INFORMATION BRIEF (RAPID REVIEW)

USE OF GAMMA KNIFE RADIOSURGERY/STEREOTACTIC RADIOSURGERY (SRS) IN TRIGEMINAL NEURALGIA

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Rapid Review
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TITLE: Use of Gamma Knife Radio Surgery/ Stereotactic Radiosurgery (SRS) in Trigeminal Neuralgia

PURPOSE

To provide evidence on safety, effectiveness and cost effectiveness of Gamma Knife Radiosurgery (GKRS)/ Stereotactic Radiosurgery (SRS) for treatment of Trigeminal Neuralgia following a request from Medical Practice Division, Ministry of Health Malaysia as this procedure is not listed in the 13th Schedule Private Healthcare and Facilities Regulation (Amendment) Order 2013.

BACKGROUND

Stereotactic radiosurgery (SRS) utilizes stereotactic head frame with external beam and high-resolution neuroimaging technologies such as MRI and CT studies to precisely target an area. The core principle of SRS is to deliver a very high precision, focused dose of radiation to destroy or inactive specific target with minimal collateral damage, often achieving results similar to traditional surgery but without incisions. Technologies like the Gamma Knife Radiosurgery (GKRS), linear accelerator (LINAC), and Cyber Knife Radiosurgery (CKR) were developed to enable precise stereotactic radiosurgery.[1]

Radiosurgery (RS) is a surgery using radiation that is the destruction of precisely selected areas of tissue using ionizing radiation rather than excision with a blade. Radiosurgery by gamma knife (also known as the Leksell Gamma Knife) was introduced by the Swedish neutrosurgeon, Professor Lars Leksell in 1968 contains 201 cobalt-60 sources placed in a hemispheric array in a heavily shielded assembly. A stereotactic head frame is affixed to the patient's head and focuses the individual beams of gamma radiation to a very precise areas of tissue while minimizing radiation exposure to surrounding healthy tissues.[2]

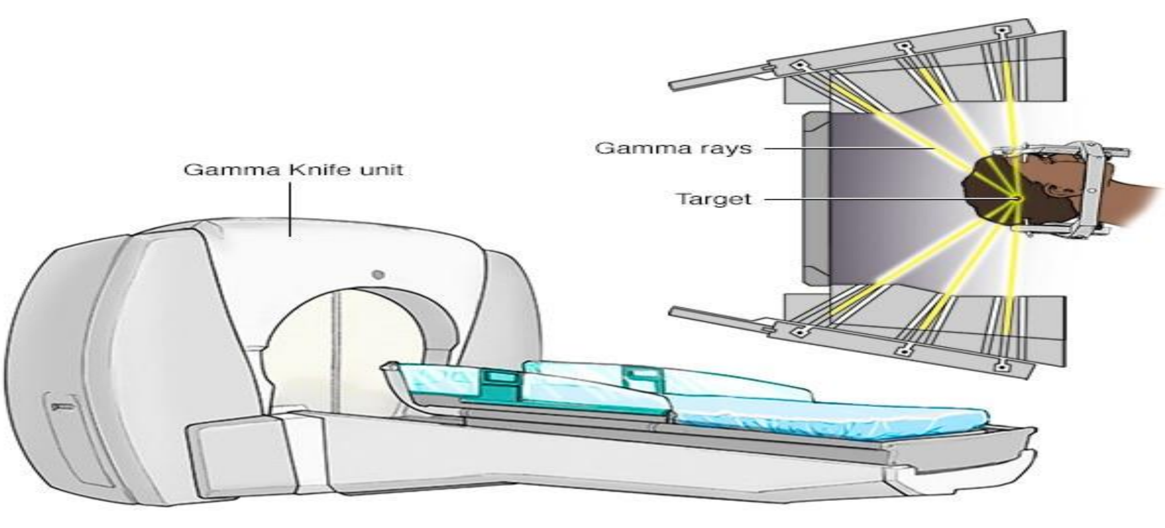

Figure 1: Gamma Knife stereotactic radiosurgery

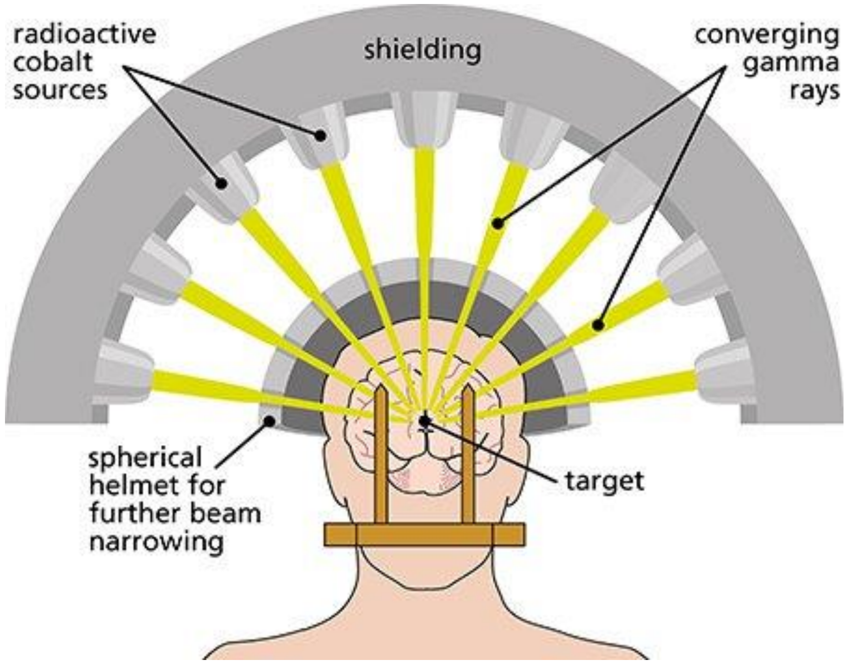

Figure 2: Gamma Knife® stereotactic radiosurgery

EVIDENCE SUMMARY

A total of 416 articles were retrieved from scientific databases, including Ovid, PubMed, Embase, Google Scholar and nonscientific database- google search engine as well as reference lists. The search focused on use of gamma knife Radio Surgery/ Stereotactic Radiosurgery (SRS) in Trigeminal Neuralgia using the keywords: "Trigeminal Neuralgia," "Trigeminal Nerve," "Gamma Knife Radiosurgery," and "Radiosurgery". The final search was conducted on 13th Ogos 2025.

Six studies were included in this review, comprising systematic reviews (SR) and Meta-Analysis (MA) and economic evaluation study. Additionally, evidences from the United States Food and Drug Administration (US FDA) website and update from The European Academy of Neurology (EAN) Guideline were also included.

EFFECTIVENESS AND SAFETY

A systematic review (SR) conducted by Tuleasca C et al. (2018) on effectiveness of SRS for classically Trigeminal Neuralgia (TN). This SR included data from 65 studies, inclusive 6,461 patients from retrospective studies and one high-quality randomized control trial (RCT). Gamma Knife Radiosurgery (GKRS) comprised the largest patient groups with 5,687 patients (88%) from 45 studies, followed by LINAC radiosurgery with 511 patients (8%) from 11 studies, and Cyber Knife Radiosurgery (CKR) with 263 patients (4%) from 9 studies. Table 1 simplified the analysis between different forms of radiosurgery for pain relief, complications and recurrence rates.

Table 1: Outcomes compares different forms of radiosurgery (GKRS, LINAC, and CKR)[1]

Key Outcome	Sub-outcome	GKRS	LINAC	CKR	Key Findings & Notes
Pain Relief	Initial Free from Pain (FFP) without medication	53.1% (average)	49.3% (average)	56.3% (average)	No statistically y significant between GKRS & LINAC or GKRS &CKR
	Long term FFP without medication	30% & 45.3% at 10 years (2 series)	N/A	N/A	Earlier GKRS (within 3 years of pain onset) led to faster pain relief and longer intervals of relief.
Dose Selection	Effective Dose	70-90Gy	N/A	N/A	Doses above 90Gy did not increase efficacy but increased complications
Complications	Crude Rates of Hypesthesia (all BNI scores)	21.7% (average)	27.6% (average)	29.1% (average)	No statistically significant difference between GKRS &LINAC or GKRS &CKR
	Bothersome Hypesthesia (BNI scores III&IV)	3.1% (mean)	N/A	9.3% (mean)	Statistically significance increase in the CKR group compare to GKRS
Recurrance Rates	Mean recurrence rates	24.60%	32.20%	25.80%	N/A

The most common complication is facial hypoesthesia (numbness) occurred when the anterior retrogasserian portion of the trigeminal nerve was targeted, while other complications (dry eye, deafferentation pain, keratitis) occurred when the root entry zone (REZ) was targeted. Five studies conducted and concluded that 70Gy to 90 Gy was the effective dose range for radiosurgery, using doses higher than 90 Gy did not improve efficacy and led to more complications, primarily hypoesthesia, due to an increased volume of the treated nerve. A double-blind randomized study and cohort study concluded that using two isocentres more likely receive higher radiation dose and significantly increased complications, primarily hypoesthesia. Figure 3 clearly showed a major increase in toxicity with the use of 2 isocentre.

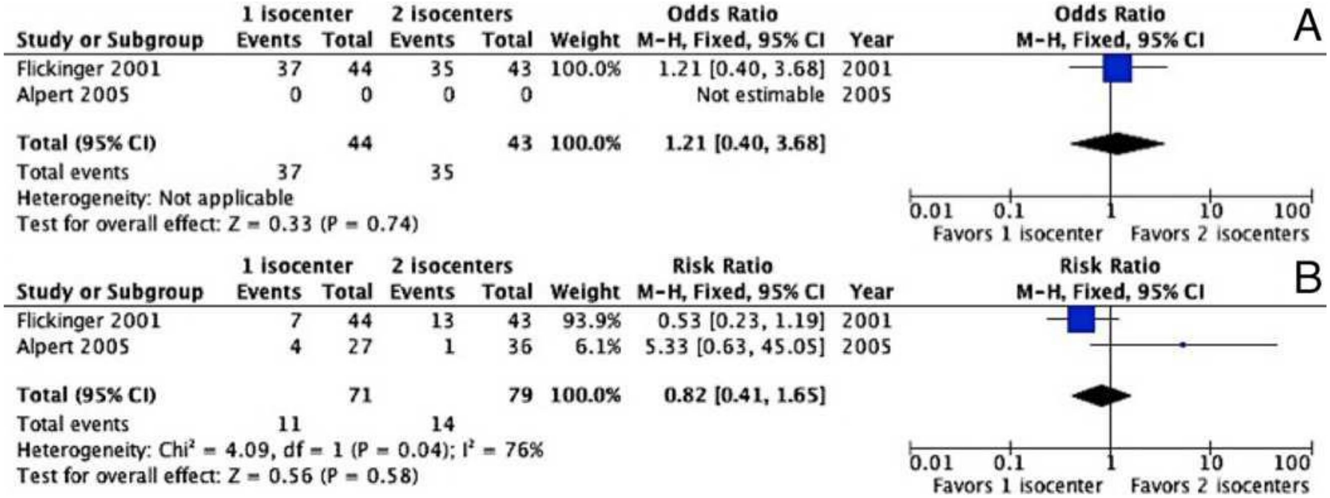

Figure 3: (A) Initial efficacy was pooled, (B) Toxicity

Source: Tuleasca C et al.2018

GKS significantly improves patient quality of life and satisfaction through pain relief. Studies showed a high degree of patient satisfaction and success following GKRS for TN, with one study reporting a median 80% improvement in quality of life (QOL), rising to 100% for those with maintained pain relief, 90% self-reported QOL improvement and 80% overall patient satisfaction. Radiosurgery showed less costly treatment option compare to microvascular decompression (MVD), especially Cyberknife radiosurgery reduced hospital costs by average of 34% per patient compare to MVD. The authors concluded SRS provide reliable pain relief with manageable complications when optimal technique such as single isocentre, appropriate dosing and anterior targeting are applied. SRS is considered as a minimally invasive option to MVD for drug resistant TN, with better outcomes when performed within three years of pain onset.[1]

Another SR with Meta-Analysis (MA) was conducted by Spina A et al. (2021) on effectiveness of GKRS in treating TN specifically in patients with multiple sclerosis (MS-TN). This SR included data from 12 article, from 2002 to 2019 inclusive 646 MS-TN patients to evaluate initial pain response and long-term treatment success. A meta-analysis study reported pooled proportion of patients to GKRS initially showed strong immediate relief with 83% (CI 74 to 90%), heterogeneity (I^2 =75.73%) a positive response rate and its effectiveness significantly declined to 47% (CI 33 to 60%), heterogeneity (I^2 =89.64%) over an average follow-up of 44.6 months. This indicates a significant reduction in efficacy over time. The most frequently reported adverse reaction for GKRS is facial hypoesthesia, with reported rates ranging from 0% to 71.4%. The authors concluded GKRS is still a valuable option due good pain control rate and its low complication rate but emphasizes the importance of its long-term effectiveness, primarily attributed to the inherent progressive nature of Multiple Sclerosis.[3]

Hajikarimloo B et al. (2025) conducted SR with MA on effectiveness and safety of SRS for tumour-related trigeminal neuralgia (TRTN). In this review, data from 19 studies with 454 patients is included. The MA reported SRS showed favourable pain relief (38% complete pain-free, 73% adequate) and low Adverse Radiation Effect (ARE),14% for TRTN, with comparable but slightly lower efficacy for petroclival meningioma-related TRTN (30% complete pain-free, 64% adequate, 13% ARE). A MA study reported MS (89%) had significantly higher rates of TN improvement than SRS (37%) ($P < 0.01$) and pain-free rates without medication were significantly higher in MS (90.7%) than in SRS (34.5%) ($P < 0.01$). Another SR study MS was associated with 0% pain persistence compared to 25% for SRS ($P = 0.001$), and 0% pain exacerbation compared to 12% for SRS ($P = 0.001$). SRS is a proper therapeutic option for managing patients with TRTN, providing favorable pain-related outcomes and low adverse reaction effects (ARE) rates, however microsurgical resection (MS) remains the first-line therapeutic option for these patients due to superior pain relief rates. SRS is presented as a valuable alternative for patients not suitable for surgical procedure.[4]

Akkara Y et al. (2025) conducted a SR and MA comparing SRS with neuroablative techniques for treating medically refractory TN. This SR included data from 3,288 patients across 37 studies. In the context of TN, V2 and V3 pathologies refer to pain or issues affecting specific nerve root distributions nerve as below:

- V1 (Ophthalmic nerve)
- V2 (Maxillary nerve)
- V3 (Mandibular nerve)

These studies reported higher rates of complete pain relief (BNI I) neuroablative cohort (63.6%) compare 36.0% for SRS. Overall recurrence was significantly lower in the neuroablative cohort with 22.5% in comparison to SRS cohort ($p<0.0001$) with 42.2%. However, SRS showed a significantly lower incidence of adverse effects compare neuroablative techniques (18.6% vs 50.5%, $p< 0.0001$), including hypoesthesia and both minor (3.4% vs 19.6%, $p<0.0001$) and major (1.3% vs 3.4%, $p<0.0001$) complications. The author concluded neuroablative offer superior pain relief and lower recurrence rates for TN compared to SRS especially for V2 and V3 nerve pain and for patients with medically refractory TN who are unsuitable for Microvascular Decompression (MVD). SRS is the preferred choice for V1 nerve pain, patients with health concerns, or when minimizing risks is crucial, despite neuroablation having higher risks such as numbness.[5]

Another SR conducted by Nugroho SW et al. (2023) comparing the effectiveness of open surgery versus SRS in treating tumour-related secondary TN due to cerebellopontine angle (CPA) tumours. This SR included data from 26 retrospective studies and one prospective study, comprising 517 patients with secondary trigeminal neuralgia caused by cerebellopontine angle (CPA) tumours. These studies reported for open surgery, there was a 97.2% pain improvement rate, with 2.8% of patients experiencing unchanged symptoms, none having worse outcomes, and a 4.5% recurrence rate. In contrast, tumour-targeted SRS showed a 79.1% pain improvement rate, 14.3% of patients with unchanged symptoms, 6.6% with worse outcomes, and a 26.5% recurrence rate. A study comprising 6 patients who had recurrent pain after initial tumour-targeted SRS showed pain improvement without recurrence after receiving secondary nerve-targeted SRS. Nine studies affecting 83 patients reported postoperative facial hypesthesia and recovered after several months whereas facial hypesthesia was reported in fewer SRS patients believed to be a radiation dose-related brainstem side effect. Surgical treatment decompressing the trigeminal nerve from compressing lesions and adhesive arachnoid to be first line treatment treating tumour -related TN due to higher rates of pain improvement and lower rates of worsened outcomes and recurrence. Tumour targeted SRS carries higher risks of persistent or worsened pain and recurrence compared to surgery. However, patients experiencing recurrent pain after initial tumor-targeted SRS showed improvement following secondary nerve-targeted SRS, which should therefore be reserved as a secondary treatment option.[6]

The European Academy of Neurology (EAN) Guideline on trigeminal neuralgia were based on three systematic reviews that compared the outcomes of different treatments concluded a longer postoperative pain-free status for microvascular decompression (MVD) compared to GKRS. The median percentage of patients who were pain-free at long-term follow-up after GKRS was 58%(range 30%–66%)., and this is less favourable compared to MVD's median of 77% (range 62%–89%). GKRS has a notably small number of reported complications compared to other procedures. No specific recommendation has been made for the choice between GKRS and MVD in patients with idiopathic TN (where MRI fails to show significant nerve compression). However, based on low quality evidence but extensive clinical experience, a recommendation is given that MVD is preferred over GKRS in patients with classical TN who are willing to and can undergo posterior fossa surgery.[7]

The Gamma Knife® initially received FDA 510(k) marketing clearance in the United States in February 2007, followed by another FDA 510(k) submission in May 2014 that represented a regulatory approval updating and expanding the specific conditions and diseases for which the device is indicated for use. This latest clearance, issued in September 2022, affirmed their substantial equivalence for a broad range of indications, with the new model Gamma Knife specifically updated hardware user interface enhancements and new control system software.[8]

An earlier Technology Review conducted by Malaysian Health Technology Assessment Section (MaHTAS) on Gyro Rotating Gamma Radiotherapy System (known as Gyro-Knife) in 2007 concluded that there was no retrievable evidence on the safety, effectiveness and cost-effectiveness of Gyro-Knife for treatment of cancer.[9]

Another information brief by MaHTAS on Gamma Knife® in 2010 concluded radiosurgery is an important alternative to conventional surgery, but there is limited evidence on safety and effectiveness of Gamma Knife® and no evidence on its cost effectiveness.[10]

The previous information brief conducted by (MaHTAS) on Gamma Knife Stereotactic Radio Surgery (SRS) in 2014 concluded GK has potential effectiveness comparable to other SRS methods like LINAC for various brain lesions. However, high quality scientific evidence is still warranted.[11]

The primary source of the radioactive waste from a Gamma Knife is the 201 cobalt-60 which is a high-level, long-lived, and sealed source. Improper disposal of radioactive waste poses a significant environmental threat. Therefore, all aspects of GK operation and the disposal of its radioactive materials should comply with regulatory requirements and be strictly governed by Malaysia's 2011 Radioactive Regulations (Peraturan-Peraturan Perlesenan Tenaga Atom Pengurusan Sisa Radioaktif).[12]

COST-EFFECTIVENESS

Gandhoke GS et al (2019) conducted cost-effectiveness analysis to compare Microvascular Decompression (MVD) with Gamma Knife Radiosurgery (GKRS) for Trigeminal Neuralgia. This study utilised a Markov cost-effectiveness model over a patient's lifetime within the U.S. healthcare system, considering health care costs, survival rates and quality –adjusted life years (QALYs). The study involved sample size comprising 1475 patients. (GKRS= 503; MVD= 208; Wang et al.'s experience= 764). The study showed the base case analysis for MVD had a higher cost approximately $19,362 (RM 81,552.71) but also provided greater effectiveness (13.68 QALYs) compared to GKRS approximately $8073 (RM34,003.46) for 12.75 QALYs. The Incremental Cost-Effectiveness Ratio (ICER) for MVD compared with GKRS was $12,154 (RM51, 530.40) per Quality-Adjusted Life-Years (QALYs) and it indicated for every additional QALY gained by using MVD, an associated extra cost of approximately $12,000 (RM 50603.98) compared to GKRS. The study used a generally accepted cost-effectiveness threshold of $50,000 (RM 210,775.00) per QALY gained in the U.S. healthcare system. Since the ICER of MVD ($12,154/QALY) is significantly below this threshold, it is considered a cost-effective intervention (Figure 4). A probabilistic sensitivity analysis, using a Mote Carlo simulation reported that MVD was a cost-effectiveness in 70%of model iterations at the
$50, 000 (RM 210, 849.92) per QALY whereas GKRS was only the preferred treatment if the willingness-to-pay threshold was below $12,000 (RM 50603.98). (Figure 4). Both GKRS [$8,073 (RM 34043.83)] for 12.75 QALYs] and MVD [$19,362 (RM 81649.52)] for 13.68 QALYs) reported to be likely cost-effective when compared to no treatment at all.

Table 2: The Incremental Cost and Incremental Quality-Adjusted Life –Years provided by Microvascular Decompression compared with Gamma Knife Radiosurgery

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness	Incremental Effectiveness	Incremental Cost-Effectiveness Ratio
Base Case					
GKRS	8073		12.75		
MVD	19,362	11,289	13.68	0.93	12,154
Sensitivity analysis					
GKRS	8073		14.29		
MVD	19,261	11,188	15.21	0.93	12,084
Both the base case incremental cost-effectiveness ratio ($12,154/quality- adjusted life-year) and the incremental cost-effectiveness ratio calculated from probabilistic sensitivity analyses ($12,084)/quality life-year) are close to one another, reiterating the robustness of the calculation and reliability of the results. GKRS: Gamma Knife radiosurgery, MVD: microvascular decompression					

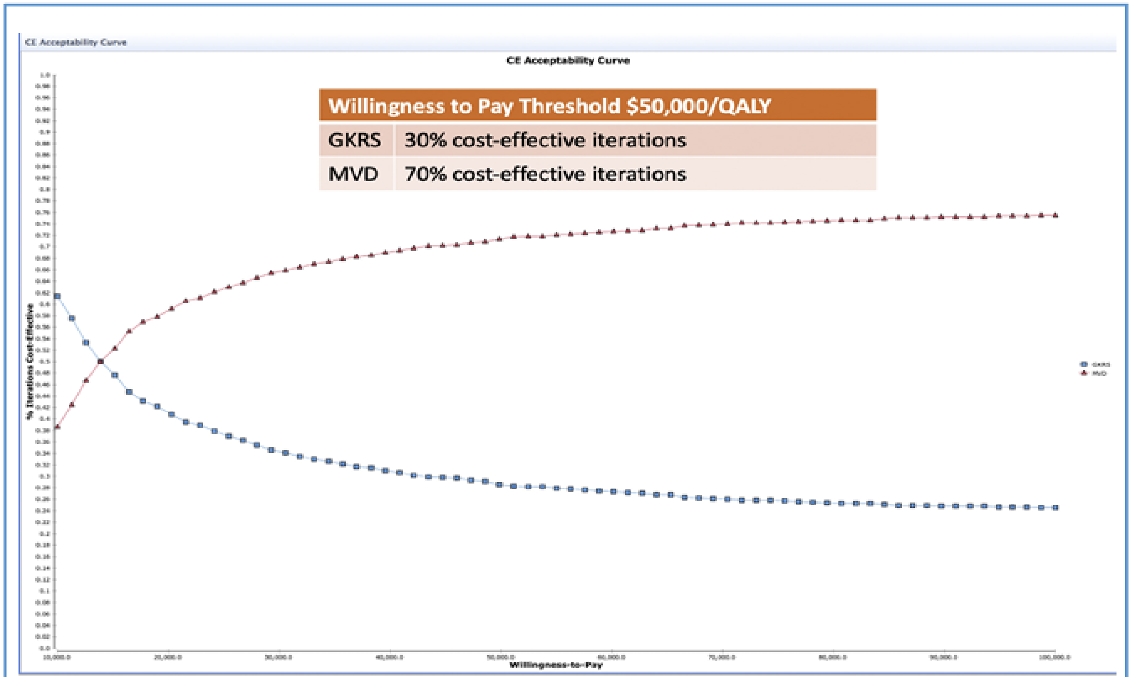

Figure 4. Cost-effectiveness acceptability curve across a range of cost-effectiveness thresholds from probabilistic sensitivity analysis. Microvascular decompression (MVD) is cost-effective in 70% of iterations at $50,000 per quality-adjusted life-year, whereas Gamma Knife radiosurgery (GKRS) has more cost-effective iterations only when the cost-effectiveness threshold is <$12,000/quality-adjusted life-year.

Figure 4: Cost-effectiveness acceptability curve across a range of cost-effectiveness thresholds from probabilistic sensitivity analysis.

Another comparison showed by analysing Medicare claims with 10-year follow up period and resulting MVD was most cost-effective than GKRS, with ICER of $ 4931 vs $ 7767 (RM 20, 794.02 vs RM 32753.43). Additionally, Berger et al. reported MVD provided 6 QALYs compared 5.4QALYs by GKRS over 7-years period and this showed its higher success rate and lower pain recurrence rate compared to GKRS. Compare with GKRS, MVD was the cost-effective modality for treating TN in medically eligible patients, primarily due to its greater durability.[13]

CONCLUSION

Based on the above review, evidence demonstrated that GKRS/SRS appeared to be effective in the treatment of classical TN due to other disorders such as multiple sclerosis (MS-TN), tumour-related trigeminal neuralgia (TRTN), medically refractory trigeminal neuralgia (TN), and cerebellopontine angle (CPA) tumours. It provides reliable pain relief with manageable complications when optimal techniques (single isocentre, appropriate dosing, and anterior targeting) is applied and serves valuable alternative for patients who are not suitable for surgical procedure. SRS had significant lower incidence of adverse effects including hypoesthesia, both minor and major complication compare to neuroablative techniques. However, high quality scientific evidence is warranted. Gamma Knife obtained regulatory approved from USFDA, with no major adverse events reported following this procedure from the evidence retrieved. In terms of cost- effectiveness, evidence demonstrated microvascular decompression (MVD) is more cost-effective than GKRS in treatment of trigeminal neuralgia.

The handling and disposal of radioactive waste must be carefully addressed, as the technology incorporates 201 cobalt-60 sources.

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