated with SRS of brain metastases were poorly reported.

The MSAC HTA concluded that

"Based on this case series data it is not possible to draw any conclusions about the relative effectiveness of LINAC and gamma knife radiosurgery in the treatment of brain metastases."

The Veteran's Affairs MDRC Technology Assessment Program HTA [12] concluded that

"In the absence of data from high quality studies, uncertainty remains about the true effectiveness of SRS for the treatment of metastases to the brain……"

Updated Literature Analysis

Analysis from updated literature search resulted in four additional studies in the treatment of brain metastases and these are summarized in Table 1. These studies include two large RTOG studies, one of which by Sperduto et al [13] is a RCT comparing whole brain radiation treatment [WBRT] alone with WBRT plus SRS.
A preliminary report on the RTOG study, reported by Sperduto et al [13] has so far failed to show any benefit in overall survival with the addition of SRS, though local control was "slightly better" in the SRS arm. Grade 3 neurotoxicity was 5% in the WBRT plus SRS arm and 2% in the WBRT arm. There was no mention in this abstract of the SRS modality used. Since WBRT represents the current standard treatment for brain metastases, this report is important in determining the future use of SRS as an adjunctive treatment to WBRT.

The second RTOG study by Shaw et al [14] reported on the use of SRS in a cohort of 156 patients who had previously received WBRT for primary brain tumour or for brain metastases. Twenty two percent of patients with brain metastases had multiple lesions.

This was a multi-centre dose seeking study that allowed the use of *gamma knife* [20%] or LINAC-based SRS [80%] technologies. Thirty percent of LINAC-treated patients had recurrent brain tumours compared to 61% of patients treated on a *gamma knife*. There was an overall 42% response rate, associated with a 13% improvement in symptom control. Primary brain tumours were 2.85 times more likely to progress locally within 3 months of SRS compared to metastases. Furthermore, patients treated with LINAC-based SRS were 2.84 times more likely to progress locally than those treated with *gamma knife*.

The RTOG study by Shaw et al 14] is the first indication that *gamma knife* might be more effective in treating brain metastases than LINAC-based SRS. However, thirty five patients [22%] experienced "unacceptable acute and chronic toxicity" associated with SRS. Of the patients who experienced severe toxicity, 15 [43%] were irreversible and 4 [11%] proved fatal. Increasing tumour size and higher performance status were independent variables for severe toxicity in a multivariate analysis although the latter was considered "counter-intuitive."

Two small case studies [15,16] reported a 42 – 57% improvement in metastases-related symptoms or performance status respectively. These are summarized in Table 1.

Trigeminal Neuralgia

The analysis did not include studies on stereotactic ablation in the treatment of neurological conditions such as epilepsy, trigeminal neuralgia and movement disorders. However, since neurosurgeons have been keen to use the *gamma knife* for the non-invasive treatment of a variety of neurological disorders, an analysis was undertaken of SRS studies from 1999 to March 2002 of the treatment of trigeminal neuralgia as an example of non-invasive precision ablative SRS

Since the treatment of neurological disorders by ablative radiation requires great precision to minimize destruction of vital neighbouring tissue, *gamma knife* has an advantage over LINAC since it is accurate to within 0.4 mm compared to 1-2 mm for LINAC-based SRS.

Only one study, by Rogers et al [17], and summarized in Table 1, was found. This study of 54 patients with trigeminal neuralgia treated with gamma knife reported that 35% of patients became pain free, 6% had occasional pain not requiring medication and 48% had some pain control requiring medication. Mild facial numbness reported in 7-13% was the only reported side-effect.

Summary Of Evidence Based Analysis Of Stereotactic Radiosurgery

- *Acoustic Neuroma and AVM*

There is no evidence that there is any difference in effectiveness between *gamma knife* and LINAC-based SRS in the treatment of AVM or acoustic neuroma.

There is level 3 evidence that microsurgery remains the best overall treatment option for AVM and acoustic neuroma.

Irrespective of whether SRS is performed using a *gamma knife* or LINAC, there is level 3 evidence that it is an important technology for surgically inaccessible acoustic neuroma and AVM lesions or for lesions considered to present a significant surgical risk.

There is level 3 evidence that, in the treatment of acoustic neuroma, fractionated LINAC-based SRS results in fewer facial nerve complications than *gamma knife*.

- *Brain Metastases*

While SRS is being increasingly employed for treatment of cerebral metastases, there is level 1 evidence that there is no benefit for SRS compared to WBRT when employed as first line radiation treatment. There are no studies demonstrating that surgical excision is better than WBRT alone.

There is level 3 evidence that SRS is beneficial in the treatment of recurrent primary brain tumours or metastases following front line radiation therapy.

There is level 3 evidence that when employed for recurrent brain metastases, *gamma knife* SRS provides improved control of local regional progression than LINAC-based SRS. However, the study reporting this observation observed that despite a 13% improvement in symptom control, 22% of patients experienced severe neurotoxicity which was irreversible in 42% of cases, and 3% all cases died as a result of neurotoxicity attributed to SRS.

- *SRS in Non-Invasive Treatment of Benign Conditions*

Side effects from *Gamma knife* treatment of trigeminal neuralgia are minimal, attesting to the precision of this treatment modality.

There is level 3 evidence that *gamma knife* SRS results in improvement in pain associated with trigeminal neuralgia in over 90% of cases, irrespective of whether patients have undergone previous other treatment or not.

It is assumed that *gamma knife* will be increasingly employed for the non-invasive ablative treatments of benign neurological conditions.

Post-Hoc Note Following Consultations With Ontario Experts

There was general agreement by experts that for most cancer-related indications, linear accelerator based SRS is the most suitable modality in Ontario, give the equivalence in effectiveness compared to *gamma knife* and the existing investments in LINAC technology for SRS.

However, there are some situations in which g*amma knife* has technical advantages over LINAC SRS. It is therefore recommended that g*amma knife* be indicated as an adjunctive, but not a substitutive technology for these indications, in additional to research as a non-invasive alternative to micro-surgery for certain neurological disorders.

Table 1 Literature Survey to Update MSAC HTA

Author/Study	Modality[s] Used in Study	Clinical Design & Sample Size	Outcome reported	Complications
Arteriovenous malformations				
Pan, DH et al [3]	*Gamma knife*	Consecutive series of 240 patients with AVMs. 76 had AVM vols >10cm3 and 164 had vols < 10cm3 Technique included multiple small isocentres to improve conformity of treatment volume.	32% obliteration rate in large vol AVMs and 55% in patients with AVM vols <10cm3. Kaplan-Meier analysis showed obliteration rate at 40 mo. of 77% in AVMs vol 10-15cm3 compared with 25% for vols >15cm3. Latter increased to 58% at 50 mo.	Bleeding rate for large vol AVMs 9.2% vs 1.8% for small vol AVMs. Reversible focal edema occurred in all large vol AVMs Permanent neurological complications in 4% irrespective of vol.
Regis J et al [4]	*Gamma knife*.	Retrospective review of 45 patients with brainstem AVMs. Mean vol 5.5cm3	82% obliteration rate	4% re-bleeding 7% neurologic deficits
Massager N, et al [5]	*Gamma knife*	Retrospective review of 87 patients with brainstem AVMs. Mean AVM vol 1.3cm3. Hemorrhage in 74% before treatment	Complete obliteration rate 73% at 36 mo. 95% of patients improved or remained neurologically stable following SRS.	Bleeding rate 3.4% [all small volume]. One of these 3 patients died.

Table 1 Literature Survey to Update MSAC HTA [cont]

Author/Study	Modality[s] Used in Study	Clinical Design & Sample Size	Outcome reported	Complications
Brain Metastases				
Suzuki et al [15]	*Gamma knife*	Case study of 24 patients with 10 or more brain metastases	Median survival 11 weeks. Of 12 patients with metastases-related symptoms, 42% improved	None documented. 100% patient satisfaction
Ma, Z et al [16] Abstract report	*Gamma knife*	Case study of 21 patients of 46 tumours.	93% local control rate 57% experienced improvement in Karnofsky Performance Status.	Treatment related mortality 4.7%.
Sperduto PW et al [13] Abstract; preliminary report of RTOG Study	SRS – modality not stated	RCT of WBRT plus SRS vs WBRT alone for 2 or 3 brain metastases Preliminary report on 139 evaluable patients	No significant difference in overall survival. Same percentage of deaths attributed to brain metastases in both arms. Local control "slightly better" for WBRT plus SRS arm.	Treatment was "well tolerated" Grade 3 toxicity [predominantly neurotoxicity] 5% for WBRT plus SRS vs 2% for WBRT alone

Table 1 Literature Survey to Update MSAC HTA [cont.]

Author/Study	Modality[s] Used	Clinical Design & Sample Size	Outcome reported	Complications
Brain metastases [cont.]				
Shaw E et al [14] RTOG Study	*Gamma knife* [20%] and LINAC [80%]	Cohort study of 156 patients to determine the maximum tolerated dose of single fraction SRS in patients with recurrent previously irradiated primary brain tumours [36%] and brain metastases [64%] of 156 patients, 22% with multiple lesions.	52% local tumour control with 42% response rate [4% complete] at 3 mo. Recurrent primary brain tumour had an odds ratio of 2.85 compared to metastases of progressing locally. Patients treated on LINAC were 2.84 times more likely to have local tumour progression than *gamma knife*.	22% experienced“ unacceptable toxicity” of which 43% irreversible grade 3 [10% of all patients], 46% were life-threatening [10% of all patients] and 11% resulted in death [3% of all patients] Toxicities most likely in pts with lesions >20mm Overall 13% symptom improvement
Acoustic Neuroma				
Lederman, GS et al [11] Abstract]	LINAC Fractionated SRS	Case study on 68 patients with acoustic neuroma treated by fractionated SRS. Median follow-up 32 mo.	For 47 tumours <3cm, 38% shrank,62% stopped growing Of 58 pts, 38 [66%] had improved balance In 22 tumours >3 cm, 59% shrank & 41% stopped growing. Overall, 11-13% improved hearing.	One pt. Experienced transient facial weakness

Table 1 Literature Survey to Update MSAC HTA [cont.]

Author/Study	Modality[s] Used	Clinical Design & Sample Size	Outcome reported	Complications
Trigeminal Neuralgia				
Rogers CL et al [17]	*Gamma knife*	Case study on 54 patients with trigeminal neuralgia with follow up >3 mo. Pain outcome measurements well-standardized	Pain relief in 96%: 35% pain free, 6% occasional pain not requiring medication, 48% some pain controlled on medication and 7% some pain, not controlled on medication.	New mild facial numbness in 13%

Appendix 1

Levels of Evidence

Adapted from: Goodman C [18]

TYPE OF STUDY (DESIGN)	LEVEL OF EVIDENCE
Large randomized controlled trial (RCT) & systemic reviews of RCTs	1
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)
Small randomized controlled trial	2
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)
Nonrandomized trial with contemporaneous controls	3 a
Nonrandomized trials with historical controls	3 b
Surveillance (database or register)	3 c
Case series, multi-site	3 d
Case series, multi-site, unpublished but reported to an international scientific meeting	3d(g)
Case series, single-site	3 e
Retrospective review	3 f
Modeling	
Expert opinion (reviews)	4
Consensus guidelines	4

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