Gamma knife and linear accelerator stereotactic radiosurgery

SUMMARY

Québec

Gamma knife and linear accelerator stereotactic radiosurgery

SUMMARY

Report prepared for AETMIS
by Raouf Hassen-Khodja

October 2002

Québec

This report was written and published by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). It is also available in PDF format on the Agency's Web site.

For information about this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et
des modes d'intervention en santé
2021, avenue Union, bureau 1040
Montréal (Québec) H3A 2S9

Tel.: (514) 873-2563
Fax: (514) 873-1369
e-mail: aetmis@aetmis.gouv.qc.ca
http://www.aetmis.gouv.qc.ca

How to cite this report:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Gamma knife and linear accelerator stereotactic radiosurgery. Report prepared by Raouf Hassen-Khodja. (AETMIS 02-03 RF). Montréal: AETMIS, 2002, xv-87 p.

Legal deposit
Bibliothèque nationale du Québec, 2002
National Library of Canada, 2002
ISBN 2-550-39753-3

MISSION

The mission of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. In order to accomplish this, the Agency advises and supports the Minister of Finance, Economy and Research as well as the decision-makers in the health-care system with respect to the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, distribution and application of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account multiple factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

Foreword

Gamma knife and linear accelerator stereotactic radiosurgery

The huge challenges posed by treating small-volume brain lesions prompted researchers and neurosurgeons to develop a new treatment technique known as "stereotactic radiosurgery" (SRS). Using stereotaxy, which permits the very precise three-dimensional localization of the treatment target, the objective of SRS is to expose the tumor to a single high dose of radiation while at the same time minimizing radiation exposure to the healthy surrounding structures. However, SRS is a leading-edge technology that requires expert skills and the use of elaborate and expensive equipment, such as a linear accelerator or a gamma knife.

The primary objective of this report is to answer the Régie de l'assurance-maladie du Québec's questions concerning the efficacy of SRS in treating brain lesions near sensitive areas. In addition to this objective was the need to determine whether or not it would be beneficial for Québec to acquire a gamma knife. This is why two university hospitals, the regional health and social services boards that these hospitals come under, and the Ministère de la Santé et des Services sociaux, which is responsible for the deployment of tertiary services throughout Québec, contacted the Agence d'évaluation des technologies et des modes d'intervention en santé to obtain an overview of this issue.

The Agency's assessment is based on a thorough examination of the existing scientific data and an analysis of the epidemiological and economic data applicable to Québec. First, this report briefly explains the underlying principles of SRS and of the different instruments used in this technique**.** It then examines the efficacy and safety of SRS for various indications. That chapter is followed by a cost comparison of the use of the main instruments utilized in SRS and a discussion of some of the results obtained. Lastly, the Agency draws the appropriate conclusions and makes the appropriate recommendations.

Given the current knowledge about the clinical, economic, technical and epidemiological aspects and given the need to adequately fulfill the offer of SRS services and to adequately meet research needs, the Agency recommends that a specialized radiosurgery centre with a gamma knife be set up at a university hospital. The institution chosen must have the necessary logistical wherewithal for SRS, i.e. a multidisciplinary treatment team, patient management quality and continuity, and the role of training. The Agency stresses that this recommendation is conditional upon the technological evolution of the various types of instruments and the emerging therapies at the time when the decision to create a centre providing SRS services is made.

In publishing this report, the Agency wishes to provide the best possible information to the policymakers concerned by this current issue in Québec's health-care system.

Renaldo N. Battista
President and Chief Executive Officer

ACKNOWLEDGMENTS

This report was prepared at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) by **Raouf Hassen-Khodja**, M.D., M.Sc., consulting researcher. We express our gratitude to him for his work. The Agency also wishes to call attention to the contribution by **Myriam Gagnon,** M.A. Cert. Tr., in the form of linguistic revision. The Agency is also grateful to **Mark Wickens**, trad. a. for translating this report from the original French version.

The Agency would also like to thank the external reviewers for their many comments, which helped improve the quality and contents of this report:

Dr. Jean-Paul Bahary	Radio-oncologist, Chief of Radio-oncology, Hôpital Notre-Dame, Centre hospitalier universitaire de Montréal, Montréal, Québec
Dr. Alain de Lotbinière	Neurosurgeon, Director of Stereotactic and Functional Neurosurgery, Department of Neurosurgery, Yale University School of Medicine, New Haven, United States
Dr. Georges L'Espérance	Neurosurgeon, Clinique médicale René Laennec, Montréal, Québec, and Director of Professional Care, Centre hospitalier de Rimouski, Québec
Dr. Marc Levivier	Professor and Chief of Clinic, Neurosurgery Unit, Hôpital Erasme, U.L.B., and Centre Gamma Knife de l'Université Libre de Bruxelles, Belgium
Ervin B. Podgorsak	Director, Medical Physics Unit, Montreal General Hospital, and Professor, Department of Oncology, Faculty of Medicine, McGill University, Montréal, Québec
Dr. Jean Regis	Hospital Practitioner, Functional Neurosurgery and Gamma Knife Radiosurgery Unit, Centre hospitalier Régional et Universitaire de Marseille, France

Lastly, the Agence wishes to thank **Dr. Philippe Couillard**, Neurosurgeon, Chief of Surgery, CHUS (Sherbrooke, Québec); **Dr. André Olivier**, Chief of Neurosurgery, Montreal Neurological Hospital and Institute, MUHC, and Director and professor holding the William Cone Chair, Neurology Division, McGill University (Montréal, Québec); and **Soran Johansson**, Vice-President, Business Developement, and **Trudy Brown**, who, when this report was being drafted, was the director of Strategic Business Services, Elekta Instruments (Norcross, GA, USA), for their collaboration and invaluable comments.

Summary

Introduction

Thanks to the technological evolution of the different imaging techniques, which are now increasingly precise, the surgical or, more specifically, neurosurgical treatment of certain brain lesions has made tremendous strides. The main challenge in stereotactic radiosurgery (SRS) was to offer greater efficacy while at the same time minimizing the risk. The emergence of approaches using various types of rays (electron, gamma, etc.) and the constant evolution of nuclear physics fostered the development of a new approach in neurosurgery—stereotactic radioneurosurgery. This type of treatment consists in exposing a lesion of small volume, determined by three-dimensional imaging, to a single high dose of ionizing rays while at the same time minimizing the dose absorbed by the surrounding structures.

What is unique about SRS is that it allows one to treat lesions (e.g., the destruction of tumors) without making a surgical incision. With SRS, very delicate and hard-to-reach areas can be treated (e.g., near the optic chiasma) where surgery is not possible because of the risks inherent in the surgical procedures (e.g., hemorrhage, irreversible lesions). The fact that the procedure involves less traumatic intervention conditions (local anesthesia) is the other attractive feature of this technique.

The cyclotron, linear accelerator and gamma knife are the three main types of instruments used in SRS. They differ from each other by their radiation source and their mobility in relation to the patient.

In Québec, the use of SRS is limited to the use of the linear accelerator (McGill University Health Centre and Centre hospitalier universitaire de Montréal).

BACKGROUND TO THIS ASSESSMENT

In order to be able to process requests for authorizing gamma knife radiosurgery outside Québec, and given the strong likelihood that a request for purchasing this technology would be submitted to the competent authorities, the Régie de l'assurance-maladie du Québec asked the Agence d'évaluation des technologies et des modes d'intervention en santé (Agency) to examine this current issue. Subsequently, two regional health and social services boards, two university hospitals and lastly, the Ministère de la Santé et des Services sociaux (given that this issue concerns tertiary care) expressed interest in a more thorough assessment.

In this report, we explain the main principles underlying SRS, discuss the indications for this technique, and present our recommendations concerning the role of SRS in Québec's health-care system.

DESCRIPTION OF SRS

SRS was used for the first time in 1951 by Dr. Lars Leksell. In accordance with the original definition of SRS, its function was to destroy a delimited area of the brain by means of a single dose of radiation and without opening the skull. To this definition, Ladislau Steiner added, in 1997, the notion of "producing desired biological effects".

The basic principle of SRS is the elimination of a functional disorder or the destruction of abnormal tissues by administering a strong dose of highly focussed radiation. This treatment modality enables one to limit the irradiation to the target (small brain lesion) and to spare the healthy surrounding tissues as much as possible. SRS is an important alternative to the many types of invasive treatment for certain types of brain tumors and enables one to closely monitor the evolution of lesions.

SRS is an external irradiation technique that involves the use of a stereotactic frame and a high-resolution imaging system, such as computed tomography or magnetic resonance imaging. The data gathered are transferred to a digitized-data processing system, which precisely calculates the target's coordinates and characteristics and the radiation doses needed to destroy the lesion by means of an extremely high-performing radiotherapy instrument.

Here are the main types of instruments used in SRS:

- The cyclotron: A circular accelerator of charged heavy particles (e.g., protons and gamma rays).
- The linear accelerator, which can be modified. A modified accelerator can be adapted (by adding stereotactic accessories) or dedicated. It can include a single or multileaf collimator.
- The gamma knife: The patient's head is positioned in the machine by setting its stereotactic coordinates, with the intracranial target located at the isocentre or isocentres. The gamma knife is exclusively dedicated to SRS.

We excluded the cyclotron from our comparison of the various instruments because it is not mass marketed, is very expensive and requires a very elaborate infrastructure.

EFFICACY OF SRS

Methodology

A literature search was performed in the Medline, Cochrane Library, Embase and HealthStar databases, and was supplemented with reports from a number of health technology assessment agencies that had looked at SRS. Upon examining the relevant scientific data, it was observed that:

- There has been a very large number of study reports on the efficacy of SRS, especially in the past ten years.
- Almost all of the studies have been of the retrospective type, with no randomization or comparison.
- Very few or even no comparative studies have examined the use of the gamma knife and linear accelerator (adapted or dedicated) for specific indications.

- Very few economic studies comparing the various instruments have been carried out, and for the most part, they are considered in the reports published by national assessment agencies.

Results of the analysis

As a general rule, all the results of studies (prospective, retrospective or case studies) support the efficacy of SRS in certain carefully selected cases. The main advantage of this type of treatment over conventional radiotherapy is the improvement in the patient's quality of life.

The indications for SRS that are generally accepted and supported by scientific studies are as follows:

- Arteriovenous malformations.
- Brain metastases. Brain metastases from extracerebral tumors seem to be a target of choice for SRS, especially radioresistant metastases, small tumors, residual or recurrent tumors after surgery, and when one seeks to preserve cranial nerve integrity.
- Meningiomas near sensitive structures.
- Vestibular schwannomas. SRS, especially gamma knife SRS, could be an alternative for overcoming interventional difficulties and avoiding the complications of the standard treatments.

The use of SRS for pituitary adenomas and certain skull base tumors is promising and depends on many different factors, such as the nature and location of the tumor and the treatment team's experience.

The effects of SRS in patients with functional disorders are not always as convincing as the established benefits of this type of treatment for certain structural brain lesions. The use of SRS will therefore be limited until its efficacy is assessed in rigorous scientific studies.

Because of the lack of comparative data on the clinical efficacy of the gamma knife and the dedicated linear accelerator, it cannot be concluded that either of these instruments is superior to the other. However, the gamma knife does seem to offer the degree of precision required for treating small lesions near sensitive structures, such as the optic chiasma and brainstem, thanks to its technical characteristics. Furthermore, the vast majority of studies have examined the use of the gamma knife for specific pathologies, such as the vestibular schwannoma. This picture could, however, change in light of the technological improvements made to the equipment (especially dedicated linear accelerators), which could increase their precision.

COMPLICATIONS

The adverse effects and complications of SRS can be immediate or late, temporary or permanent, acute or chronic, the healthy adjacent tissues being the main area affected. These effects are usually observed on images of perilesional abnormalities, which depend on various factors, such as the dose administered and the tumor's volume and histological type. The complications range from simple edema to extensive radiation necrosis. Depending on the location and type of lesion, these complications manifest clinically as transient headaches or a specific symptomatology associated with the location of the necrosis.

A good knowledge of the probability of adverse effects occurring, rigorous dose planning and a longer follow-up for certain pathologies can limit the adverse effects and complications.

SAFETY AND PREVENTIVE MEASURES

Like any other treatment that uses radiation sources, SRS requires the preventive measures inherent in radiotherapy. Setting up an SRS unit involves applying and maintaining the necessary radiation protection standards (structures, patients and personnel) and establishing control measures—in some cases, specific—for certain instruments. While the preparation and adjustment protocol may be uniform for the gamma knife, it is not so for linear accelerators, especially those that are not neurosurgery-dedicated. As a general rule, there are four control steps: adjusting the machine, preparing the patient, locating the target and transferring the data, and lastly, determining the ballistics and dosimetry.

For these measures, each treatment team member must have specific skills and qualifications. Patient management depends on several factors, including the technical-medical team's multidisciplinary makeup. Apart from the personnel normally present during radiotherapy, a neurosurgeon and a neuroradiologist should participate in the treatment.

CURRENT AND POTENTIAL NEEDS IN QUÉBEC

The results of the various prospective studies all indicate that the number of patients who will eventually require SRS is about at least 40 per one million population per year. In Québec, this would work out to about 300 cases a year (1,200 for all of Canada). This calculation concerns only three indications (metastases, schwannomas and vascular malformations). Other authors arrive at much higher figures in the order of 180 cases per one million population per year (or 1,260 in Québec). In our opinion, and based on data from the Fichier des tumeurs du Québec and from Canadian Cancer Statistics 2000, a more cautious calculation brings the number of eligible cases in Québec to 400. More specifically, and based on existing epidemiological data, we estimate the number of cases of arteriovenous malformations to be between 100 and 120 per year, while the number of cases of brain metastases potentially eligible for SRS would be between 400 and 1,200 per year.

THE COST OF SRS

In a first approximation, if the comparison involves the same number of treated patients, each gamma knife treatment would cost slightly less than if a dedicated linear accelerator were used (assuming that the instruments' lifespans are 20 and 10 years, respectively) and more expensive than treatment by means of an adapted linear accelerator. If the use of an adapted linear accelerator is shared between radiotherapy and radiosurgery, the number of cases that could be treated by radiosurgery at each facility would reach a ceiling.

The number of patients treated is an important variable in determining the average cost per treatment, since this cost (excluding physicians' fees) can drop from $11,000 to $4,500 CAD as the number of treatments performed with the gamma knife and dedicated linear accelerator increases from 100 to 250. However, the optimal treatment capacity depends on the amount of time it takes to reach this capacity and the number of truly eligible cases in the population.

Based on an evaluation carried out in Québec, the purchase and installation costs for a gamma knife are approximately $6.44 million. A dedicated linear accelerator would cost about one half this amount, but its operating costs (physical and human resources) would be 50% higher. It follows that the total cost, including amortization of the instruments, the radiation sources and the installation, are approximately the same. As for the adapted linear accelerator, its total cost is 15 to 30% less than that of the gamma knife, given an annual treatment volume of between 175 and 100. All of these figures are based on the purchase of new instruments.

It is difficult to perform a cost-effectiveness analysis because of the lack of randomized studies comparing the various instruments with respect to their clinical efficacy and because the cost of treatment often depends on the patient's clinical status and on the type of treatment considered (first-line treatment, treatment of recurrences, adjuvant SRS).

In the end, if it is assumed that the treatment is of equal efficacy regardless of the instrument used, the economic comparison criterion would be limited to the per-treatment cost. However, the evaluations do not show an important difference between the dedicated linear accelerator and the gamma knife, which are more comparable from the standpoint of clinical performance. Lastly, the number of cases that are truly eligible and actually treated is a crucial factor.

Conclusions

Stereotactic radiosurgery

- The efficacy of SRS has been established for a certain number of indications, including brain metastases, arteriovenous malformations, as an alternative to conventional surgery in cases of interventional difficulties, and in the prevention of the complications of the standard treatments in cases of meningioma and vestibular schwannoma. SRS is a promising approach in the treatment of pituitary adenomas, certain skull base tumors, and specific functional disorders.

- Given the evolution of the technologies and the costs associated with SRS, the instruments that might best meet the efficacy and safety criteria are the dedicated linear accelerator and the gamma knife.

- The use of an adapted linear accelerator is possible but limited in cases of lesions in very close proximity to sensitive structures, since the manipulations required to adapt the equipment in order to perform SRS can be a source of imprecision when focussing the beams. Furthermore, the need to perform quality control before each treatment lengthens the treatment time.

- Presently, SRS facilities are clearly needed in Québec. If we consider all the lesions eligible for SRS on the basis of the existing data and evaluations, more than 300 patients could benefit from SRS.

Therapeutic efficacy by instrument

- Even if, in theory, the gamma knife and dedicated linear accelerator are both more suitable for the various indications for SRS, technological developments in the specific area of SRS (especially in the case of the dedicated linear accelerator) and the lack of randomized, controlled trials concerning a given indication do not permit us to conclude that either of these instruments is superior to the other from the standpoint of efficacy. However, the degree of precision offered by the gamma knife permits the treatment of lesions that are no more than 2 mm in size and which touch vital structures, such as the cranial nerves, optic chiasma and brainstem, without (theoretically) causing any injury to healthy tissues.

SRS in the Québec context

- Given the current knowledge about the clinical, economic, technical and epidemiological aspects and given the need to adequately fulfill the offer of SRS services and to adequately meet research needs, the Agency recommends that a specialized radiosurgery centre with a gamma knife be created at a university hospital. Where this specialized centre will be set up will depend on geographical and/or functional accessibility and well-established service pathways.

- The institution chosen must have the necessary logistical wherewithal (structural and professional) needed to perform this type of treatment. The mandatory presence of a multidisciplinary team (neurosurgeon, neuroradiologist, radiation therapist, radiophysicist, paramedical personnel), the need to provide continuous patient management quality and the need to promote the acquisition of new professional skills clearly warrant creating the centre at a university hospital.

These conclusions are conditional upon the technological evolution of the various types of instruments and the emerging therapies (fractionated stereotactic radiotherapy) at the time when the decision to create a centre providing SRS services is made.

Angioma: A malformational (dysgenetic angioma) or acquired (neoplastic angioma) vascular tumor of the cells that line blood (hemangioma) or lymph (lymphangioma) capillaries.

Astrocytoma: A benign glial tumor whose malignant transformation is very frequent in certain parts of the central nervous system.

Bragg's peak: The distribution of the radiation dose along the protons' trajectory (proton therapy). The dose delivered increases as the particles' energy decreases.

Brain metastasis: The occurrence, in the brain, of cancer cells that have spread from a distant primary tumor outside the brain.

Craniopharyngioma: A suprasellar pituitary tumor arising from Rathke's pouch. It is sometimes cystic and lined with a malpighian epithelium.

Cyclotron: A circular heavy-particle accelerator that uses a fixed magnetic field and an electric field of constant frequency.

Ependymoma: A tumor of the glioma group that arises from ependymal cells during the first two decades of life. It usually occurs in the posterior fossa and spinal cord and generally has a benign prognosis.

External radiotherapy: The therapeutic use of x-rays emitted by an external source (roentgenotherapy).

Fractionated: Refers to radiotherapy administered in doses spread out over several sessions. In stereotactic radiosurgery, treatment is administered in a single dose.

Gamma knife: A radiosurgery device that uses, as its radiation source, a beam of gamma rays of microscopic diameter whose convergent application destroys the diseased area. Leksell Gamma Knife® is a registered trademark of stereotactic radiosurgery equipment using cobalt-60 sources.

Glial: Relating to the neuroglia.

Glioblastoma: A malignant brain tumor composed of a proliferation of undifferentiated glial cells.

Glioma: Any tumor that has developed from the adult or embryonic neuroglia. Includes all primary tumors of the brain and spinal cord (astrocytoma, ependymoma, neurocytoma).

Hamartoma: A benign pseudotumor characterized by an excessive quantity or abnormal arrangement, in a tissue or an organ, of cells that normally occur there.

Hemangioblastoma: A type of angioma (vascular tumor) specific to the central nervous system. It usually occurs in the posterior cranial fossa and is characterized by the presence of nerve tissue between the vascular bundles (cerebellum, spinal cord, etc.). Called also *angioblastoma*.

Hemangioma: A true angioma, composed of newly formed, dilated vessels.

Isocentre: A point located at the intersection of the central axis of a beam and the axis of the rotating or curved movement of the x-ray tube.

Karnofsky's index: A score, expressed as a percentage, defining a patient's clinical and functional status (commonly used in terminally ill patients).

Linear accelerator (or **linac**): An instrument that emits electrons of very high kinetic energy by means of an electric field. It is said to be adapted (or modified) when accessories are added for the purpose of using the instrument in stereotactic radiosurgery or dedicated when it is manufactured to be used exclusively in stereotactic radiosurgery.

Medulloblastoma: A radiosensitive tumor that usually occurs in children, most often in the vermis.

Meninges: The set of three membranes that completely envelop the brain and spinal cord. They are, from the outside in, the dura mater (pachymeninx), arachnoid and pia mater, the latter two being, respectively, the parietal and visceral layers of the leptomeninges and between which cerebrospinal fluid flows.

Meningioma: A benign intracranial or intraspinal tumor arising from the meninges.

Multileaf collimator: A collimator in which the position of each leaf is calculated by computer. Each leaf is used to precisely guide a beam of rays to the lesion and to prevent irradiation of the healthy, adjacent tissues. There are many different models of linear accelerators with multileaf collimators.

Neurinoma: A benign tumor arising from the sheath of Schwann of the peripheral nerves or spinal roots, usually occurring on the auditory nerve. Called also *schwannoma*.

Neuroglia: The supporting tissue of the nervous system. It consists of a network of highly branched cells (glial or neuroglial cells). Called also *glia*.

Percentage depth dose: The ratio, expressed as a percentage, of the dose absorbed at a given depth in the body to the dose absorbed at a reference point on the axis of radiation.

Pituitary adenoma: A benign tumor of the pituitary gland; it is implicated in many different conditions, such as acromegaly and Cushing's syndrome.

Pituitary tumors: Tumors of the pituitary gland, including secreting pituitary adenomas and craniopharyngiomas.

Relative biological efficacy: A factor used by some authors to compare various types of radiotherapy.

Schwannoma: See *neurinoma*.

Stereotactic radiosurgery: A treatment technique developed by Leksell in which the brain is irradiated with tiny beams under stereotactic conditions and which involves exposing a lesion of small volume, determined by three-dimensional imaging, to a single high dose of ionizing rays.

Stereotactic radiotherapy: A type of fractionated radiotherapy performed under stereotactic conditions using a frame whose position can be changed.