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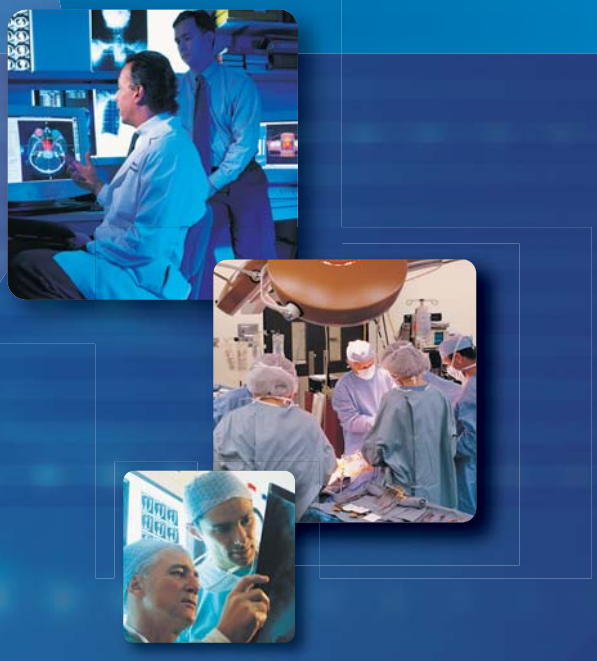
TomoTherapy, Gamma Knife, and CyberKnife Therapies for Patients with Tumours of the Lung, Central Nervous System, or Intra-abdomen: A Systematic Review of Clinical Effectiveness and Cost-Effectiveness



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Canadian Agency for Drugs and Technologies in Health

TomoTherapy, Gamma Knife, and CyberKnife Therapies for Patients with Tumours of the Lung, Central Nervous System, or Intra-abdomen: A Systematic Review of Clinical Effectiveness and Cost-Effectiveness

Rhonda Boudreau, BA (Hons) BEd MA[1]
Michelle Clark, MSc[1]
Emmanuel Nkansah, BEng MLS MA[1]

September 2009

[1]Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario

Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

Reviewers

These individuals kindly provided comments on this report:

David Mathieu, MD FRCS(C)
Assistant Professor of Neurosurgery
Université de Sherbrooke
Medical Director, Gamma Knife Radiosurgery
Centre Hospitalier Universitaire de Sherbrooke
Sherbrooke, QC

Rebecca Wong, MBChB MSc FRCP
Doctor
Princess Margaret Hospital
Toronto, ON

ACRONYMS AND ABBREVIATIONS

cGy	centigray
CKS	CyberKnife surgery
CT	computed tomography
DNA	deoxyribonucleic acid
EBRT	external beam radiation therapy
FR	fractionated radiotherapy
GKS	Gamma Knife surgery
Gy	gray
HTA	health technology assessment
Linac	linear accelerator
KPS	Karnofsky Performance Scale
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee of Australia
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RTOG	Radiation Therapy Oncology Group
RPA	recursive partitioning analyses
SF-36	short-form health survey
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
WBI	whole brain irradiation
WBRT	whole brain radiotherapy

TABLE OF CONTENTS

TITLE: TomoTherapy, Gamma Knife, and CyberKnife Therapies for Patients with Tumours of the Lung, Central Nervous System, or Intra-abdomen: A Systematic Review of Clinical Effectiveness and Cost-Effectiveness

DATE: September 2009

EXECUTIVE SUMMARY

Context and Policy Issues

Stereotactic radiosurgery (SRS) and stereotactic radiotherapy, which deliver high doses of radiation to tumour sites, are used to stop the division of tumour cells. Three such therapies are TomoTherapy, Gamma Knife surgery (GKS), and CyberKnife surgery (CKS).

SRS refers to radiation treatment that is provided in one session. Stereotactic radiotherapy occurs over multiple sessions or days. GKS is a "framed" therapy in which the patient's head is fixed to the treatment table and treatment is restricted to the brain, head, and neck. CKS and TomoTherapy, which are frameless, allow radiation treatment to occur in regions other than the brain, head, and neck. Before the radiation is administered, patients undergo imaging, which is generally performed using computed tomography, positron emission tomography, or magnetic resonance imaging.

Some jurisdictions are making decisions about whether to buy the Tomotherapy, GKS, or CKS systems. Evidence-informed decisions require a rigorous evaluation of the clinical effectiveness and cost-effectiveness of these therapies. This report focuses on the use of these technologies in the treatment of tumours of the lung, central nervous system, and intra-abdomen.

Research Questions

1. What is the comparative clinical effectiveness of TomoTherapy, Gamma Knife, and CyberKnife therapies for patients with cancer of the lung, central nervous sytem, or intra-abdomen?
2. What is the comparative cost-effectiveness of TomoTherapy, Gamma Knife, and CyberKnife therapies for patients with cancer of the lung, central nervous system, or intra-abdomen?

Methods

Published literature was obtained through a search of the Cochrane Library (Issue 2, 2009) and University of York Centre for Reviews and Dissemination databases between 2004 and May 27, 2009. The websites of health technology assessment (HTA) and related agencies were also searched, as were specialized databases such as those of the National Institute for Health and Clinical Excellence (NICE), ECRI, and EuroScan. The Google search engine was used to search the Internet. Two independent reviewers screened articles using predefined criteria.

Summary of Findings

One HTA, one randomized controlled trial (RCT), and nine cohort studies addressing the clinical effectiveness of GKS or CKS were included. Most of these studies focused on GKS and found it to be clinically effective. No clinical studies on TomoTherapy met the inclusion criteria.

The HTA, which was released by the Medical Services Advisory Committee of Australia, focused on intracranial lesions. The authors concluded that GKS was an effective and safe treatment. The authors of the RCT reported that GKS was generally well tolerated in patients with single brain metastases and had a high local tumour control rate. The patients who were treated using GKS experienced a higher percentage of distant tumour recurrences than patients undergoing surgery and whole brain radiation therapy (WBRT). Of the nine cohort studies, seven focused on GKS and concluded that GKS was clinically effective or at least similar to other standard treatments. These studies included patients with vestibular schwannoma, cavernous sinus meningiomas, metastatic brain tumours with various primary cancers, and brain metastases from ovarian cancer. An eighth cohort study compared GKS

and CKS in patients with single brain metastases, and no clinically important differences in tumour control or overall survival were found. The ninth cohort study reported that CKS and conventional radiation therapy provided similar benefits in patients who had breast cancer with spine metastases.

No full economic evaluations that compared TomoTherapy, GKS, or CKS with each other were identified. One HTA evaluated the costs of GKS and CKS. One cost-effectiveness study compared GKS with WBRT, and a second compared CKS with external beam radiation therapy. No economic studies on TomoTherapy were included.

Based on a partial economic evaluation, the Medical Services Advisory Committee authors stated that GKS was more costly than linear accelerator (Linac)-based SRS. The costs per patient, based on 150 patients treated per year, were $3,757 for GKS compared with $3,549 or $960 for Linac adaptation equipment (the price was lower if the cost of the Linac unit was excluded). One cost-effectiveness study reported a payer perspective cost-utility analysis and concluded that when compared with external beam radiation therapy, CKS was a cost-effective treatment for patients with inoperable spinal metastases. A second cost-effectiveness study concluded that compared with WBRT, GKS was more cost-effective per quality-adjusted life-year for patients with multiple brain metastases.

Conclusions and Implications for Decision- or Policy-Making

For TomoTherapy, GKS, and CKS, there was a lack of evidence from RCTs. Most of the studies evaluated GKS rather than CKS, and no studies evaluated TomoTherapy. This may reflect the fact that GKS is the oldest and perhaps more widely used technology. Most of the literature on TomoTherapy, GKS, and CKS were case series reports, which were outside the scope of this report because such studies do not allow for direct comparisons of clinical or cost-effectiveness.

GKS was found to be clinically effective or to have produced similar benefits compared with other standard treatments (for example, WBRT) and conventional radiotherapy. The primary patient outcome measures in the included studies were typically tumour growth control or survival.

No cost-effectiveness analyses comparing TomoTherapy, GKS, and CKS were identified. CKS and GKS were found to be more expensive than traditional SRS. They remained cost-effective in specific situations and when compared with comparators other than TomoTherapy, GKS, or CKS. No economic studies on TomoTherapy were included.

Given the current evidence, it is not possible to reliably estimate the comparative clinical effectiveness and cost-effectiveness of TomoTherapy, GKS, and CKS.

1 CONTEXT AND POLICY ISSUES

Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) can be used to provide accurate and targeted radiation to one or more lesions or tumours in various parts of the body.[1-3] Three of the available SRS or SRT technologies are Gamma Knife surgery (GKS), CyberKnife surgery (CKS), and TomoTherapy (Appendix 1).[2-4]

These three technologies run on two types of radiation sources. The Cobalt-60 radiation source with a rigid skeletal fixation system is used in GKS. The modified linear accelerator (Linac)[5] is used in CKS and TomoTherapy.[3,4] Linac, robotics, and image guidance are used in CKS.[5] Linac and a computed tomography (CT) gantry are used in TomoTherapy.[3]

SRS and SRT are used to deliver high doses of radiation through a series of beams from various angles that converge on the tumour site. The intent is to stop the division of tumour cells by altering their DNA.[2,4,6] The rapid radiation dose fall-off reduces radiation exposure to adjacent healthy tissues.[7] The rate at which the irradiated tumour is reduced is thought to be consistent with the normal growth curve of the tumour. Thus, benign tumours will take longer to shrink than malignant or metastatic tumours.[2]

Radiosurgery is radiation treatment that is provided in one session. Fractionated radiotherapy (FR) is repeated over multiple sessions or days, usually up to a maximum of 30 days.[7] Hypo-fractionated treatments are generally given over five to eight days.[7] During framed radiotherapy or radiosurgery, the patient's head is fixed to the treatment table, and treatment is restricted to the brain, head, and neck.[4,6] The frameless models allow the treatment to occur outside the brain, head, and neck regions, and the head is not fixed to the treatment table.[5] Patients in the frameless models have masks or frames on their body, although the degree of immobilization is less than that with framed treatment.[2] CT, positron emission tomography, or magnetic resonance imaging (MRI) is required before the radiation is administered using SRS and SRT.[7]

Health care decision-makers decide what technology is best for their jurisdiction. In at least one Canadian health care jurisdiction, there is a need to make a decision about whether to buy TomoTherapy, GKS, or CKS as an addition to treatment options for patients with cancer. This requires evaluation of the clinical effectiveness and cost-effectiveness of these therapies. SRS and SRT can be used for treating patients with a variety of tumours. This report focuses on tumours in the lung, central nervous system, and intra-abdomen.

2 RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of TomoTherapy, Gamma Knife, and CyberKnife therapies for patients with cancer of the lung, central nervous sytem, or intra-abdomen?
2. What is the comparative cost-effectiveness of TomoTherapy, Gamma Knife, and CyberKnife therapies for patients with cancer of the lung, central nervous system, or intra-abdomen?

3 METHODS

Peer-reviewed literature searches were conducted to obtain published literature. All search strategies were developed by the information specialist with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches were run in PubMed, the Health Economic Evaluations Database (HEED), and the Cochrane Library (Issue 2, 2009). The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the

retrieval to systematic reviews, health technology assessments (HTAs), meta-analyses, randomized controlled trials (RCTs), and economic studies. An observational filter was applied to a focused search (main concepts must appear in the title field) for targeted observational studies only. Appendix 2 shows the detailed search strategies.

The search was restricted to English language clinical articles that were published between 2004 and April 2009. Regular alerts were established on EMBASE and MEDLINE, and information that was retrieved through alerts was current to May 27, 2009.

Grey literature (literature that is not commercially published) was identified by searching the websites of HTAs and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional information.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTA reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs, observational studies with comparator groups, and economic evaluations.

Two independent reviewers selected articles for inclusion. Any disagreement was resolved through discussion until consensus was achieved. To be included, a randomized or non-randomized design could have been used in the study, as long as a comparator group was present. Thus, case series and case studies were excluded. Only studies that focused on tumours in the lung, central nervous system, or intra-abdomen were of interest. Studies that focused on endocrinological tumours (for example, pituitary, thyroid) and gynecological tumours were excluded. In addition, the article had to mention TomoTherapy, GKS, or CKS. Appendix 3 provides details on study inclusion criteria. The clinical endpoints of primary interest were tumour control rates, overall survival rates, and adverse events. Health-related quality of life measures were collected, when available.

4 SUMMARY OF FINDINGS

Of the 981 publications that were identified in the literature search, 890 were excluded after the screening of titles and abstracts, and 91 were retrieved for full-text screening. Twelve publications were included, and the remaining 79 articles were excluded, mainly because of a lack of a comparison group or a failure to specify the technology used. A diagram documenting the study selection appears in Appendix 4.

One HTA,[8] one RCT,[9] and nine cohort studies were included for the assessment of clinical effectiveness.[10-18] No systematic reviews were identified. Most of the studies focused on GKS and found it to be clinically effective.

The authors of the HTA[8] concluded that GKS was an effective and safe treatment for patients with intracranial lesions. The authors of the RCT[9] concluded that GKS was generally well tolerated in patients with single brain metastases and had a high local tumour control rate, although patients who underwent GKS experienced a higher percentage of distant tumour recurrences than patients undergoing surgery and whole brain radiation therapy (WBRT).

Of the nine cohort studies, seven focused on GKS and concluded that the use of GKS was clinically effective or showed no statistically significant differences in clinical effectiveness when compared with standard treatment. These studies included patients with vestibular schwannoma,[10,13,17] cavernous sinus meningiomas,[18] metastatic brain tumours with various primary cancers,[14] and brain metastases from ovarian cancer.[16] One study[15] found that the use of GKS provided good tumour growth control but that this control did not translate into longer survival. The cohort study that compared GKS and CKS treatments in patients with single brain metastases found no differences in tumour control or overall survival.[11]

One cohort study evaluated the use of CKS compared with conventional radiation therapy in patients who had breast cancer with spine metastases.[12] The authors found that the use of CKS and conventional radiation provided similar benefits.

No clinical studies on TomoTherapy met the inclusion criteria.

One HTA[8] and two economic studies[14,19] evaluated the costs of GKS or CKS. The HTA reported a partial economic analysis and found GKS and CKS to be more costly than Linac radiosurgery.[8] When compared with external beam radiation therapy (EBRT), CKS remained cost-effective for patients with inoperable spinal metastases.[19] A cost-utility study concluded that the use of GKS was cost-effective when compared with WBRT for patients with inoperable spinal metastases.[14] No economic studies on TomoTherapy met the inclusion criteria.

4.1 Health Technology Assessments

The Medical Services Advisory Committee (MSAC) of Australia released an HTA on GKS radiosurgery in 2006.[8] The objectives included an assessment of the clinical effectiveness, cost-effectiveness, and safety of GKS for intracranial lesions. The authors concluded that the use of GKS was an effective and safe treatment for patients with intracranial lesions.

Based on the HTA[8] and advice from an advisory panel (that included experts in the subject area), the MSAC recommended to the Australian government to not change the Medicare funding arrangements, because the use of GKS was found to be safe and likely clinically effective but not cost-effective when compared with the use of Linac SRS.

The articles were selected systematically, with two reviewers selecting articles that were retrieved between 2001 and September 2005 and a second reviewer verifying the data extraction. Studies had to have a comparator group to be included in the evaluation. The report was an update to an MSAC report that was published in 2000.[20] Findings from the HTA are summarized here by indication.

4.1.1 Metastases

There was no evidence on the safety of GKS or CKS offered as a single therapy. The authors concluded that when SRS is added to WBRT, there may be an increased risk of toxicities related to the radiation treatment.

The clinical effectiveness of GKS was addressed in one HTA that was an update to the previous MSAC.[20] Based on data from one cohort study (the size of the study was not reported), the authors of the HTA concluded that the use of GKS resulted in better local tumour control when compared with Linac. One RCT (the size of the study was not reported) was included. The authors reported that based on a post-hoc analysis, there was no statistically significant difference ($P = 0.094$) in survival between GKS and Linac when GKS and Linac treatments were used in addition to WBRT. No additional statistical information was provided. No studies addressed the comparative effectiveness between GKS and CKS, and GKS and TomoTherapy.

4.1.2 Acoustic neuromas

The authors concluded that patients with acoustic neuromas who were treated using GKS may experience fewer medium-term complications and procedural mortality when compared with patients who were treated with microsurgery. This was partly based on the results of one HTA that stated the use of GKS resulted in a 20% increase in complication rates (mostly short-term complications). This HTA concluded that the use of GKS may result in a higher complication rate but that the complications exclude death, which can occur after the use of microsurgery. Three primary cohort studies addressed the safety of GKS among patients with acoustic neuromas. The authors of the MSAC report concluded that longer-term safety could not be assessed and that the methodological limitations of the studies

prevented any conclusions being made about the magnitude of effect. There was no evidence to compare safety between GKS and Linac. The evidence in the primary studies was Level III-2 and Level III-3. Level III-2 was defined as "Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with control group."[8] Level III-3 evidence was defined as "Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group."[8]

The authors concluded that patients with acoustic neuromas who were undergoing GKS may experience similar tumour control when compared with patients who were treated with microsurgery. Patients who were treated with GKS may also have improved quality of life, facial nerve function, and hearing preservation compared with patients who were treated with microsurgery. The authors rated the evidence base as Level III-2 and Level III-3. The included studies were two HTAs, one rapid response HTA, one systematic review, and no primary studies.

4.1.3 Primary malignant lesions

Because no evidence was found on the safety of GKS or CKS for patients with primary malignant lesions, no conclusions were made by the authors of the HTA.

The authors surmised that no conclusions could be made about the clinical effectiveness of GKS or CKS for patients with primary malignant lesions. No HTAs, systematic reviews, or meta-analyses were included, because none separately reported outcomes for GKS or CKS after treatment of primary malignant lesions. In one RCT, an additional, non-randomized analysis of patients treated with GKS or Linac was performed. No survival benefit was found for patients who were treated with GKS compared with those who were treated with Linac radiotherapy. This evidence was given a rating of Level III-2.

4.1.4 Meningioma

No higher level studies (HTA, systematic review, meta-analyses) assessed the safety of GKS or CKS in patients with meningioma separately. There were three comparative cohort studies with Level III-2 evidence on the safety of GKS. The authors stated that no definitive conclusions could be made. The authors also reported that complications from the use of GKS were short-to-medium term and mainly transitory and that no deaths were reported.

Two systematic reviews of case series reported on the clinical effectiveness of GKS and Linac. These reports concluded that the tumour progression rates were similar and that both treatments were effective for controlling meningiomas. The effectiveness was influenced by the characteristics of the tumour. Three retrospective cohort studies assessed the use of GKS. No primary studies on CKS met the inclusion criteria. The authors stated that the evidence was Level III-2. The authors concluded that no meaningful conclusions could be drawn given the poor quality of the methods that were used — for example, differing patient characteristics between treatment arms.

4.2 Randomized Controlled Trials

In 2007, Muacevic et al.[9] conducted a Phase III trial that compared the use of local modality GKS (31 patients) with the use of local modality microsurgery plus WBRT (33 patients) for patients with single metastases. The study investigators concluded that the use of GKS was less invasive, generally well tolerated, and had a high local tumour control rate compared with microsurgery plus WBRT.

All patients in the study had a Karnofsky Performance Scale (KPS) score of at least 70. The KPS is used to score a patient on the ability to carry on normal activity, including work.[8] The scores range between 0 and 100.[8] The higher the score, the better able a patient is to carry on normal activity and work without special care (additional information on KPS is provided in

Appendix 1). Patients were between 18 years and 80 years of age, had a single resectable metastasis that was less than 3 mm in diameter, and were expected to live at least another four months. No statistically significant differences between groups were present at baseline.

The median survival in both groups was approximately 10 months and was found to be statistically similar (P = 0.8). The one-year tumour control rate was 96.8% for patients after GKS compared with 82.0% for patients after microsurgery plus WBRT (P = 0.06). Patients in the microsurgery plus WBRT group had a statistically significantly lower rate of distance tumour recurrence at one year compared with patients in the GKS group (3.0% versus 25.8%; P < 0.05).

Mild and moderate adverse events were reported. Those in the GKS group demonstrated statistically significantly fewer Grade 1 and Grade 2 combined toxicities (P < 0.01). More information regarding the grading of toxicities is provided in Appendix 1. Twelve patients in the GKS group reported Grade 1 acute complications. The most commonly reported toxicities were nausea and neurological issues. One patient in the GKS group reported a late toxicity (nausea). No Grade 2 toxicities were reported by patients in the GKS group. In the microsurgery plus WBRT group, 25 patients reported Grade 1 acute toxicities; the most common were neurological issues. Four patients reported late toxicities (nausea and neurological issues). Five patients in the microsurgery plus WBRT group reported Grade 2 toxicities, which included nausea and skin-related issues. Two patients reported late toxicities: one reported nausea and one reported a neurological issue.

Randomization occurred through a data centre (by telephone), but how this was administered was not reported. The allocation of patients to treatment groups was not reported. The RCT was underpowered, because the sample size that was required to detect a one-year survival difference of 15% was 121 patients. This study enrolled 64 patients because of a difficulty in recruitment. No elaboration on this difficulty was provided. The authors noted that patients who were treated with GKS experienced more distant tumour recurrences than patients who were treated with microsurgery plus WBRT and that it was unknown whether additional radiosurgical salvage therapy could be effective in controlling these recurrences that are more likely to occur after initial radiosurgery. A summary table for this RCT can be found in Appendix 5 Table 1.

4.3 Observational Studies

The observational studies are summarized by indication (Appendix 5 Table 2).

4.3.1 Brain metastases

In 2009, Wowra et al.[11] compared the use of GKS to that of CKS in patients with single brain metastases. No statistically significant differences were found in overall survival from the time of treatment, tumour control, or reported adverse events. The authors concluded that GKS and CKS treatments did not demonstrate any statistically significant differences in tumour control and overall survival.

The authors matched patients based on the volume of brain metastasis (less than 10% or 0.25 cm^3 difference), patient age (less than or equal to a five-year difference), gender, and Radiation Therapy Oncology Group's (RTOG's) recursive partitioning analyses (RPA) class. Appendix 1 provides more information on the RTOG classification. Patient recruitment for GKS occurred from October 1994 to June 2005, and patient recruitment for CKS occurred from July 2005 to October 2007. From 423 tumours in patients treated using GKS and 73 tumours in patients treated using CKS, 63 tumours from each group were included in the matched-pair analysis. The number of patients was not reported. No statistically significant differences were found in overall survival from the time of treatment, tumour control, or reported adverse events.

Lee et al.[14] published a cohort study in 2009 that compared 56 patients who were treated using

GKS with 100 patients who were treated using WBRT. All patients had brain metastases. The authors stated that the mortality rate for patients who were treated using GKS was statistically significantly lower compared with that of patients who were treated using WBRT when patients had between two and five tumours and an initial KPS score of 70 or greater.

Patients were assigned to the treatment groups by the referring doctor's preference. There were no statistically significant differences between the patient groups in age, gender, median Gray (Gy) dose, mean number of metastases, mean RPA classification, or mean pretreatment KPS scores (no statistics were reported). In both treatment groups, most of the patients had primary lung cancer.

The median survival times did not differ statistically. The patients in the GKS group survived a median of 9.5 months compared with 8.3 months among patients in the WBRT group ($P = 0.72$). Statistically significant differences in mortality emerged when only patients with two to five tumours were compared between treatment groups (78.9% for 38 patients in the GKS group compared with 95.5% for 67 patients in the WBRT group, $P < 0.05$). Statistically significant differences in mortality also emerged when patients with a KPS score of at least 70 (43 patients in the GKS group and 68 patients in the WBRT group) were compared. Patients who were treated with GKS experienced a statistically significantly lower mortality rate (74.4% compared with 97.1%, $P = 0.02$). Seven patients in the WBRT group experienced neurological complications compared with three patients in the GKS group. The duration of follow-up was unclear.

In 2008, Lee et al.[16] published a study in which 15 patients with brain metastases whose names were included in an ovarian cancer registry were analyzed. The authors concluded that GKS was a valuable treatment for patients with brain metastases from ovarian cancer.

Of the 18 patients who were originally included in the study, two were diagnosed with germ cell tumours and one was treated only with chemotherapy. Between 1983 and 2005, eight patients were treated using WBRT. From 2000 to 2005, seven patients were treated using GKS. No statistical analysis comparing the baseline characteristics was reported.

The median survival was statistically significantly longer for the patients who received GKS (29 months [range three months to 63 months] compared with six months [range one month to 19 months], $P = 0.0061$).

In 2004, Datta et al.[15] published a cohort study that compared 53 patients with brain metastases who were treated using GKS with 67 patients who were treated using whole brain irradiation (WBI) through Linac. The authors concluded that the promising tumour response that was demonstrated by patients who received GKS did not translate into longer survival.

From 2000 onward, GKS was available at the institution. Thus, patients who were eligible for SRS were treated using GKS. Patients who were treated using GKS between 2000 and 2001 were analyzed. The comparator group was patients who were treated using WBI between 1998 and 1999. There were no statistically significant differences in patient sex, median age, or diagnosis of primary lung, breast, or "other" cancer.

The mean survival did not differ between the two groups (7.8 ± 0.8 months for patients in the WBI group compared with 6.7 ± 0.6 months for patients in the GKS group, log-rank test $P = 0.80$). The overall tumour response rate was unavailable for patients in the WBI group, because the CT or MRI scans to estimate tumour response were done only in patients in the WBI group who survived more than 12 months. The scans were performed during regular follow-up appointments for the patients in the GKS group. Among these patients, 89% experienced brain metastases that stabilized, reduced, or disappeared. Two patients in the GKS group developed radiation necrosis. Twelve patients in the GKS group, including those who experienced radiation necrosis, were also treated with WBI. The authors suggested that more prospective studies are needed to investigate

those patients who might benefit more from the use of GKS. It was suggested that conservative dosing should be used for GKS.

4.3.2 Cavernous sinus meningiomas

Metellus et al.[17] published a study in 2005 of patients who had cavernous sinus meningiomas. Patients received GKS or FR. The authors concluded that GKS and FR were clinically effective and relatively safe treatments for cavernous sinus meningiomas. The authors asserted that GKS should be offered to patients first and that FR should be offered to those who are not amenable to GKS.

Thirty-six patients were recruited to the GKS group between 1994 and 1997, and 38 patients were recruited to the FR group between 1986 and 1999. Patients had to have tumours less than 3 cm to be treated using GKS. The mean volume of tumours in patients undergoing treatment was statistically significantly smaller for the GKS group (5.2 cm^3) compared with the FR group (13.5 cm^3) $P < 0.05$. Patients who were treated using FR were statistically significantly more likely to have higher grade (III and IV) tumours than those who were treated using GKS (68.4% compared with 27.8%, $P = 0.0005$) and to have extensive lesions (69.5% compared with 19.4%, $P = 0.0003$).

More patients who were treated with GKS experienced tumour regression (19 compared with 11, $P = 0.04$). Two patients from each group experienced tumour recurrence. More patients in the FR group reported complications. The five-year progression-free survival was approximately 95% for both groups (94.7%, 95% CI 78.6 to 99.2 for the FR group compared with 94.4%, 95% CI 83.1 to 93.3 for the GKS group).

4.3.3 Spine metastases

In 2007, Gagnon et al.[12] published a retrospective matched-pairs analysis comparing CKS with conventional EBRT. The patients had primary breast cancer with spinal metastases. The authors concluded that CKS provided the patients in this population with benefits that were similar to those provided by conventional irradiation, without an increase in toxicities.

Eight patients who were recruited between March 2002 and January 2005 were given CKS. The treatment was 2,400 cGy or 2,100 cGy depending on tumour site and size. These therapies were provided in three fractions. Patients were matched with eight patients who had the same diagnosis and who were treated with conventional external-beam techniques (conformal radiotherapy) between 1995 and 2000. The matching was mostly performed using time from diagnosis to metastasis. No differences were found between the two groups in age, ethnicity, disease stage, KPS score, or pain. Based on a matched-pair analysis, there were no statistically significant differences in survival curves between the treatment groups ($P = 0.27$). The time frame for survival and the number of patients surviving were not reported. No statistically significant differences in the frequency of adverse events was found, with 56% of patients who were treated using conformal radiotherapy and 39% of patients treated using CKS experiencing one or more acute toxicities.

4.3.4 Vestibular schwannoma

Myrseth et al.[10] published a prospective study in 2009 of patients who received GKS or microsurgery to treat vestibular schwannomas. The authors recommended GKS to those patients with vestibular schwannomas who were eligible for GKS and for microsurgery.

Eligible patients were at least 20 years of age, with tumours less than or equal to 25 mm in the cerebellopontine angle. Eligible patients also had unilateral de novo non-neurofibromatosis 2 vestibular schwannoma. Among the 88 patients who were included in the study, 60 chose GKS and 28 chose microsurgery. Of the original 63 patients in the GKS group, three withdrew from the study before the first follow-up period. More patients chose GKS ($P = 0.001$). No other statistically significant baseline differences emerged. For example, there were no statistically significant differences in hearing ability, facial nerve function, or mean tumour

diameter. The follow-up period spanned two years.

The mean hospital stay for patients who were treated using GKS was 2.5 days (range two days to five days). For patients treated using microsurgery, the mean hospital stay was 12.5 days (range 10 days to 30 days). This difference was statistically significant in favour of patients who were treated using GKS ($P < 0.0009$). Hearing preservation was measured at two years post-treatment using the Gardner Robertson classification. Appendix 1 contains more information on the Gardner Robertson classification. At the two-year follow-up, seven patients who were treated using GKS had improved hearing (25 [42%] with Grade A or B compared with 17 [28%] with Grade A or B at baseline). No patients who were treated using microsurgery had Grade A or B at the two-year follow-up, compared with 13 (46%) patients at baseline. Thus, hearing did not improve. No further statistics were reported. No between-group differences emerged in patient complaints of vertigo, tinnitus, unsteadiness, or quality-of-life indicators as measured using the short-form health survey (SF-36). The authors stated that studying the use of GKS in the treatment of vestibular schwannoma in large-volume centres would be valuable.

In 2006, Pollock et al.[13] examined the clinical effectiveness of using GKS or microsurgery for patients with vestibular schwannomas. The authors concluded that radiosurgery may be a "best management strategy" for most patients with vestibular schwannomas based on current short-term evidence.

Patients were assigned to a treatment group based on patient preference. The GKS group comprised 46 patients, and the microsurgery group comprised 36 patients. Patients were statistically significantly younger in the microsurgery group (48.2 years compared with 53.9 years, $P = 0.03$). No other reported baseline characteristics were statistically different, including tumour size, percentage of patients with facial weakness or facial numbness, or mean tinnitus score. The mean follow-up was 42 months (range 12 months to 62 months). At the last follow-up session, tumour control did not differ between the two groups (100% versus 95%, $P = 0.50$). No further details were provided, and it was unclear what the percentages indicated, to which group they applied, and what the mean follow-up duration was for each treatment group. Data on survival were not presented. Facial movement, hearing preservation, and quality of life were reported. Patients who were treated using GKS were statistically significantly more likely to experience normal facial movement (as measured on the House-Brackmann scale) at one year (100% compared with 69%; $P < 0.001$). Compared with patients who were treated using microsurgery, patients who were treated using GKS were statistically significantly more likely to have experienced hearing preservation (as graded on the American Academy of Otolaryngology — Head and Neck Surgery scale) at one year (63% compared with 5%; $P < 0.001$). As measured using a health status questionnaire that was developed to evaluate dizziness, tinnitus, and headache, patients who were treated using microsurgery experienced a statistically significant decline in physical functioning ($P = 0.04$) and increased bodily pain ($P = 0.04$) between baseline and one year follow-up. The questionnaire did not seem to be validated. There were no follow-up differences at one year for the patients in the GKS group. The authors stated that long-term evidence may not corroborate these findings.

Myrseth et al.[18] published a study in 2005 that evaluated the clinical effectiveness of using microsurgery or GKS for patients with vestibular schwannomas. Quality of life after treatment was also measured. The authors concluded that patients who were treated using GKS fared statistically significantly better in facial nerve function, hearing, and quality of life.
Patient preference was used to direct assignment to a group. Eighty-six patients chose microsurgery, and 103 patients chose GKS. All tumours were less than or equal to 30 mm. For the GKS group, 83.5% of the tumours were less than or equal to 20 mm compared with 68.5% of the tumours in the microsurgery group. No statistics were reported on the differences in tumour diameters. Patients who were treated

using GKS were statistically significantly older than patients who were treated using microsurgery (59.7 years of age compared with 50.1 years of age; P < 0.001). Other demographic or descriptive information on patients, such as gender, were not reported.

At 14 years after treatment (approximate time that was taken from a figure in the report), there was no statistically significant difference (P = 0.5) between the two groups in tumour control. Tumour control for patients in the GKS group was achieved if the tumour did not grow by more than 140%. For those in the microsurgery group, it was freedom from retreatment. After the treatment, patients in the GKS group were statistically significantly more likely to have good facial nerve function compared with patients in the microsurgery group (P = 0.0026). Facial nerve function was measured using the House-Brackmann scale. Good facial nerve function was defined as Grade 1 or Grade 2.

The Glasgow Benefit Inventory and the SF-36 were used to measure quality of life. For more information on these instruments, see Appendix 1. The patients in the GKS group scored significantly higher on the general psychosocial health section (approximately −20 for patients in the GKS group compared with +5 for patients in the microsurgery group). No other statistics were reported. The numbers were extracted from a graph in the report. The difference between the mean SF-36 scores was not statistically significant.

4.4 Economic Evaluations

As part of the full HTA, MSAC tried to perform an economic evaluation of the use of GKS and CKS.[8] Because of the lack of comparative evidence on clinical effectiveness (benefit and harm) and costs of the technologies, the authors stated that it was not possible to determine whether the use of GKS was equally, less, or more cost-effective than the use of Linac or CKS, and a full economic evaluation could not be performed.

The authors stated that they updated the basic economic costing and the literature search from a previous HTA.[20] Two additional primary economic studies and one HTA were identified. Based on these studies, the authors concluded that the use of GKS was more costly when compared with the use of Linac-based SRS and less costly when compared with the use of CKS.

The base case average capital equipment costs per patient were estimated to be $3,757 for GKS, $5,441 for CKS, $4,186 for a Linac-dedicated SRS system, $960 for Linac adaptation equipment (excluding the cost of the Linac unit), and $3,549 for Linac adaptation (including the cost of the Linac unit). These numbers were based on 150 patients per year. The clinical effectiveness of either technology was not taken into account. It was unclear whether these amounts were in Australian dollars. Sensitivity analyses (for example, working life of equipment, maintenance charges) revealed that the use of GKS was less costly than the use of CKS and Linac-dedicated systems, but it was more costly when compared with the use of Linac adaptation equipment (whether the cost of the unit was included or excluded). Varying the discount rate between 0% and 8% (5% was used for the estimates) did not change the results.

Papatheofanis et al.[19] published a cost-utility analysis on the use of CKS in 2009. The authors reported that, based on a payer perspective, the use of CKS was a cost-effective treatment for patients with inoperable spinal metastases.

The overall cost of using CKS was lower, and it was more effective than EBRT. This translated into a net gain of 0.08 quality-adjusted life-years (QALYs). For a definition of QALY, see Appendix 1. The study was based in the US and included the direct costs of treatment, medical care, diagnostic and laboratory tests, physician visits, and other health care services in 2006 dollars. The conclusions were based on 27 studies (15 reported on CKS, and 12 reported on EBRT). The authors tried to match patients using one of the two technologies for attributes including age, KPS score, RPA class, number and size of lesions, presence or absence of

extracranial disease, and primary tumour histology. To help compensate for other criteria that were not considered in the study, such as costs and pain relief, sensitivity analyses were conducted. Patients in the model were more than 18 years of age, with a KPS score of at least 50. The use of CKS retains its cost-effectiveness (less than US$50,000 per QALY) when pain relief persists for a median duration of seven months.

Lee et al.[14] published a cohort study in 2009 that compared 56 patients who had GKS treatment with 100 patients who had WBRT. The authors concluded that the use of GKS was more cost-effective per QALY than the use of WBRT for patients with multiple brain metastases. The cost of GKS was US$10,831 per QALY, and the cost of WBRT was US$17,622 per QALY ($P < 0.05$). One major factor for this difference was that patients in the GKS group had statistically significantly reduced costs associated with hospital stay (US$2,531 ± US$1,596 compared with US$4,910 ± US$2,522; $P < 0.05$). The patients in the GKS group stayed in hospital for a mean of approximately 26 days, compared with patients in the WBRT group who were in hospital for a mean of approximately 62 days. The pricing year and discount rates were not reported.

4.5 Limitations

There were few comparative studies on TomoTherapy, GKS, and CKS. Without randomized studies or well-designed and controlled comparative studies, it is difficult to make reliable estimates. For example, the potential for selection bias resulting from treatment group assignment by patient or physician preference could affect the results against or in favour of the treatment.

The literature search for this review was not exhaustive. Thus, restrictions were placed on the search. For example, non-English, unpublished, and non–peer-reviewed articles were not searched for. In addition, the literature review was not intended to be comprehensive in capturing all related studies of any design. Case series were excluded because they do not allow for direct comparisons of effectiveness across treatments. The results of these decisions may have affected the conclusions of this report.

There were more relevant studies on GKS than CKS and no comparative studies on TomoTherapy. This makes comparisons between the technologies unreliable.

A small number of economic studies were included, but because of the lack of well-designed comparative studies to determine clinical effectiveness for TomoTherapy, GKS, and CKS, no comparative cost-effectiveness analyses between these three technologies were identified. Some costing was performed on GKS and CKS, but no economic evaluations were identified on TomoTherapy. No Canadian economic studies were retrieved. Thus, the applicability to Canadians is unclear.

Most of the literature that was identified described the use of GKS. This may reflect the fact that GKS is the oldest technology and perhaps the most widely used technology compared with CKS and TomoTherapy. The main level of evidence for TomoTherapy, GKS, and CKS seems to be retrospective case series.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Most of the evidence focused on the use of GKS. Overall, the use of GKS was found to be clinically effective or to produce similar benefits when compared with other standard treatments such as microsurgery, WBRT, and conventional radiotherapy. The primary outcome measures typically were tumour growth control and survival. One study compared GKS and CKS treatments for brain metastases and found similar survival and tumour control rates. One study evaluated CKS treatment of spinal metastases and found that patients who were treated using CKS had equivalent benefits

compared with conventional radiation therapies. No comparative clinical studies on TomoTherapy were found.

No studies that compared the cost-effectiveness of TomoTherapy, GKS, or CKS were identified. The authors of the HTA[8] performed a partial economic evaluation and found the use of GKS to be less costly than CKS but more costly than Linac-based SRS. One cost-utility study[19] compared the use of CKS with that of EBRT, and one cost-effectiveness study compared the use of GKS with that of WBRT.[14] CKS and GKS were found to be more expensive than traditional SRS but remained cost-effective in specific situations. No economic studies on TomoTherapy were included.

Three primary studies[10,13,18] and the HTA[8] found that patients who were treated using GKS had similar or improved quality of life compared with microsurgery.

The studies included a variety of patient populations who needed treatment using TomoTherapy, GKS, or CKS. The heterogeneity across studies occurred in various tumours, primary tumours, KPS scores, and RPS classifications. Treatment effectiveness and safety have not been studied in all populations. Future research that focuses on patient subpopulations may provide insight into which patient populations demonstrate a better response to the use of TomoTherapy, GKS, CKS, or conventional treatment. The results of studies that have design characteristics associated with high internal validity (for example, randomization of interventions) can be used to determine more reliable clinical estimates of effectiveness. This is also true for determining the cost-effectiveness of TomoTherapy, GKS, or CKS.

For treatment outside the brain, head, and neck, the use of CKS or TomoTherapy is the only option, because GKS is not used for therapy outside these regions. Depending on the patient populations who are treated, this may be a factor to consider when determining which technology to buy.

There is insufficient evidence that can be used to reliably estimate the comparative clinical effectiveness (benefit and harm), cost-effectiveness, and impact on quality of life of TomoTherapy, GKS, and CKS. The specific patient caseloads and sites requiring radiosurgery or radiotherapy may be factors to consider before buying one of these three technologies.

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APPENDIX 1: DEFINITIONS AND TECHNOLOGY DESCRIPTIONS

CyberKnife[2,4]

The CyberKnife is one of the most common Linac-based machines used.[2] It is a frameless SRS and a real-time system.[2] This allows for treatment of extra-cranial sites including those sites that move with patient respiration.[4] It comprises the Linac system that is mounted to a robotic treatment delivery system.[2] One high-energy photon beam adjusts for any patient movement during treatment, which allows for the maintenance of precision.[4]

Before radiation therapy or treatment, if treatment is outside the skull and spine, gold fiducials are placed near or in the target, and CT or MRI scans are performed.[4] The placement of fiducials is an outpatient procedure that is usually done several days before the CT scan.[4] The patient can return home during the planning phase when the radiation oncologist, surgeon, and physicist plan the treatment.[4]

Some of the advantages compared with microsurgery are that it is an outpatient treatment, it generally requires no sedation (during framed SRS, sedation is required when the frame is affixed), it allows fractionated dosing, it allows for extracranial targets, it allows for treatment of patient groups who are otherwise untreatable (for example, infants), and it reduces preparation time and post-treatment manipulation and recovery.[2]

Gamma Knife[4]

The Gamma Knife may be the best known Cobalt-60 based SRS. A series of beams is made to converge on the targeted area. A frame is affixed to the patient's head. The patient then undergoes CT or MRI scan and awaits radiosurgery. The neurosurgeon, radiation oncologist, and physicist meet to plan the treatment.

Gardner Robertson Classification[21]

The Gardner Robertson Classification is used to measure hearing. It is based on the Speech Discrimination Score, which is the percentage of words identified on a hearing test at a certain volume, and the Pure Tone Average. For GKS, there are three classifications. The first is Grade A, which indicates that the patient's hearing is maintained in the same hearing class. Grade B indicates that hearing has been preserved at a "useful" level with a Gardner Robertson score of 1 or 2. Grade C indicates that there is maintenance of some hearing function that can be measured.

Glasgow Benefit Inventory[18]

The Glasgow Benefit Inventory questionnaire comprises 18 questions to assess quality of life. In response to questions about comparisons between quality of life before and after treatment, the patient selects "much better," "better," "unchanged," "worse," or "much worse." Of the 18 questions, 12 focus on general and psychosocial health, three reflect social support, and three focus on physical health. A higher score indicates better quality of life.

Karnofsky Performance Scale[8]

The KPS is a commonly used tool with excellent reliability and strong predictive validity. It is used to assess the ability of patients with cancer to perform normal activities. The scores that a patient can receive are between 0 and 100. A patient who scores between 80 and 100 is able to carry on normal activity and work without special care. A patient who scores between 50 and 70 is able to live at home, but not work, and requires varying levels of assistance. A patient who scores between 0 and 40 requires the equivalent

of hospital or institutional care. The use of this performance scale helps predict prognosis and helps plan the treatment path for the patient. It can also be used as an outcome measure in research studies.

Linear Accelerator[1,2]

Linear accelerators, also known as "Linacs," are general purpose radiation delivery machines.[1] They produce radiation, which can also be referred to as "high energy X-ray."[1] Modifications to Linacs are usually required to deliver SRS or SRT. Linacs use one large intense radiation beam that is redirected in many "arcs" to lessen the adverse effects on healthy tissue.[2] Linacs can be dedicated or non-dedicated. If dedicated, the additional equipment required to perform SRS or SRT is a permanent attachment.[1] If Linacs are not dedicated, then they can be used for conventional radiation therapy and SRS or SRT by adding the necessary attachments.[1] Some centres use the Linac radiosurgery unit after the conventional radiation therapy is completed for the day.[2]

National Cancer Institute Common Toxicity Criteria[22]

Adverse events are historically called "toxicities" in cancer research. Adverse events are graded from 0 to 5, with 0 representing no adverse event and 5 representing death. Ratings of 1, 2, 3 are mild, moderate, and severe adverse events respectively. A rating of 4 indicates a life-threatening or disabling adverse event.

Radiation Therapy Oncology Group Recursive Partitioning Analysis Classification[23]

The RTOG developed three prognostic classes for brain metastases using RPA of a large database. Class I patients have KPS scores of 70 or more, are younger than 65 years of age, and have controlled primary and no extracranial metastases. Class III patients have KPS scores less than 70. Class II patients are all other patients.

Short-Form Health Survey[18]

The SF-36 questionnaire is designed to indicate general health status. Eight health concepts are measured using 36 questions: physical functioning, role-physical, social functioning, role-emotional, general health, mental health, bodily pain, and vitality. This tool can be used to distinguish between stages of illness.

TomoTherapy[3]

The TomoTherapy HiArt system is a Linac with an attached CT scanner. This allows a scan of the site just before each treatment where the fractionated radiotherapy is administered. It administers intensity-modulated radiation therapy.

APPENDIX 2: SEARCH STRATEGIES

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE <1996 to 2009 Week 19> Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 9, 2009
Alerts:	Weekly search updates began April 16, 2009 and ended May 27, 2009.
Study Types:	Systematic reviews, meta-analyses, health technology assessments, randomized controlled trials, observational studies, economic studies
Limits:	Publication years 2004 to May 2009 English language
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
*	At the end of a word, indicates truncation
ADJ#	Adjacency within # number of words (in any order)
.ti.	Title
.ab.	Abstract
.hw.	Heading Word; usually includes subject headings and controlled vocabulary
.pt.	Publication type
.jw.	Journal word
.md.	Methodology
.mp.	Mapping alias (searches title, abstract, heading words, table of contents, and key phrase identifiers)

Ovid EMBASE MEDLINE Strategy	
Line #	**Search Strategy**
Tomotherapy_Gammaknife_Cyberknife_Radiosurgery	
1	exp radiosurgery/
2	(Radiosurgi* or Radio surgi* or stereotactic Radiotherap* or steretactic Radiotherap* or stereotaxic Radiotherap* or stereotaxy Radiotherap* or cyberknife* or cyber knife* or gamma knife* or Gammaknife* or xknife or x knife or shaped beam system or Tomotherap* or Tomo therap* or HiArt).ti,ab.
3	1 or 2
Oncology_Cancer_Neoplasm	
4	exp Neoplasm/
5	exp Medical Oncology/ or exp Oncology/
6	(cancer* or carcinoma or neoplasm* or lymphoma* or tumor* or tumour* or oncolog* or malignan* or sarcoma* or metasta* or benign*).ti,ab,jn.
7	or/4-6

Ovid EMBASE MEDLINE Strategy	
Line #	**Search Strategy**
8	3 and 7
9	limit 8 to english language
10	limit 9 to yr="2004 - 2009"
Systematic Review / HTA / Meta-analysis Filter	
11	meta-analysis.pt.
12	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
13	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
14	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
15	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
16	(data synthes* or data extraction* or data abstraction*).ti,ab.
17	(handsearch* or hand search*).ti,ab.
18	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
19	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
20	(meta regression* or metaregression* or mega regression*).ti,ab.
21	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
22	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
23	(cochrane or health technology assessment or evidence report).jw.
24	(meta-analysis or systematic review).md.
25	or/11-24
26	25 and 10
Randomized Controlled Trial Filter	
27	Randomized Controlled Trial.pt.
28	Randomized Controlled Trials as Topic/
29	Randomized Controlled Trial/
30	Randomization/
31	Random Allocation/
32	Double-Blind Method/
33	Double Blind Procedure/
34	Double-Blind Studies/
35	Single-Blind Method/
36	Single Blind Procedure/
37	Single-Blind Studies/
38	Placebos/
39	Placebo/
40	(random* or sham or placebo*).ti,ab,hw.
41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
43	or/27-42
44	43 and 10
Economic Filter	
45	*Economics/

Ovid EMBASE MEDLINE Strategy	
Line #	**Search Strategy**
46	exp "Costs and Cost Analysis"/
47	(sensitivity analysis or sensitivity analyses).ti,ab.
48	(cost or costs or costing or cost-effective*).ti,ab.
49	or/45-48
50	49 and 10
Focused Search Strategy: Observational Studies	
51	(cyberknife* or cyber knife* or gamma knife* or Gammaknife* or Tomotherap* or Tomo therap*).ti.
52	53 and 7
53	limit 54 to english language
54	limit 55 to yr="2004 - 2009"
Observational Studies Filter	
55	Observational study/
56	Observational stud*.ti,ab.
57	Cohort analysis/
58	(cohort stud* or cohort analys?s).ti,ab.
59	Longitudinal study/ or longitudinal stud*.ti,ab.
60	Prospective study/ or prospective stud*.ti,ab.
61	Retrospective study/ or retrospective stud*.ti,ab.
62	follow-up stud*.ti,ab.
63	Case control study/
64	(case control* stud* or case control* analys?s).ti,ab.
65	Case study/
66	case series.ti,ab.
67	Population-based case control study/
68	population-based stud*.ti,ab.
69	Population-based case control study.ti,ab.
70	or/55-69
71	70 and 54
72	or/26, 44, 50, 71

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 4, 2009;	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	April 1, 2009 to April 2, 2009
Keywords:	Tomotherap* OR cyberknife OR gamma knife OR HiArtt
Limits:	Publication years 2004 to May 2009

The following sections of the CADTH grey literature checklist "Grey Matters: A Practical Search Tool for Evidence-Based Medicine" (http://www.cadth.ca/index.php/en/cadth/products) were searched:

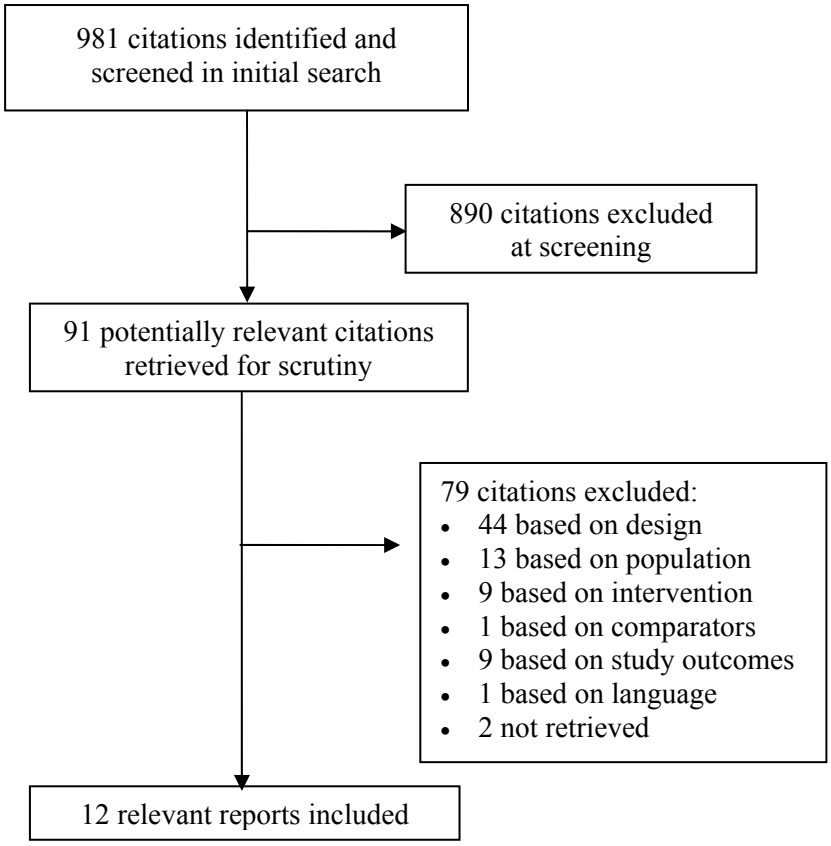
- Health Technology Assessment (HTA) Agencies
- Health Economics
- Databases (free)
- Internet Search
- Open Access Journals.

APPENDIX 3: STUDY INCLUSION CRITERIA

Table 1: Study Inclusion Criteria	
Design	Health technology assessment, systematic review, randomized controlled trial, controlled clinical trial, cohort
Patient Population	Tumours of brain, spine, lung, intra-abdomen (e.g., pancreas, liver, small intestine) Tumours of endocrine system excluded (such as pituitary adenoma) Human studies only
Intervention	Gamma Knife, TomoTherapy, CyberKnife
Comparator	Any comparator allowed
Outcome	Patient-relevant outcomes including tumour control, survival rates, quality of life, and adverse events
Language	English only

APPENDIX 4: SELECTION OF PUBLICATIONS

The flow chart depicts how studies were excluded from the initial literature search. In the literature search, 981 citations were found, and 12 were included in the final report.



APPENDIX 5: INCLUDED STUDIES

Table 1: Statistics for Included Randomized Controlled Trial (Muacevic et al.[9])

Patient Description		Dose	Outcomes		
Tumour Description	**Number and Age**	**Dose Given to Tumour Site**	**Survival**	**Tumour Control**	**Adverse Events**
Diagnosis Single brain metastases **Location** MS + WBRT Supratentorial 26 Infratentorial 7 GKS Supratentorial 23 Infratentorial 8 **Tumour diameter (Mean ± SD)** GKS 2.1 ± 0.8 cm MS + WBRT 2.4 ± 0.6 cm **RPA class** GKS I 13 II 12 **MS + WBRT** I 20 II 19	**Number** MS + WBRT 33 GKS 31 **Mean age (SD)** MS + WBRT 58.3 ± 9.6 years GKS 54.3 ± 11.7 years	**MS + WBRT** 50 Gy (2 Gy over 20 fractions) **GKS** 21 Gy (range 14 to 27)	**Median survival** **MS + WBRT** 9.5 months **GKS** 10.3 months, ns	**1 year** MS + WBRT 82.0% GKS 1 year: 96.8%, P = 0.06 **1-year distant recurrence rate** MS + WBRT 3.0% GKS 25.8%, P < 0.05	**Acute toxicity (patients)** MS + WBRT Grade 1: Nausea (5) Hearing loss (1) Skin (15) Neurological (4) Grade 2: Nausea (2) Skin (2) Neurological (1) Grade 3: Neurological (1) Other (2) Acute Grade 1: Nausea (6) Hearing loss (1) Skin (2) Neurological (3) Grade 3: Neurological (4) **Late toxicity (patients)** MS + WBRT Grade 1: Nausea (2) Skin (2) Grade 2: Nausea (1) Skin (1) GKS Grade 1: Nausea (1) Grade 4: Neurological (1)

GKS = Gamma Knife surgery; Gy = Gray; MS = microsurgery; ns = not significant; RPA = recursive partitioning analyses; SD = standard deviation; WBRT = whole brain radiation therapy.

Table 2: Statistics for Included Comparative Cohort Studies[10-18]						
Study	**Patient Description**		**Dose**	**Outcomes**		
Author	**Tumour Description**	**Number, Per Cent Female, Age**	**Dose Given to Tumour Site**	**Survival**	**Tumour Control**	**Adverse Events**
Myrseth et al.[10]	**Diagnosis** Vestibular schwannoma **Mean tumour diameter** MS 18 mm (cerebellopontine angle) GKS 16 mm (cerebellopontine angle)	**Number** MS 28 GKS 60 **Female** MS 57.1% GKS 56.7% **Mean age (range)** MS 52.5 years (26 to 73) GKS 57.5 years (36 to 79), P = 0.06	**Mean dose (Gy)** GKS 12	NR	NR	**Complications (patients)** GKS 0 MS Perisurgical complications (4) including cerebrospinal fluid leaks (2), small hematoma (1), hoarseness (1)
Wowra et al.[11]	**Diagnosis** Single brain metastases **Tumour size** GKS 5.2 cm^3 ± 5.5 CKS 5.1 cm^3 ± 7.6; ns **RTOG score** GKS 1: 12 2: 38 3: 13 CKS 1:12 2: 38 3: 13	**Number** GKS 63 patients, 423 tumours CKS 63 patients, 73 tumours	**Minimum dose** GKS 19.4 ± 2.5 CKS 18.4 ± 1.5; P < 0.0005	**Survival after treatment** GKS median = 1.1 years (range 0.8 to 1.2 years) CKS median = 1.1 years (range 0.8 to 1.9 years); ns	**At 12 to 18 months** GKS 94.6% (CI 98.6% to 80.2%) CKS 93.8% (CI 98.6% to 75.4%)	**Adverse radiation reactions** GKS found in 9 tumours CKS found in 14 tumours, ns
Lee et al.[14]	**Diagnosis** Brain metastases **GKS** KPS ≥ 70: 43 patients RPA I: 13 II: 25 III:18	**Number** GKS 56 WBRT 100 **Female** GKS 64.3% WBRT 58.0%	**Dose** GKS NR	**Median survival time** GKS 9.5 WBRT 8.3, ns	NR	**Patients with complications** GKS Headache and brain edema (1) Mental confusion (1) Motor weakness (1)

Table 2: Statistics for Included Comparative Cohort Studies[10-18]						
Study	**Patient Description**		**Dose**	**Outcomes**		
	WBRT KPA ≥ 70, 68 patients RPA I: 18 II: 42 III: 40	**Mean age (SD)** GKS 58.8 ± 11.84 years WBRT 61.8 ± 13.46 years				WBRT Headache and intracranial pressure (3) Mental confusion (1) Motor weakness (1) Seizures (1)
Lee et al.[16]	**Diagnosis** Brain metastases from ovarian cancer	**Number (patients)** GKS 7 WBRT 8 **Median age** GKS 55 years (range 26 to 76 years) **WBRT** 56 years (range 29 to 76 years)	NR	**Median survival (months)** GKS 29 (range 3 to 36) WBRT 6 (range 1 to 19), P = 0.0061	NR	NR
Gagnon et al.[12]	**Diagnosis** Spine metastases, breast cancer primary	**Number (patients)** GKS 8 CRT 8 **Female** GKS and CRT 100% **Age** GKS and CRT NR	**Dose (Gy)** GKS 2,400 cGy over 3 fractions or 2,100 cGy, over 3 fractions	**Survival:** GKS and CRT, ns	NR	**Adverse events (patients)** GKS Nausea (1) Fatigue (2) Dysphagia (2) CRT Nausea (2) Nausea and vomiting (2) Dysphagia (2) Diarrhea (4) Esophagitis (2) Other (9)
Pollock et al.[13]	**Diagnosis** Vestibular Schwannoma **Mean diameter** GKS cerebellopontine angle 12.3 mm MS cerebellopontine angle 14.1 mm, ns	**Number** MS 36 GKS 46 **Female** GKS 34.8% MS 47.2%	**Mean dose (Gy)** GKS 12.2	NR	**Tumour control percentage** 100 and 96, P = 0.5 (group assignment unclear)	**Complications (patients)** GKS Trigeminal neuralgia (1) Increasing ataxia (2) Laser resection for tumour enlargement (2)

Table 2: Statistics for Included Comparative Cohort Studies[10-18]						
Study	**Patient Description**		**Dose**	**Outcomes**		
		Mean age GKS 53.9 years MS 48.2 years, P = 0.03				MS Cerebrospinal fluid leakage (5) Wound infection (1) Deep vein thrombosis (1) Required tarsorrhaphy (5) Gold weight placement for eye protection (1)
Myrseth et al.[18]	**Diagnosis** Vestibular schwannomas	**Number (patients)** GKS 103 MS 86 **Mean age (range)** GKS 59.7 years (22 to 82) MS 50.1 years (25 to 83)	**Dose (Gy)** GKS 10 to 12 except 4 cases given 15 to 20	NR	No statistically significant differences between groups (> 140% tumour growth for GKS patients compared with freedom of retreatment in MS patients)	NR
Datta et al.[15]	**Diagnosis** Brain metastases WBI treatment using Linac	**Number (patients)** GKS 53 WBI 67 **Female** GKS 42% WBI 46% **Median age (range)** GKS 57.5 years (36 to 79 years) **WBI** 53.4 years (29 to 78 years)	**GKS** Mean 16 Gy (range 13 to 19 Gy) **WBI** 30 Gy, 3 Gy per fraction	**Mean survival (SD)** GKS 6.7 months (0.6) WBI 7.8 months (0.8), ns	**Tumour control** GKS Reduced 37% Stabilized 25% Disappeared 27% WBI not calculable	**Late effects (> 10 months)** GKS 0 reported (10 patients) WBI 0 reported (13 patients)

Table 2: Statistics for Included Comparative Cohort Studies[10-18]						
Study	**Patient Description**		**Dose**	**Outcomes**		
Metellus et al.[17]	**Diagnosis** Cavernous sinus meningiomas **Mean tumour volume (range)** GKS 5.2 cm^3 (1.1 to 15.6) FR 13.5 cm^3 (5.6 to 33.6), P < 0.05 **Cavernous sinus grade (patients)** GKS I or II: 26 III or IV: 10 V: 0 FR I or II: 11 III or IV: 26, P < 0.05 V: 1	**Number (patients)** GKS 36 FR 38 **Female** GKS 80.1% FR 81.6% **Mean age (SD)** GKS 51 years (± 6.2) FR 53 years (± 6.4)	**Mean Dose in Gy (range)** GKS 28 (12 to 50) for central FR 52 (50 to 55)	**5-year progression-free survival** GKS 94.4% FR 94.7% **10-year progression-free survival** GKS 94.4% FR 94.7%	**Tumour volume decrease (patients)** GKS 19 FR 11, P = 0.04 **Tumour unchanged (patients)** GKS 15 FR 27 **Tumour recurrence (patients)** GKS 2 FR 2	**Complications (patients)** GKS Grade IV: 1 FR required short-term corticotherapy 6% Poor tolerance, stopped treatment temporarily: 1 Short-term memory loss: 1

cGy = centigray; CI = confidence interval; CKS = CyberKnife surgery; CRT = conformal radiotherapy; FR = fractionated radiotherapy; GKS = Gamma Knife surgery; Gy = Gray; KPS = Karnofsky Performance Scale; MS = microsurgery; NR = not reported; ns = not significant; RPA = recursive partitioning analyses; RTOG = radiation therapy oncology group; SD = standard deviation; WBI = whole brain irradiation; WBRT = whole brain radiation therapy.