Comparing the cost-effectiveness of a new hospital-based health technology in a low-middle-income country (Vietnam) with a high-income country (Germany)

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SUMMARY

Background:

The rapid acceleration of medical technology development significantly contributes to the achievement of health service performance, the quality improvement of health care for the population. On the other hand, it leads to an increase of medical costs, which accounts for at least half of all medical cost growth, nowadays. New health technology (NHT) adoption is therefore a clearly complex process. It is a process that is typically different between high-income- and low-middle-income countries, as the diffusion of NHT in low-middle-income countries is far less and lagged far behind than in the high-income countries. The diffusion of NHT never fully reaches the demand of eligible population in low-middle-income countries. An example is the use of two treatment methodologies, the long established surgical resection (SR) and the newer stereotactic radiosurgery (SRS), in the treatment of brain metastasis. Whereas SRS has been used for a relatively long time and previously defined more cost-effective than SR in developed countries, it has just started to be adopted and a lack of evidence-based information on the health technology assessment of SRS versus SR in developing countries. Generally, the results of health technology assessment and cost-effectiveness analysis for particular different health technologies are relatively well defined in high-income countries, but little is known about these in low- and low-middle-income countries. There is a shortage of methodological guidance to adjust cost-effectiveness results from one to another country setting. This raises the questions of whether the NHT of SRS is or is not more cost-effective than SR in the contexts of a low-middle-income country and of a high-income country; and of what factors systematically determine differences in the cost-effectiveness between these two countries.

Main objective:

To compare the cost-effectiveness of a new hospital-based health technology of a low-middle-income country with a high-income country, *by taking a case study of the two treatment modalities of SRS versus SR in the treatment of brain metastasis in Vietnam, which represents a low-middle-income country, and Germany, which represents a high-income country.*

Specific objectives

(1) To analyse for SRS and SR which is more cost-effective in the treatment of brain metastases in the context of Vietnam and of Germany, from the perspective of health insurance

(2) To find the factors which systematically determine the difference in cost-effectiveness between high- (Germany) and low-middle-income countries (Vietnam)

Methods:

A combination of primary data methods from population-based registration, administration, hospital-based, patient level data; and secondary data methods from academic and grey literature for the research in multiple fields of demography, epidemiology, clinical practice, patient characteristics, health services and health finance was used to assess the adoption of the NHT of SRS versus the standard treatment technology of SR in the treatment of brain metastasis.

Results:

From the perspective of health insurance, SRS is clearly dominant to SR in the treatment of brain metastasis in the high-income country of Germany, while there is high uncertainty regarding cost-effectiveness between these two methodologies in the low-middle-income country of Vietnam.

The repeated treatment of the new technology of SRS for the patient with reoccurrence of brain tumors in the allowed clinical conditions significantly influences the higher cost-effectiveness of SRS comparing to surgical resection, which was more feasibly performed in the high-income rather than low-middle-income countries.

The difference between the results of the cost-effectiveness of SRS versus SR in the treatment of brain metastatic in these two countries was affected by different factors which include:

(1) Basic demography whereas it is an aging population in Germany on the contrary to the relatively young population in Vietnam.

(2) Epidemiology of brain metastasis is rather different between two countries in the cancer incidence rate (it is lower in Vietnam than in Germany), cancer pattern (more frequent occurrence of primary tumor sites which act as main sources of brain metastasis in Vietnam than in Germany). However, both countries have high demand to the NHT of SRS for the treatment of brain metastasis.

(3) Clinical practice whereas Germany has more standardized clinical protocol/practice; more strict quality accreditation; and more available medical evidence-based information than these in Vietnam.

(4) Health services which are more available in Germany, where the regulation on NHT diffusion is transparent and harmonized in comparison to the market driven decision making of NHT diffusion in Vietnam. In addition, NHT services are relatively sufficient to respond to the demand as clinically required in Germany, while that is rather limited to the ability to pay of patient on the access to health technology services in Vietnam. This difference is mainly determined by the coverage of health insurance and the rate of copayment for the NHT services between two countries.

(5) Patient characteristics which includes the ability to access new technology of each patient, and their adherence to the treatment, regular check-up during the follow-up period which is found more strict for the patient in Germany comparing to the patient in Vietnam.

(6) Health finance, it is totally different between two countries, where German hospital get reimbursement by DRG scheme; the cost of NHT is under certain circumstances added to the price paid by public payment; there are sufficient resources in the investment of NHT which is contrary to Vietnam, where the reimbursement of the health technology service is by fee-for-service scheme, and the NHT investment cost is responsible more by Government and out-of-pocket payment of the patient, giving shortage of resources for investment of new health technology.

Conclusion:

The cost-effectiveness of an NHT of SRS versus SR in the treatment of brain metastasis in a low-middle income country (Vietnam) is lower than that of a high-income country (Germany).

To be better advised for the decision making regarding NHT adoption, each country needs to conduct its own study of cost-effectiveness assessment of an NHT, in which an assessment of the cost-effectiveness of an NHT is examined in the broad context of demography, epidemiology, clinical practice, patient characteristics, health services and health finance.

It is suggested that the low-middle-income country (Vietnam) strengthens the role of the coordinator in the medical technology adoption, rapidly increases the coverage of health insurance to cover the costs of treatment, move towards a prospective payment system based on DRG, establishes more standard protocol and quality control of clinical practices, and improve the health care knowledge and awareness of the population.

ZUSAMMENFASSUNG

Hintergrund:

Die rasante Beschleunigung der Medizintechnik-Entwicklung trägt erheblich zum Erfolg der Leistungsfähigkeit der Gesundheitsdienste bei, waseine Qualitätsverbesserung für die Bevölkerung zur Folge hat. Auf der anderen Seite wird heute mehr als die Hälfte des gesamten Wachstums der Behandlungskosten durch den Kostenanstieg dieser neuen Technologien verursacht. Die Einführung neuer Gesundheitstechnologien (NHT) ist daher eindeutig ein vielschichtiger Prozess. Dieser Prozess verläufttypischerweise zwischen einkommensstarken Ländern und Ländern niedriger mittlerer Einkommensstufe sehr unterschiedlich, da die Verbreitung neuer Gesundheitstechnologien in letzteren geringer ist und verzögert stattfindet. Der Bedarf derBevölkerungwird deswegen nie völlig gedeckt.

Der Vergleich zwischen der schon lange etablierten chirurgischen Resektion (SR) und der neuerenstereotaktischen Radiochirurgie (SRS) bei der Behandlung von Hirnmetastasen ist ein Beispiel dafür. Stereotaktische Radiochirurgie wird in Industrieländern schon seit längerer Zeit als die kostengünstigere Option angewendet. In Entwicklungsländern hingegen wird gerade erst damit begonnen, stereotaktische Radiochirurgie durchzuführen, und es mangelt noch immer an evidenzbasierten Technologiebewertungen SRS und SR vergleichend. Generell sind Gesundheitstechnologiebewertungen und Kosteneffektivitätsanalysen in einkommensstarken Ländern relativ gut etabliert. Dagegen ist in Ländern der niedrigen oder niedrigen mittleren Einkommensstufe nur wenig darüber bekannt.Methodologische Leitlinien fehlen, die die Übertragung von Wirtschaftlichkeitsanalysen länderübergreifend ermöglichten. Daher stellt sich die Frage, ob stereotaktische Radiochirurgiein Ländern der niedrigen mittleren Einkommensstufe tatsächlich wirtschaftlicher ist als chirurgische Resektion.Zu beantworten wäre ferner welche Faktoren die Unterschiede der Wirtschaftlichkeit der hier genannten Ländergruppensystematisch bestimmen.

Hauptziel:

Hauptziel der Arbeit war die Wirtschaftlichkeit einer neuen, krankenhausbasierten Gesundheitstechnologiein einem Land der niedrigen mittleren Einkommensstufe

(Vietnam) mit der eines einkommensstarken Landes (Deutschland) zu vergleichen. *Zu diesem Zweck wurden zwei Behandlungsstrategien von Hirnmetastasen (SRS und SR) in Vietnam verglichen.*

SpezifischeZiele:

(1) Die Analyse der Wirtschaftlichkeit von SRS und SR bei der Behandlung von Hirnmetastasen in Vietnam und Deutschland aus der Perspektive der Krankenversicherung.
(2) Faktoren zu identifizieren, die die Wirtschaftlichkeitsunterschiede zwischen einkommensstarken (Deutschland) und Ländern der mittleren niedrigen Einkommensstufe (Vietnam) systematisch bestimmen.

Methoden:

Primärdaten aus Bevölkerungsregistern, Verwaltungs-, Krankenhaus- und Patientendaten wurden erfasst. Sekundärdaten wie z.B. akademische Forschungsliteratur und unveröffentlichte Berichte („graue Literatur") unterschiedlicher Interessensfelder wie Demografie, Epidemiologie, klinische Praxis, Patientencharakteristika, Gesundheitswesen und Gesundheitsfinanzierung wurden genutzt, um die Einführung von SRS als neue Gesundheitstechnologie im Vergleich mit der Standardtechnologie (SR) in der Behandlung von Hirnmetastasen einzuschätzen.

Ergebnisse:

Aus Perspektive der Gesundheitsversicherung ist in dem einkommensstarken Land, Deutschland, SRS SR überlegen. In Vietnam als Land der niedrigen mittleren Einkommensstufe gibt es dagegen große Unsicherheit über die Kosteneffektivität dieser zwei Behandlungsarten.

Die erforderliche mehrfacheSRS-Behandlung bei rezidivierenden Hirntumoren in den erlaubten klinischen Konditionen beeinflusst die höhere SRS-Kosteneffektivität signifikant im Vergleich zur chirurgischen Resektion, welche in den einkommensstarken Ländern eher durchführbar ist als in Ländern der mittleren niedrigen Einkommensstufe.

Der Unterschied in der Kosteneffektivität von SRS im Vergleich zu SR in diesen beiden Ländern wurde von unterschiedlichen Faktoren hervorgerufen:

(1) Demographie, denn während Deutschland eine alternde Bevölkerung aufweist, besitzt Vietnam eine relativ junge Bevölkerung.

(2) Epidemiologie, denndie Inzidenz von Gehirnmetastasen ist in Vietnam geringer als in Deutschland, wobei Primärtumoren, die Gehirnmetastasen bilden, häufiger sind. Beide Länder haben dennoch einen hohen SRS-Bedarf für die Behandlung von Gehirnmetastasen.

(3) Klinische Praxis, denn Deutschland verfügt im Vergleich zu Vietnam über mehr standardisierte klinische Protokolle, Qualitätssicherungsmechanismen und evidenzbasierte Informationen.

(4) Gesundheitsdienstleistungen, denn in Deutschland ist die Regulation der NHT-Diffusion transparenter und harmonisierter als die ausschließlich marktgesteuerte in Vietnam. Außerdem sind NHT-Leistungen in Deutschland relativ ausreichend, um den klinischen Bedarf zu decken.In Vietnam hingegen ist der Zugang zu Gesundheitstechnologiedienstleistungen von der begrenzten Zahlungsfähigkeit der Patienten bedingt. Als Ursachen können hier hauptsächlich der abweichende Versicherungsschutz und unterschiedliche Zuzahlungen in den zwei Ländern genannt werden.

(5) Patientencharakteristika, wie dieFähigkeit neue Technologienabzurufen, Therapietreue und die Regelmäßigkeit der Nachkontrolluntersuchungen.Letztere wird für deutsche Patienten strenger gehandhabt.

(6) Gesundheitsfinanzierung, die in beiden Ländern völlig unterschiedlich funktioniert. Ein deutsches Krankenhaus wird per DRGs vergütetund die Kosten von NHT werden unter bestimmten Umständen dem erstatteten Preishinzugefügt; es existieren ausreichend Mittel bezüglich NHT-Investitionen.In Vietnam werden Gesundheitstechnologieleistungen per Fee-for-service vergütet, und NHT-Investitionskosten belasten die öffentliche Hand sowie diePatientenauslagen.Dadurch wird ein Ressourcenmangel für NHT-Investitionen verursacht.

Schlussfolgerung/ Fazit

Im Fall von Gehirnmetastasen ist die Kosteneffektivität der stereotaktischen Radiochirurgie (SRS) im Vergleich zur chirurgischen Resektion (SR) niedriger für ein Land der niedrigen mittleren Einkommensstufe (Vietnam) als für ein einkommensstarkes Land (Deutschland).

Um Beschlussfassungen bei der Einführung neuer Gesundheitstechnologien (NHT) besser zu informieren sollte jedes Land eigene Kosteneffektivitätsstudien durchführen, die Demographie, Epidemiologie, klinische Praxis, Patientencharakteristika, Gesundheitswesen und Gesundheitsfinanzierung landesspezifisch in Betracht ziehen.

Für Länder der niedrigen mittleren Einkommensstufe (hier Vietnam) wird vorgeschlagen, die Rolle des Koordinators in der Einführung von Gesundheitstechnologien zu stärken, den Krankenversicherungsschutz zügig zu erweitern, damit Behandlungskosten gedeckt werden, den Übergang zu einer auf DRGs basierenden prospektiven Vergütung von Krankenhausleistungen anzustreben, „Best-Practice“-Leitfäden und Qualitätssicherungsmechanismen für die klinische Praxis zu etablieren sowie die Gesundheitsversorgungskenntnisse und Bewusstsein der Bevölkerung zu verbessern.

ABBREVIATION

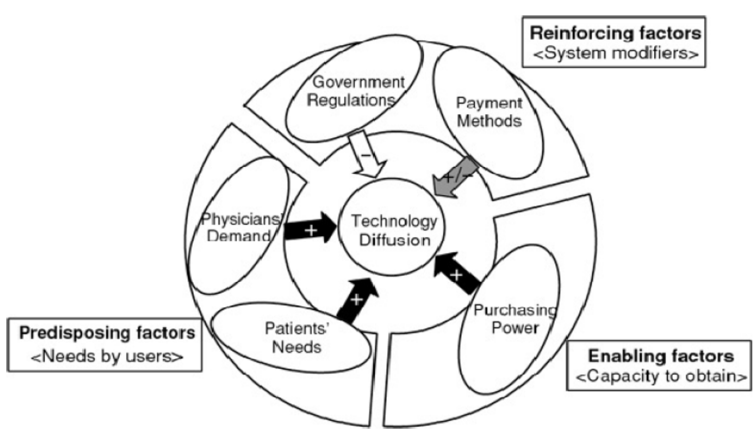
AFC	Actual full costs
ASR	Age Standardized Rate
AUDIT	Alcohol Use Disorders Identification Test
BQS	Federal Office for Quality Assurance
CBA	Cost-benefit analysis
CBMHP	Community-based mental health program
CBS	Community based service
CEA	Cost-effectiveness analysis
CEAC	Cost-effective acceptability curve
CHE	Catastrophic health expenditure
CI	Confidence Interval
CNS	Central nervous system
CUA	Cost-utility analysis
CT-Scanner	Computerized Tomography-Scanner
DAAD	German Academic Exchange Service
DGS	Direct government support
DirPC	Direct provider cost
DMP	Disease management program
DRG	Disease related group
ECOG	Eastern Cooperative Oncology Group
EU	European
FFS	Fee-for-service
G-BA	Joint Federal Committee
GCS	Glasgow Coma Scale
GDP	Gross domestic product
G-DRG	German-Disease related group
GKS	Gamma knife surgery
GKV	Statutory health insurance
GP	General Practitioner
HCE	Health care expenditures
HCFP	Health care for the poor
HR	Hazard Ratio
HTA	Health technology assessment
ICD	International Classification of Disease
ICD–O	International Classification of Disease - Oncology
ICER	Incremental cost effective ratio
InpBD	Inpatient bed day
IntInpBD	Internal medicine inpatient bed day
IntInpC	Internal medicine inpatient cases
KPS	Karnofsky performance status
KTQ	Quality in Hospitals
LOS	Length of stay
LYS	Life year saved
MHS	Mental health services
MOET	Ministry of Education and Training Vietnam
MOH	Ministry of Health
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	North East
NHT	New health technology
NHTP	National Health Target Program
NSCLC	Non- small cell lung cancer
NW	North West
OOP	Out of pocket
OP	Operation
OS	Overall survival
OutPV	Outpatient visit
PFS	Progression-free survival
PPP	Purchasing power parity
PSM	Propensity score matching
PTS	Primary tumor site
QALY	Quality Adjusted Life Year
QEP	Quality and Development for Practice
ROC	Receiver operating characteristic
RPA	Recursive Partitioning Analysis
RTOG	Radiation Therapy Oncology Group
SBM	Solitary brain metastases
SD	Standardized difference
SE	South East
SHI	Statutory health insurance (SHI)
SoHI	Social health insurance
SR	Surgical resection
SRS	Stereotactic radio-surgery
SurInpBD	Surgical inpatient bed day
SurInpC	Surgical inpatient cases
SW	South West
TPP	Third party payments
UF	User fee
UK	United Kingdom
USA	United States of America
VND	Vietnamese dong
WBRT	Whole-Brain Radiotherapy
WHO	World Health Organization
WIdO	Wissenschaftliches Institut der AOK

PART I. INTRODUCTION

Explosion of new health technology

Keeping pace with general technological innovation, the development of medical technologies has been rapidly accelerated in recent years with breakthroughs in the different areas of antiviral, biotechnology, diagnostic imaging, molecular diagnostics, organ and tissue replacement, surgical techniques, wound care, etc. In the field of diagnostic imaging, since the discovery of X-Ray in 1895 there had been only one imaging device to support diagnosis for nearly a century. Then, following the discovery of ultrasound in 1960s, a series of diagnostic imaging devices were developed: Single-photon emission computed tomography in 1963, the CT-Scanner in 1972, MRI in 1973, Digital Mammography/Virtual Colonoscopy in 2000, Positron Emission Tomography-Computerized Tomography in 2001, etc. (Goodman, 2004; Cappellaro *et al*., 2011). Similarly, in the neurosurgical techniques, the transspenoidal surgery in the pituitary resection is a really complex evolution. Before the invention of intra-operative image technology, many different attempts had been made to resect the pituitary, such as the transcranial and temporal approaches in 1893, infranasal approach in 1909, sublabial approach in 1910, transethmoidal approach via the medial orbit in 1912. Then, in 1958, the intra-operative image intensification and fluoroscopy was introduced that allowed one to intra-operatively visualize the deep view and position of surgical intruments. It opened a period of subsequent innovations in intra-operative image guidance in pituitary and neurosurgery in general, such as the microscope for pituitary surgery in 1967; the endoscope as an addition to the microscope in 1977, that used intra-operative CT and MRI images to offer anatomical landmark visualization; and further steps which included the development of "framed stereotaxy", then "frameless stereotaxy" and computer monitoring in the 1990s, and the explosion of frameless-guidance systems which enable the precise guidance of surgical instruments with minimal invasion (Gandhi *et al*., 2009). In the field of neurosurgical management, there are non-invasive surgery approaches known as radiation surgery, one of which, SRS, was developed in 1968. SRS is a technology with a highly conformal form of radiation therapy that delivers a high dose in a single treatment to the target volume while sparing adjacent normal tissues (Hazard *et al*., 2005), and is used to treat intracranial lesions and vascular malformations as an addition or replacement to WBRT and SR. SRS has a powerful local treatment modality especially for small, multiple and deep metastases. As a result of its less invasive nature, ability to achieve the optimal treatment in different complex conditions and apparent effectiveness in a relatively short time, SRS has emerged as an important non-invasive option in the neurosurgery against brain metastasis and as an alternative form of local therapy. It has been chosen with increasing frequency over surgical resection (Smith and Lee, 2007; Ranasinghe and Sheehan, 2007). It was even suggested that SRS would supplant craniotomy as the new gold standard (Flickinger and Kondziolka, 1996).

The development of NHT significantly contributes to the achievement of health service performance, enables medical doctors to treat what was previously untreatable and improves the quality of health care of the population in terms of both survival rates and quality of life. On the other hand, the technological changes lead to increases in medical costs, which account for at least half of all medical cost growth nowadays (WHO, 2000; Bloor and Maynard, 2006; Cutler, 2007; Elias *et al*., 2008; Cappellaro *et al*., 2011;); and the adoption, diffusion of new health technologies has become clearly a complex process, influenced by many factors which can or do constrain the adoption process. Those factors consist of the motivations of physicians and administrators to adopt a particular treatment; the financing and reimbursement system; regulations; the culture and structure of the relevant organizations; training, knowledge, and attitudes of physicians; and patients' backgrounds, needs, and preferences (Rydén *et al*., 2004; Oh *et al*., 2005; Nandakumar *et al*., 2009). The financing system includes the total health expenditure per capita (to reflect the purchasing power), and the method of payment, for instance, the diffusion of medical technology innovation can be slowed down by the fixed global-budget schemes and enhanced by the case-fee payments and DRG system (Slade and Anderson, 2001; Grilli *et al*., 2007; Chang and Hung, 2008; Cappellaro *et al*., 2009) (Figure 1).



Source: from (Oh et al., 2005)

Figure 1. Model of technology diffusion determinants

Health technology assessment

Technology assessment was introduced in 1965 by the Committee on Science and Astronautics of the US House of Representatives. Initially, HTA had been focused on the safety, effectiveness, cost and other related issues of a new technology (Goodman, 2004), driven by two common concerns among health policy makers/analysts and clinicians. Firstly, new, 'health – tech' medical interventions need be assessed for their clinical effectiveness. Secondly, there was much concern that many existing medical practices had not been adequately assessed for their clinical effectiveness (Oliver *et al.*, 2004). Furthermore, it was developed as the analytical process of gathering and summarizing information to provide evidence-based information in regard to the use of technology in health services in terms of the effectiveness, appropriateness and cost of technologies. It does this by asking four fundamental questions: does the technology work, for whom, at what cost, and how does it compare with alternatives (Goodman, 2004)? It is in fact not the only source of information, nor always the most important source. However, it can provide important evidence-based information for further steps in health technology adoption which may be converted into policy or policy advice (Stevens and Milne, 2004).

HTA consists of multiple methods which can be categorized into two groups. Primary data methods include original data collection from randomized controlled trials to case studies. Secondary or synthesis methods are called integrative methods that involve the combination of data or information from existing sources, ranging from quantitative, structural approaches like meta-analyses or systematic literature reviews to informal, unstructured literature reviews (Goodman, 2004; Nielsen *et al.*, 2008). HTA can be streamely catergorized into four main streams as policy analysis; evidence-based medicine (i.e. clinical epidemiology); health economic evaluation; social and humanistic sciences. Of which, the methodological frames for HTA are mainly based on evidence-based medicine and health economic evaluation (Kristensen *et al.*, 2008).

Recently, health economic evaluation is increasingly used to facilitate the allocation of scarce resources in the health sector. Despite important methodological developments since the 1960s, the basic concept of an economic evaluation in health care has not changed. It is defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences. Hence, its tasks are to identify, measure, value, and compare the costs and consequences of the alternatives being considered (Drummond *et al.*, 2005). The health economic evaluation can involve primary data and integrated methods to assess the relationship between costs and outcomes in order to interpret the value of a health care intervention (Goodman, 2004; Wonderling *et al.*, 2005). The viewpoint of the analysis is very important as a technology may look significantly better when considered from different viewpoints. The viewpoints consist of individual patients, specific institutions, targeted groups, the ministry of health, and the community or society at large (Drummond *et al.*, 2005). Of which, health economic evaluation in the HTA is generally concerned more about the socioeconomic consequences of the health technology's influence on the patient with regard to their contribution to labor market; the requirement of disability compensation and other macroeconomic factors (Kristensen *et al.*, 2008). But in the high-income countries, the perspective of health insurance is nowadays more focused on the consequences of new and better health technology adoption that may increase the demand for care and health insurance to cover increasing costs (Nandakumar *et al.*, 2009; Cappellaro *et al.*, 2011).

Health economic evaluation includes three basic methods: CEA, CUA and CBA. They are are important advances, focusing on the costs and quantification of the additional health benefit which is derived from an intervention. All three types of economic evaluation measure resources expended in monetary terms (costs), and the difference lies in how improved clinical incomes (consequences) can be measured. CEA most often measures clinically relevant outcomes in directly quantifiable, objectively observed health outcomes such as average number of life years gained or morbid events averted. CUA goes further and incorporates the patient themselves through reported quality of life or utility values (subject’s stated preferences for different health states) into this measurement. CBA requires program consequences to be valued in monetary units, then makes a direct comparison of the program’s incremental cost with its incremental consequences in commensurate units of measurement (Tella *et al.*, 2003; Drummond *et al.*, 2005-chapter 2). They are all designed to compare a given intervention with other interventions or usual care in a specific patient population, meaning that CEA, CUA, CBA are used to evaluate an intervention that produces better health outcomes at a greater cost, in other words, they are ways to analyze the tradeoff between additional resources and expanded, improved clinical outcomes.

CEA is the most useful and widely used technique of economic evaluation, and within a given budget it is one of the most common measures supporting the decision-making process among various options of treatments or health programs, especially in developed countries. CEA is one form of full economic evaluation, concerned with the assessment of the effect and cost of treatments, resulting in a unit of effect gained in a natural unit of health such as lives gained, relative to a cost of different treatments or health interventions which enables a comparison of different treatments or different magnitudes of effect derived from alternative programs within a given field (Wonderling *et al.*, 2005; Grilli *et al.*, 2007; Chang and Hung, 2008; RKI, 2008). It is not only a criterion for deciding how to allocate resources but is also important in determining whether it is worthwhile to spend the money on the treatment or health interventions or whether it represents a neglected opportunity, and it even shows the ways to redirect resources to achieve better results (Jamison and Breman, 2006; Wonderling *et al.*, 2005; Drummond *et al.*, 2005-chapter 5). A subset of CEA called CUA is an economic evaluation where the outcomes are measured in a health unit, which capture not just the quantitative but also the qualitative aspects of the outcome, such as the extension of the length of life and changes in the quality of life, with the most commonly used measure the QALY. The comparison of different interventions is measured by ICER which is calculated through the number of patients who need to be given treatment to achieve an extra unit of effectiveness and the incremental cost of treating each of those patients, or to achieve a unit of effectiveness by using a particular treatment rather than the standard. So, if the measure of effectiveness is the probability of surviving, then the ICER is the cost of saving a life/preventing a death; and if the measure of effectiveness is the mean of survival or the mean of quality-adjusted survival, then the ICER is the cost of achieving a life year or QALY gained. So, the ICER is essentially considered the cost of an additional unit of effectiveness, to decide whether a particular treatment is adopted over the standard treatment (Willan and Briggs, 2006).

CEA enables a comparison of different treatments or programmes in a given field. However, the same treatments or programmes in different setting countries may result in different cost-effectiveness. The naïve interpretation or unthinking use of cost-effectiveness results from these countries in other country settings should be cautious (Bryan and Brown, 1998; Goeree *et al.*, 2007). Some key factors have been found to affect the variation of cost-effectiveness results across countries. These are related to demography and epidemiology of diseases such as the age structure of the population and the incidence of various diseases; health care service and resources; clinical practice variation; overall health care system such as incentives to health care providers; payment system, such as fee-for-service system, or DRGs, or global budget, etc; and prices or costs of health care resources (Drummond *et al.*, 2005). All information should be considered in terms of transferability, generalizability, portability and extrapolation in the adjustment or interpretation from one to another country setting. Before the 1990s there was no study concerning the effect of cross-national differences in the cost-effectiveness of health technologies, since then a variety of methods have been introduced to identify and adjust the cost-effective results to country-specific differences (such as the approach of matching trial data with routine data of national databases). However, the barriers to cost-effective result extrapolation from one to another still exist, and there is a significant lack of methodological guidance, and multinational studies of cost-effectiveness have been continuously advised to play a crucial role for the decision maker in different countries and for the development of cross-national adaptation methods (Drummond *et al.*, 1992; Hutton and Baltussen, 2005; Reinhold *et al.*, 2010).

Diffusion of new health technology in high- and low-middle-income countries

The diffusion of new technology in low-middle-income countries is less than in the high-income countries, for example, in the area of technology of information and communication there is a much smaller proportion of the population using cell phones in Africa in comparison to the USA (6.5 and 84% of population, respectively) (Cheng, 2008). Similarly, in the health sector Hutubessy found that the total number of MRIs in proportion to the population in Asia region is quite small in comparison to most countries of the Organization for Economic Cooperation and Development (OCED) (Hutubessy *et al.*, 2002). Many medical technologies are very complicated, especially those that may called ‘big ticket medical technologies’, suitable only in high-income countries and are not properly designed for low and low-middle-income countries where a shortage of trained staff exists (WHO, 2010b). In addition, with a lower GDP and a much smaller health care expenditure per capita, it accounts for much higher proportion of HCE for the investment of medical technology in the low- and low-middle-income countries comparing to high-income countries. It creates a paradox as there is subsequently less HCE funding available for the basic requirements of preventive medicine or primary care in low- and low-middle-income countries. Therefore, those countries do not offer large financial incentives for investment in advanced health technologies, and the complicated health technologies tend to be more concentrated in high-income countries (Lazaro *et al.*, 1994; Hutubessy *et al.*, 2002; Elias *et al.*, 2008). Moreover, in high-income countries, the regulation of health technology adoption by law, payment or restriction on services is much more transparent and harmonized (Silva and Viana, 2010; Rydén *et al.*, 2004). In poor countries on the other hand, the decisions about health technology adoption are primarily made by administrators of individual hospitals and clinics and strongly influenced by physicians and sales representatives of the medical industry (Silva and Viana, 2010). In addition to the low purchasing power to adopt costly or even low-cost technologies on their own, such constraints make the diffusion of health technology in low- and low-middle-income countries slower and at a lower level of overall penetration compared to high-income countries. It never fully reaches the eligible population (Nandakumar *et al.*, 2009).

Indicators	Vietnam	Germany
Area (km^2)	331,051	357,112
Population (million)	86,024	82,002
Economy status	Low-middle Income	High-income
	Agricultural (employs 48% working age people)	Industrial
GDP per capita (PPP US$)	2,790	36,850

Table 1. General information of Vietnam and Germany (in 2008)

Vietnam (located in south east Asia) and Germany (situated in central Europe) have many common features such as area (Germany has an area of 357,112 km^2 and Vietnam 331,051 km^2); number of inhabitants (82,002 and 86,024 million habitants, respectively) (GSO, 2009-In: Population and labor; Statistisches Bundesamt, 2010); historical and political power features, as before the reunification of each, both countries had two isolated parts, one of which was governed by a communist party. However, since the reunification joining East and West Germany and North and South Vietnam, Germany has been a federal republic while Vietnam is a socialist republic which continuously maintains the communist party. Germany has been a developed country; a member of the group of leading industrial countries (G8 group); a main exporter of cars, chemicals, steel, iron manufacturing and manufactured goods; and has a GDP per capital equal to US$36,850. Vietnam, following a shift from a highly-centralized planned economy to a socialist-oriented market economy, is now the second fastest growing economy in Asia but it is still classified as a low-middle-income country and ranks at 161 in the World (with respect to the GDP per capita, it is equal to PPP-US$2,790) (World Bank, 2011). The majority of the population depends on agriculture for subsistence, a sector which employs 48% of people of working age, the highest proportion among different economic sectors, and accounts for 16.1% of GDP (GSO, 2009-In: Population and labor) (Table 1). However, within this thesis, I do not intend to find out the causes of these differences. The similarities and differences within the health care services, especially the cost-effectiveness of NHT adoption between these two countries will be the focus of this research.

Aims of this thesis

The results of HTA in generally and CEA in particularly of different health technologies are relatively well defined in high-income countries. Unfortunately, little has been known about that of low- and low-middle-income countries (James, 2004; Silva and Viana, 2010). Additionally, there is a shortage of methodological guidance to adjust cost-effectiveness results from one to another country setting and multinational studies on cost-effectiveness of NHT is advised to play a crucial role for the health technology adoption in a country and the development of the cross-country adaptation methods. Specifically, looking at the two technologies of SRS versus SR in the treatment of brain metastasis in Vietnam and Germany, whereas SRS has a relatively long adoption in Germany (since the early 1990s, as one of leading European countries in using Gamma Knife) but it has just started in the adoption curve in Vietnam (started in 2005). This raises the questions of whether the NHT of SRS is or is not more cost-effective than SR in the contexts of a low-middle-income country and of a high-income country; and of what factors systematically determine differences in the cost-effectiveness between these two countries.

Main objective

To compare the cost-effectiveness of a new hospital-based health technology of a low-middle-income country with a high-income country, *by taking a case study of the two treatment modalities of stereotactic radio-surgery versus surgical resection in the treatment of brain metastasis in Vietnam, which represents a low-middle-income country, and Germany, which represents a high-income country.*

Specific objectives

(1) To analyse for SRS and SR which is more cost-effective in the treatment of brain metastases in the context of Vietnam and of Germany, from the perspective of health insurance

(2) To find the factors systematically determine the difference in cost-effectiveness between high- (Germany) and low-middle-income countries (Vietnam)

Outline of this thesis

The thesis is comprised of five main parts: Introduction (part I); Epidemiology and therapeutic management of brain metastasis (part II, which consists of the first three chapters: 1, 2, 3); Health care services and hospital finance (part III, which consists of three chapters: 4, 5, 6); Cost-effectiveness of a new hospital-based health technology in a low-middle-income country and high-income country (part IV, which consists of two chapters: 7, 8); and the last part which contains a discussion and conclusion (part V). Six of those eight chapters have been included in scientific manuscripts (except chapter 2 and 6).

Part I has briefly introduced the fast acceleration of NHT and its diffusion in different setting of high-income and low-middle-income countries, the need for HTA and basic methodologies of health economic evaluation to be used in HTA. Part II provides the current situation of cancer diseases and its trend over the last decades in Vietnam, then brain metastasis will be discussed in detail in terms of its epidemiology, clinical aspects, factors which predict the survival of a patient with brain metastasis and current therapeutic management approaches for brain metastasis. Part III describes the health care services and finance of the two countries, Vietnam and Germany, and how do they respond to the health care demands of the populations, and what are the challenges for the different health care systems and health care finance (focusing more on hospital finance). Part IV consists of two original pieces of research about the same disease of brain metastases and the same therapeutic management approaches of SRS and SR. These two pieces of research provide the results in regard to the cost-effectiveness of SRS versus SR in the treatment of brain metastasis in Vietnam and in Germany. The thesis will end with a discussion and conclusion (part V), which is a combination of all three main parts (II, III, IV), in order to answer the main study questions.

PART II. EPIDEMIOLOGY AND THERAPEUTIC MANAGEMENT OF BRAIN METASTASIS

Chapter 1. Temporal trends of cancer incidence in Vietnam, 1993-2007

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Abstract

Purpose: There is a lack of an overview of overall and site-specific cancer incidence time trends in Vietnam, especially for the time after the year 2000. This paper aims at describing the development of cancer incidence for some cancer sites during 1993-2007.

Methods: The Age Standardized Rate (ASR) of cancer incidence data from population based cancer registries of Hanoi, Ho Chi Minh and Cantho cities were used to analyze temporary trends of cancer incidence by site, age and sex group.

Results: The ASR of cancer incidence increased from $151.13/10^5$ in the period 1993-1998 to $160.00/10^5$ in the period 2006-2007 for males and from $106.75/10^5$ to $143.88/10^5$ for females. By age, the highest ASR was found in the group of 75+ years in males and between 70-74 years in females with an ASR of $1,109/10^5$ and $619/10^5$, respectively (2006-2007). Lung remains the most frequent site, followed by stomach and liver in males. In females, the most commonly affected site has shifted from cervix uteri in 1993-1998 to breast in recent years, followed by stomach and lung. Increasing trends were observed in incidence rate of 21 out of 34 cancer sites in males and 27 out of 35 cancer sites in females.

Conclusion: Cancer incidences in general have continuously increased during 1993-2007. More effort should be concentrated on developing and implementing tobacco-related cancer prevention interventions.

Keywords: Cancer, Trends, Incidence data, Vietnam…

Introduction

In Vietnam, cancer has been considered as an emerging major public health problem since the 1990s (Ngoan, 2006b). According to previously reported data from Hanoi Cancer Registry, the overall ASR of cancer incidence increased between 1990 and 1996 from $133/10^5$ to $166.5/10^5$ in males and from $91.7/10^5$ to $116.8/10^5$ in females (Anh & Duc, 2002). Despite that overall increase, the incidence rate of some cancer sites has not changed or even slightly decreased. For example in the period between 1990 and 2000, lung cancer incidence (ASR) declined in Vietnam from $30.4/10^5$ to $30.1/10^5$ in males and from $6.7/10^5$ to $6.6/10^5$ in females, although the magnitude of decrease varies among regions: in the area of Hanoi lung cancer incidence rate decreased from $34.9/10^5$ to $33.1/10^5$ in males and from $6.3/10^5$ to $5.8/10^5$ in females whereas in the area of Ho Chi Minh city the reductions were from $24.6/10^5$ to $23.7/10^5$ in males and from $6.8/10^5$ to $5.6/10^5$ in females. The reductions in the lung cancer incidence in both males and females have been attributed to the implementation of the National Tobacco Control Program, which started in 1989 (Ngoan, 2006a). Similarly, incidence of penis cancer has significantly decreased, it used to be frequently reported in the early case series within 1950s-1960s, later it was rarely seen (Joyeux & Nguyen, 1950; Luong & Pham, 1964; Anh *et al*., 1993).

The description of changes in cancer patterns over time is of vital interest in cancer control (Coleman *et al*., 1993). The study of time trends in cancer incidence is relevant for at least three reasons: to evaluate the population impact of interventions such as diagnostic and therapeutic modalities; to assess the potential influence of risk factors and to estimate needs raised by cancer burden to the public health care system (Doll, 1991; Franceschi *et al*., 1994; Geddes *et al*., 1994).

To date, the time trends of cancer incidence have not been studied in detail, with the exception of the reports cited above. There is a lack of an overview of overall and site-specific cancer incidence time trends, especially for the time after year 2000. The aim of this paper is to close this gap by describing the development of cancer incidence for some cancer sites during 1993-2007.

Material and methods

Data sources

We used data from population-based cancer registries accessed through the Globocan Database for data from Hanoi Cancer Registry (1993-1997), and Ho Chi Minh City Cancer Registry (1995-1998) (Globocan, 2002). The data from Hanoi Cancer Registry and Cantho Cancer Registry for two periods 2001-2004 and 2006-2007 were provided by the National Cancer Institute (NCI). All data were available in the form of ASRs for each primary cancer site.

Hanoi is the capital with the second largest population city in Vietnam (3,289,300 inhabitants) (MOH, 2009). It is located in the central part of former North Vietnam. Ho Chi Minh City is the largest city of Vietnam (6,347,000 inhabitants) (MOH, 2009) and it is located in the center of former South Vietnam. The cancer registries of these two areas were established around 20 years ago (Hanoi registry in 1987 and Ho Chi Minh registry in 1990). Unfortunately, the cancer registry of Ho Chi Minh City ceased in the beginning of 2000s, so data of this registry was available only for 1995-1998. Cantho is located in the South of Vietnam, as the heart of Mekong Delta, about 170 km South of Ho Chi Minh City (1,154,900 inhabitants) (MOH, 2009). Cantho Cancer Registry was established in 2001. Hence, we consider Cantho cancer registry is the best appropriate to replace the registry from Ho Chi Minh City, which was the only one existing in the South.

Methods

Trends in ASRs of cancer incidence were examined by site, sex and age at first cancer diagnosed from a pooled data of two registries in each time period, 1st period 1993-1998 (6 years); 2nd period 2001-2004 (4 years); 3rd period 2006-2007 (2 years).

Cancer site and histology had been coded using the ICD–O first edition; then these codes were converted to ICD-10 for tabulation (which was available in the database). ASRs of cancer incidence were age adjusted by the method of direct standardization on the basis of the World Standard Population in 16 categories (0-4, 5-9,..., 75+), and expressed per 10^5 of population (Doll, 1982; Jensen *et al.*, 1991). As the purpose of this study is to provide an estimation of a descriptive epidemiology in cancer over time, so no inference was made on the statistical significance of rates and trends.

Graphic representations were produced with MS Office Excel application. In addition, the linear trend was calculated for those cancers which showed the bigger gradient of increasing or decreasing throughout the three periods.

Results

The ASR of all cancer site incidences both in males and females have been continuously increasing since 1st period (Figure 2), which however is more steep for women. The observed ASR increased from 151.13/10^5 in the 1st period to 160.00/10^5 in the 3rd period for males. Between each period, the rising in cancer incidence was moderate (proportion of 3rd /2nd period and 3rd /1st period: 101.7% and 105.8% respectively). For females, overall cancer incidence raised much more steeply as compared to men in the same period of time. Whereas ASR of cancer incidence was 106.75/ 10^5 in the 1st period raised to 143.88/10^5 in the 3rd period, steadily converging to the incidence by men (proportion of 3rd /2nd period and 3rd /1st period: 116.7%; 134.8% respectively).

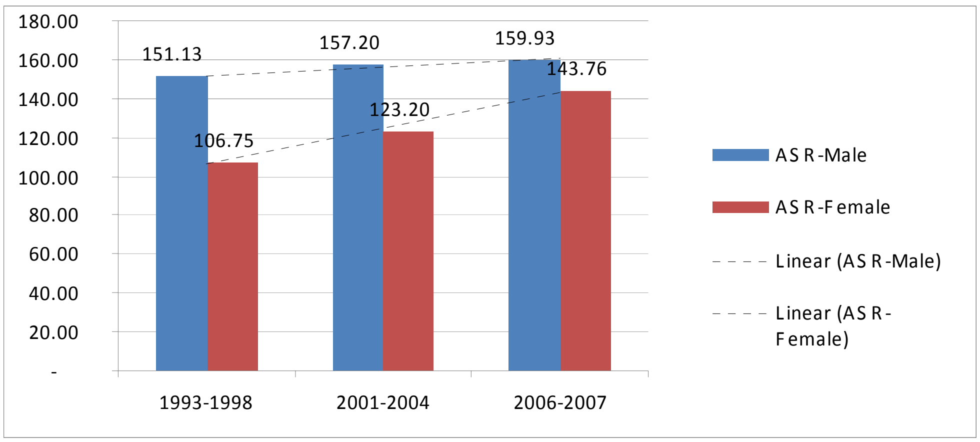

Figure 2. Trends of ASR of all site cancer combined incidences by sex

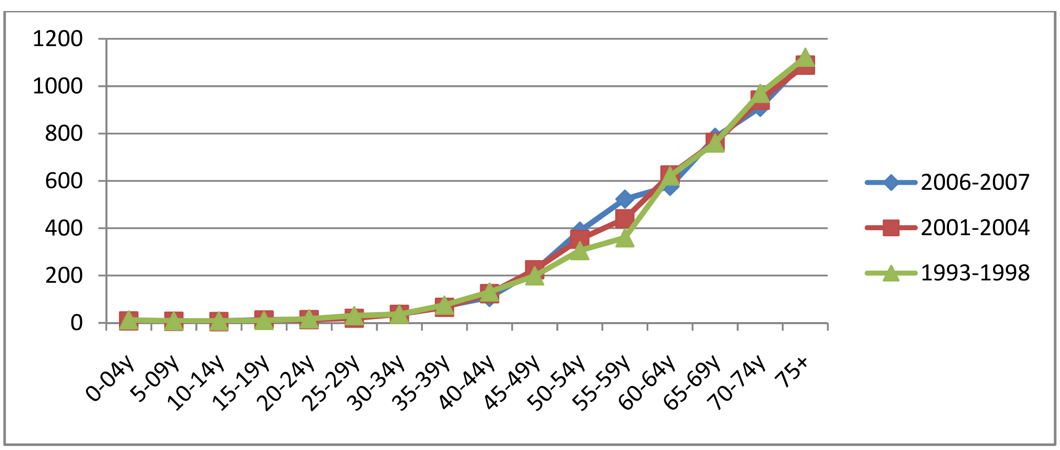

Figure 3. Trends of all site cancer age group at first diagnosis in males

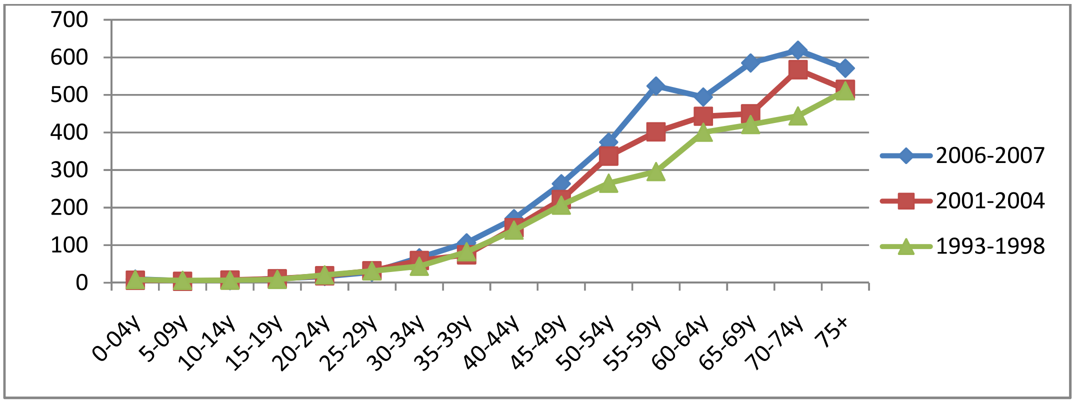

Figure 4. Trends of all site cancer age group at first diagnosis in females

Figure 3 and Figure 4 show the 5 year age interval distributions of ASR of all site cancer incidences at first diagnosis. In males, those 3 slopes (one for each of 3 observed periods) were in parallel and steadily moving upward through out all 3 periods from the first age group to the last group of 75+ years and peaking at the group of 75+ years, with ASR of 1,109/10^5 (of 3rd period).

A similar pattern was observed for women with an increase from the earliest age group to the peak at group of 70-74 years with ASR of 567/10^5, 619/10^5 (in 2nd, 3rd periods), then going down at group of 75+ years with ASR of 515/10^5, 571/10^5 (in 2nd, 3rd periods). As small difference was observed in the 1st period's curve as the trend moved upward without any bump upward to the peak at the last age group of 75+ years.

Table 2 shows the ASR incidence of specific cancer sites for males and females respectively, and gives the rank for the ten most frequent sites in brackets. Despite an increase in overall incidence of cancer among both males and females, the incidence of some cancer sites have considerably decreased.

Among females the ten most frequent cancer sites in the 3rd period were breast, cervix uteri, lung, stomach, colon, thyroid, rectum and anus, liver, ovary etc. and leukemia. Those cancer sites account for 74.8% of all cancer site ASR incidences. This proportion has slightly increased since the 1st period (72.1%). For males, which were lung, stomach, liver, colon, pharynx, esophagus, rectum and anus, non-Hodgkin lymphoma, leukemia and prostate, the ten accounted for 76.5% of all cancer site ASR incidence. This proportion has stayed rather unchanged compared to the 1st and 2nd periods (76.9%; 75,6%).

For males, although the lung cancer incidence rate has slightly decreased over time (30.67/10^5; 26.95/10^5 and 27.30/10^5 respectively for the 1st, 2nd and 3rd periods), but it has been the most frequently affected site in all observed periods. Stomach and liver cancer represent the 2nd and 3rd rank with ASR incidences of 23.00/10^5, 21.98/10^5 respectively.

However the incidence of stomach cancer has slightly increased over time whereas the incidence of liver cancer has slightly decreased. Prostate cancer had not been on the list of 10 most frequent cancer sites in the 1st period but has become the 10th cancer site after almost doubling its incidence from 2.61/10^5 to 4.13/10^5 in the last period. Overall, the incidence of Tobacco-related cancers (lung, oral cavity and pharynx, esophagus, kidney, bladder) (ACS, 2009) has remained unchanged (55.6/ 10^5, 56.5/10^5 in 1st and 3rd periods), although lung cancer incidence has decreased. This decrease has been mainly compensated by a rise in the incidence of esophagus cancer.

For females, the most interesting development is the shifting from cervix uteri as the most frequently affected site in the 1st period to breast cancer in the following periods. Whereas the incidence of cervix uteri cancer slightly decreased from 17.77/10^5 to 16.25/10^5, the incidence of breast cancer has nearly doubled between 1st and 3rd periods (17.32/10^5, 32.80/10^5 respectively). Stomach and lung cancer took the 3rd and 4th places among the most frequent cancer sites. The incidence of pharynx cancer, which was among the 10 most frequent sites in 1st period, has decreased over time and is not any more among the top ten.

Increasing trends in incidence (with positive coefficient) were observed in 21 out of 34 cancer sites in males and 27 out of 35 cancer sites in females (Table 2). Among these, the most rapid growth rates are seen for multiple myeloma, esophagus, other endocrine and prostate in males with a ratio of 3rd: 1st period equal to 3.50:1; 2.34:1; 1.93:1 and 1.58:1 respectively. For females, the steepest increases are observed in multiple myeloma, thyroid, melanoma of skin, colon, breast with the ratio of 3rd: 1st period equal to 4.71:1; 2.92:1; 2.11:1; 2.07:1 and 1.89:1 respectively.

ICD 10	Label	Females				Males			
		1993-1998**	**2001-2004***	**2006-2007***	**Linear trend**	**1993-1998****	**2001-2004***	**2006-2007***	**Linear trend**
(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**
C00	Lip	0.36	0.30	0.15	↓↓	0.10	0.15	0.03	↓
C01-02	Tongue	0.94	0.80	1.08	↑	1.57	1.60	1.85	↑
C03-06	Salivary glands	1.23	0.90	0.83	↓↓	1.39	1.80	1.83	↑
C07-08	Mouth	0.37	0.35	0.50	↑	0.65	0.75	0.80	↑
C09-14	Pharynx	3.89$^{(9)}$	2.90	3.41	↓	10.56$^{(4)}$	8.75$^{(4)}$	8.74$^{(5)}$	↓
C15	Esophagus	0.63	1.05	0.90	↑	3.67$^{(10)}$	6.30$^{(6)}$	8.60$^{(6)}$	↑↑
C16	Stomach	10.66$^{(3)}$	10.90$^{(3)}$	10.05$^{(4)}$	↓	22.86$^{(3)}$	24.85$^{(2)}$	23.00$^{(2)}$	↑
C17	Small intestine	0.11	0.15	0.20	↑	0.11	0.30	0.25	↑
C18	Colon	4.12$^{(7)}$	5.85$^{(6)}$	8.50$^{(5)}$	↑↑	6.49$^{(5)}$	8.75$^{(5)}$	10.15$^{(4)}$	↑
C19-21	Rectum and anus	3.94$^{(8)}$	4.85$^{(8)}$	6.26$^{(7)}$	↑	5.33$^{(6)}$	6.05$^{(7)}$	6.78$^{(7)}$	↑
C22	Liver	5.79$^{(5)}$	6.20$^{(5)}$	5.88$^{(8)}$	↑	23.58$^{(2)}$	23.60$^{(3)}$	21.98$^{(3)}$	↓

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
C23-24	Gallbladder etc.	0.71	1.15	1.30	↑	1.04	1.15	1.23	↑
C25	Pancreas	1.04	1.60	1.35	↑	1.93	2.20	2.18	↑
C30-31	Nose sinuses etc.	0.52	0.50	0.70	↑	0.88	0.80	0.73	↓↓
C32	Larynx	0.28	0.20	0.43	↑	3.06	2.30	3.00	↓
C33-34	Lung (incl. trachea and bronchus)	7.36[4]	8.55[4]	10.50[3]	↑	30.67[1]	26.95[1]	27.30[1]	↓
C40-41	Bone	0.88	1.05	0.88	↑	1.52	1.45	1.05	↓↓
C43	Melanoma of skin	0.19	0.20	0.40	↑↑	0.27	0.50	0.53	↑
C44	Other skin	2.90	2.80	4.15	↑	3.72[9]	3.45	3.55	↓
C47+C49	Connective tissue	1.10	0.95	1.33	↑	1.55	1.55	1.20	↓
C50	Breast	17.32[2]	24.55[1]	32.80[1]	↑	0.62	0.50	0.63	↑
C60	Penis					1.84	2.15	1.95	↑
C61	Prostate					2.61	2.75	4.13[10]	↑↑
C62	Testis					0.71	0.75	0.55	↓
C51-52 C55, C58	Other female genital organs	2.73	1.50	2.52	↓				
C53	Cervix uteri	17.77[1]	15.15[2]	16.25[2]	↓				
C54	Corpus uteri	2.30	3.15	2.48	↑				
C56-57	Ovary etc.	4.33[6]	5.60[7]	5.55[9]	↑				
C64-66, C68	Kidney etc.	0.53	0.80	0.95	↑	0.93	1.30	1.31	↑
C67	Bladder	0.64	0.85	0.88	↑	3.07	3.60[10]	3.00	↓
C69	Eye	0.29	0.25	0.33	↑	0.40	0.20	0.18	↓↓
C70-72	Brain, central nervous system	0.98	1.45	1.25	↑	1.48	1.70	2.03	↑
C73	Thyroid	2.60	4.55[9]	7.58[6]	↑↑	1.30	1.45	1.80	↑
C74-75	Other endocrine	0.14	0.10	0.26	↑	0.14	0.20	0.26	↑↑
C81	Hodgkin lymphoma	0.41	0.25	0.23	↓↓	1.03	0.60	0.33	↓↓
C82-85, C96	Non-Hodgkin lymphoma	2.54	3.80	3.88	↑	5.25[7]	5.70[8]	5.95[8]	↑
C88+C90	Multiple myeloma	0.17	0.35	0.80	↑↑	0.16	0.35	0.56	↑↑
C91-95	Leukemia	3.18[10]	3.90[10]	4.19[10]	↑	4.21[8]	4.35[9]	5.64[9]	↑
C00-C96	All sites	106.75	123.20	143.88	↑	151.13	157.20	160.00	↑
C00-C96 exp C44	All sites but non-melanoma skin	103.85	120.40	139.70	↑	147.41	153.75	156.48	↑

*[1-10] is the order of major ASR of cancer site incidence. Source: Globocan** & NCI **

Table 2. *ASR of Each Site Cancer Incidence of 3 Periods (per 10^5 populations).*

As already mentioned, despite a general trend for increasing cancer incidence both in males and females, 7 out of 35 cancer sites in females and 13 out of 34 cancer sites in males show a decrease in incidence (with negative coefficient) in observed periods. For females, cancer incidence of lip, Hodgkin lymphoma, mouth more steeply decreased with a ratio of 3^{rd}: 1^{st} period equal to 0.42:1; 0.57:1 and 0.68:1 respectively. For males, those are Hodgkin lymphoma, eye, bone, nose sinuses with ratios of 3^{rd}: 1^{st} period equal to 0.32:1; 0.46:1 and 0.69:1 respectively.

Discussion

To our knowledge, this is the first overview on cancer incidence trends in Vietnam during 1993-2007. In this article we provided a descriptive overview of the development of overall and site specific cancer incidence in three periods of time (1993-1998, 2000-2004 and 2006-2007).

The data used have some limitations. First, the incidence rates for whole of Vietnam have been estimated by pooling data from regional cancer registries. The registries pooled (2 in each observation period) covered the biggest cities in both the South and the North, thus they might be not fully representative of the Vietnamese population (together, both registries cover about 10% of the population). There are important socioeconomic differences between those live in urban and rural areas. For example 24.5% of inhabitants living in urban areas share 38.7% of per capital household income and 38.6% of per capital household expenditure (GSO, 2004). Another limitation raises from the fact that one of the registries (Ho Chi Minh city) stopped its activity in the year 2000 and had to be replaced by another one (Cantho city). When studying the cancer incidence patterns over time using population-based cancer registries, it is important to consider the degree of completeness of registration of incident cancer as gaps in registration (for example due to logistic problems, changes in registration routines, etc.) can lead to spurious incidence decreases (Wabinga *et al*., 2000; Bullard *et al*., 2000). It is probable that during the first years of operation there was some degree of under-registration in the cancer registries used in this study (Nguyen *et al*., 1998). As a low rate which derived from over a million person-years of observation, is likely reflect reality if under-registration can be ruled out (Muir *et al*., 1994). Despite this potential for underestimating cancer incidence in the beginning of registration, the two cancer registries in Hanoi and Ho Chi Minh City have produced the first reliable data on cancer incidence in Vietnam (Anh & Duc, 2002). Despite these limitations, our study allows to identify cancer incidence trends over 3 observed periods during 1993-2007 based on the best available data from Vietnam.

The latest available age-standardized incidence rates of all cancers in Vietnam were $160.00/10^5$ and $143.88/10^5$ in males and females respectively, with standardized males/ females rate ratio of 1.11. Overall, an increasing trend was found in both males and females but magnitude of increase was greater in females than in males thus leading to a narrowing of the sex-rate ratio males/females from 1.42 and 1.28 to 1.11 in the 1^{st}, 2^{nd} and 3^{rd} periods respectively. Compared to other countries in Eastern Asia, ASR of all cancer site incidence of Vietnam (in 2006-2007) in males is lower than the average of whole area, China or Japan with $219.4/10^5$; $204.9/10^5$ and $261.4/10^5$ respectively. But in females, it is slightly higher than the whole area and China (136.810^5 and 129.510^5, respectively), and lower than Japan ($167.4/10^5$) (Parkin *et al*., 2005). The observed incidence of cancer remains clearly below the cancer incidence among Vietnamese people living in California (US) with $360.6/10^5$ and $272.1/10^5$ (in 1997-2001) for males and females respectively (Sandy *et al*., 2005).

The increasing temporal trend of overall cancer incidence is probably most and foremost explained by the increasing life expectancy in Vietnam. Life expectancy at birth was 65.1 in 1993 and has increased by nearly 8 years to reach 72.84 in 2007 (GSO, 1993; GSO, 2007). Cancer incidence patterns approach those seen in European Union and the United States with heterogeneous patterns across age groups, older adults could drive the increasing cancer incidence with 67% increasing of the cancer incidence attributable to older adults while only 11% to younger adults (Devesa *et al*., 1987; Verveli *et al*., 1998; Smith *et al*., 2009). The increase in health insurance cover rate from 9% of population in 1993 up to 49% in 2007 (Tim, 1995; Ekman *et al*., 2008) may partly lead to a better access to health services, especially to the higher technology health service such as cancer histology confirmation. In addition, pesticide has been known as significant risk factor to some special cancer sites (Beard *et al*., 2003; Chrisman *et al*., 2009), its consumption for agriculture work in Vietnam has an increasing tendency during last decades with about 20% to 30% per year, while 70% of Vietnamese population has work in agriculture fields (Chen, 2006; TN, Agencies).

Cancer trends of the 10 most frequent cancer sites were rather stable during the three observation periods. Among males, lung cancer remained the most frequently affected site during the three observed periods, despite showing a small decrease in incidence. Tobacco-related cancers still have a high incidence and account for around 35.3% of all new cancer cases in males. This is not surprising since Vietnam still ranks among the countries with the highest prevalence rate of male smoking in the world with 56.1% among males aged 25-64 years, even up to 72.8% found in one survey done in 1997 (Jenkins *et al*., 1997; MOH, 2003; Ngoan, 2006a).

The second most frequently affected site in males is stomach, which is also the 3rd commonest site among women. The reason is not really known, but it is probably related to Helicobacter pylori infection as Vietnam which shows a very high prevalence of 74.6%

(Hoang *et al*., 2005). The incidence of stomach cancer in Vietnam is plausibly similar to that of other countries with high incidence of Helicobacter pylori infection (Nguyen *et al*., 1998) such as Japan and Korea (Yanaoka *et al*., 2008; Lee *et al*., 2002).

Liver cancer ranks third among the most frequent affected sites in males (ASR $21.98/10^5$ in 2006-2007) and is also one of the 10 most frequent affected sites in females (ASR $5.88/10^5$ in 2006-2007). This finding is probably related to the high prevalence of Hepatitis B Virus (HBV) infection in Vietnam – which in rural areas can be considered endemic. The prevalence of HBV infection among Vietnamese adults has been reported as being between 8.8 and 19.0% (David *et al*., 2003; Nguyen *et al*., 2007; Duong *et al*., 2009). Such high prevalence rates of HBV infection are common in the Southeast Asian area. Despite the high HBV infection prevalence, the incidence of liver cancer in Vietnam is strikingly low compared to other countries in the region, such as the Philippines (ASR $25.6/10^5$ in males; $9.0/10^5$ in females) (Corazon & Edward, 2002), Thailand (ASR $38.1/10^5$ in males; $15.1/10^5$ in females) (Sriplung *et al*., 2006); and China (ASR $40.0/10^5$ in males; $15.3/10^5$ in females) (Yang *et al*., 2005).

In females, cervix uteri was the most frequent affected site in 1993-1998, then breast cancer increased faster to occupy the first place of the most frequent affected sites. The increase in breast cancer already observed in previous analysis from Vietnam (Anh & Duc, 2002; Nguyen *et al*., 1998) is confirmed and sustained when taking into account longer observation periods as we did in our analysis. This shift could be explained by the fact the high incidence of cervix cancer was related to the high rate of HPV infections during the Second Indochinese War in the South of Vietnam which was significantly associated with the development of invasive cervical cancer (Huynh *et al*., 2004).

The increasing rate of breast cancer in Vietnam is a trend comparable to that of other developing countries, being rapidly emerging as a leading cause of death in women (Parkin *et al*., 1997). It is also similar to the trend reported for Korea during 1993-2002, the incidence rate was grew from 14.5 in 1993 to $26.2/10^5$ in 2002 (Lee *et al*., 2007). Besides demographic shifts towards longer life, the increase in breast cancer incidence may be partly explained by changes in other known risk factors such as the age of first pregnancy carried out. Hazel *et al*. found that women having their first-delivery at the age of 25 years or later had 1.5 times higher risk of developing breast cancer than those who first-delivery before age 25 (95% CI, 1.2-1.95) (Hazel *et al*., 2005). In Vietnam, the age of first delivery is mostly coherent with the age of first marriage which has increased for both males and females in the period of 1999 to 2006 by 1.3 years in males and 0.5 year in females (Tokyo. 2008). Another possible explanation could be an increase in knowledge and awareness of breast cancer and the introduction of screening mammography service which both could contribute to an increase of breast cancer incidence (Jemal *et al*., 2007; Jemal *et al*., 2008).

For males, the ASR of all site cancer by age group at first diagnosis of all 3 observed periods (Figure 3) fit each other very well. But for females, the patterns show some changes between the first and third period, especially in the age groups 55-59 years and 70-74 years (Figure 4). This change may partly be due to the above average increase of cancer incidence in females in these age groups during the last period. This assumption should be more concretely studied by a study of some specific cancer site incidence rate by age-group- analysis, in order to find what are the facts that probably explain the increase in the cancer incidence during last decades of Vietnam especially in females.

Conclusion

Cancer incidence in Vietnam has continuously increased during 1993-2007. Trends for specific sites show increases in the incidence of specific cancers. According to the data presented here, Vietnam's health decision makers should consider to refine the primary health preventive strategy. More effort should be concentrated on developing and implementing tobacco-related cancer prevention interventions, in men, as well as in women.

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Chapter 2. Brain Metastases: Epidemiology and therapeutic management

Epidemiology

Brain metastasis is when a cancer from another site in the body spreads to the brain, and is even far more prevalent than primary brain cancer (See the Appendix: Primary brain tumors). It develops depending on the complex interaction of many tumor cell factors. Most of them are not completely understood. Brain metastases mostly occur in three ways: by local extension from the tumor to the surrounding tissues; by the blood-stream (hematogenous) to distant sites; or by the lymphatic system to neighboring or distant lymph nodes. Each kind of cancer may have a typical spreading route. But the most common way of metastasizing to the brain is the bloodstream. It could be presumed that the entire brain is "seeded" by micro-metastases, even when only one intracranial lesion exists. Metastasis in the brain generally parallels the bloodstream, approximately 80% occurring in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem (Delattre *et al.*, 1988; Andrews *et al.*, 2004).

Brain metastasis is a serious clinical problem of cancer patients, and has disabling impacts on cognition, memory, language, mobility, and adaptive skills which limit the survival and worsen the quality of life of cancer patients. It is considered a terminal stage of the disease, a serious cause of morbidity and mortality and a significant challenge for neurosurgeons (O'Neill *et al.*, 2003; Ranasinghe and Sheehan, 2007; Tappe *et al.*, 2008; Kim *et al.*, 2009). Brain metastasis is the most common neurological complication of systemic cancer, and the most common CNS, occurring in 20-40% of all adult patients with cancer, and two–thirds of them become symptomatic during their lifetime (Walker *et al.*, 1985; Nussbaum *et al.*, 1996; Cappuzzo *et al.*, 2000; Wen *et al.*, 2001). For example, in 2006 the United States had about 1.4 million new cancer cases, so the incidence of brain metastases may well exceed 300,000 cases each year (Nguyen and Deangelis, 2004). Some authors have even observed extremely high incidence rates of between 10%-85% based on radiologic, autopsy, surgical, and medical records data. Up to 10% of brain metastasis patients are identified at the time of their cancer diagnosis and are considered synchronous (DiLuna *et al.*, 2007). Brain metastasis is classified as synchronous if identified within 60 days of the cancer diagnosis, and as metachronous if identified 60 days after the cancer diagnosis (Kim *et al.*, 1997). Of the 70%–80% of the brain metastasis patients who suffer from one to three metastases (oligometastases), solitary metastasis comprises 40% to 60%, and those patients with more than three metastases account for a smaller proportion of 20%–30% (Delattre *et al.*, 1988; Schackert, 2002; Gupta, 2005).

Nowadays, brain metastasis appears to be part of a trend toward an increasing incidence of brain tumors. There are some reasons that could explain this: firstly, the traditional thought that most brain metastatic patients died of systemic disease has now been rejected, but thanks to earlier diagnosis and/or more effective treatment regimes for systemic disease, such as superior imaging modalities, the advances in chemotherapy and hormonal therapies, and particularly the advent of highly effective biological and other targeted therapies, systemic malignancies can live longer as options for systemic control improve. Second, with modern neuro-imaging techniques the brain metastasis is detected earlier and controlled better. Many brain tumors in general and brain metastasis in particular, are identified in asymptomatic patients through screening neuro-imaging studies. The long-term control of CNS disease may even be an increasingly important determinant of the survival and quality of life of brain metastasis patients (Sheehan *et al.*, 2003; Kondziolka *et al.*, 2005; Eichler and Loeffler, 2007). Third, there is a shortage of adequate penetration into the CNS of many chemotherapy agents, so the brain is still a sanctuary for metastatic tumor foci (O'Day *et al.*, 1999; Andrews *et al.*, 2004).

Signs and symptoms

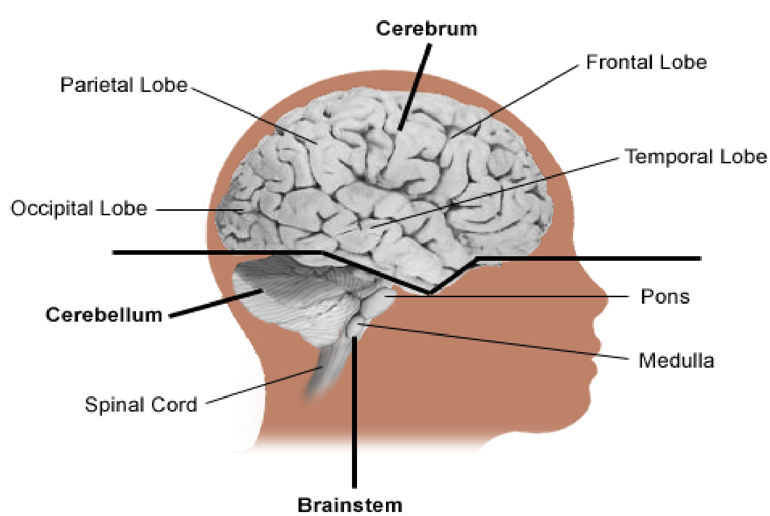

Figure 5. The anatomy of the brain

Brain metastasis can be located in any sites of the brain, such as frontal lobe, parietal lobe, temporal lobe, basal ganglia or thalamus, occipital lobe, brainstem, and cerebellum (Figure 5). But the most common locations are the parietal lobe (27%) and front lobe (21%) (Sheehan *et al.*, 2003). It acutely or slowly causes symptoms and shows signs depending on its size, its disruption of the neuro-anatomic structures, the edema caused by swelling and a buildup of fluid around the tumor, or the hydrocephalus which occurs when the tumor blocks the flow of cerebrospinal fluid and builds up in the ventricles. The common clinical features include headache, neurological deficit, and seizures (Kashi *et al.*, 2010). Some common preoperative symptoms were observed in a series of 69 patients: seizures (7%), motor or sensory deficits (54%), visual deficits (13%), headaches (19%), none (neurologically asymptomatic) (30%) (Sheehan *et al.*, 2003). Within 10 clinically detectable patients of Bouffet and colleagues (1997), the following neurologic symptoms and signs were observed: lethargy (4 patients), symptoms of increased intracranial pressure (2 patients), diplopia (2 patients), speech disorders (2 patients), hemi-paresis (2 patients), facial palsy (1 patient), seizure (1 patient) (Kim *et al.*, 2008b; Bouffet *et al.*, 1997) (Table 3).

SIGNS AND SYMPTOMS	PERCENTAGE WITH FEATURE
Cognitive or mental status change	34%
Headache	31%
Weakness	24%
Seizure	19%
Ataxia	11%
Visual changes	5%
Other	4%
Nausea or vomting	4%
Sensory	2%
Papilledema	0.5%
None	9%

Sources: Adapted from (Pirzkall A, 1998)

Table 3. Signs and symptoms of brain metastasis

Prognostic factors

In order to prolong the survival time of brain metastases patients, and to avoid unnecessary treatment, the independent prognostic factors should be carefully taken into account before deciding upon the appropriate intervention for the patient. The prognostic factors consist of two major variables, demographic and clinical, which have been well studied in all different continentals (Gaspar *et al.*, 1997; Lagerwaard *et al.*, 1999).

Demographic variables

The more common demographic variables established as prognostic factors in the survival time of patients with brain metastases included gender (Hofmann *et al.*, 2007; Arrieta *et al.*, 2009) and age (Moazami *et al.*, 2002; Sheehan *et al.*, 2003; Rades *et al.*, 2007; DiLuna *et al.*, 2007). In a study by Sheehan and colleagues, it was found that younger age significantly affected the survival rate of patients with brain metastases (p=0.0076). Rades and colleagues concluded the improved survival was significantly associated with ages equal to or less than 60 years (versus >60 years) in the setting of patients with 1 or 2 brain metastases in RPA class 1 and 2. In a prospective study with 283 consecutive patients who had recent histological diagnosis of advanced NSCLC in IIIB-IV clinical stage, Arrieta and colleagues found that the overall survival period was 7 ± 0.48 months, and male gender was associated with statistical significance with poor OS (univariate analysis, p = 0.02; multivariate analysis, RR = 1.4; 95% CI, 1.002–1.9; p = 0.048) (Arrieta *et al.*, 2009). Hofmann and colleagues studied 133 consecutive patients with melanoma brain metastases, and detected a significantly longer survival period of 36 weeks (range, 3-196) in females compared to 17 weeks (range, 1-159) in males (Hofmann *et al.*, 2007).

Clinical variables

Primary tumor site

All cancers have a potential to metastasize to the brain, but different PTS has different potential proportions of brain metastatic development. However, the majority of brain metastases are most commonly found in primary cancer sites of lung carcinoma (18-64%), breast carcinoma (2-21%), melanoma (4-16%), colorectal carcinoma (2-12%), renal carcinoma (1-8%), others (1-16%) and unknown tumor site (1-18%) (Table 4). In a study by Vuong and colleagues of a large sample of 5074 patients who were insured by AOK in Germany and admitted to the hospital within one year in 2008, with a main or secondary diagnosis of brain metastasis (C79.3), the PTS as sources of brain metastases were lung (51.2%), breast (12.3%), unspecified primary site (7.5%), kidney and renal pelvis (4.0%), and melanoma of skin (3.9%). By sex, the common most sites were lung and unknown primary site in male patients, and lung and breast in female patients (Vuong *et al.*, 2011). At the American Joint Committee on Cancer stage III, the prevalence of brain metastases is around 10-13%; and 18-46% of stage IV patients develop brain metastases; and 55-75% exhibiting it at autopsy (DiLuna *et al.*, 2007).

The PTS were defined as significant factors for prognosis by Golden and colleagues. With 479 patients who underwent SRS and SR plus WBRT, the median survival time for less than 3 versus more than 3 metastases was 15.6 and 16.9 months for breast, 16.5 and 11.3 months for lung, 9.0 and 5.6 months for melanoma (Golden *et al.*, 2008). Kashi and colleagues analyzed 54 patients with brain metastasis treated by WBRT, in which breast cancer comprised 22.2%, followed by lung at 21.9%, and unknown primary site at 16.6%. The PTS of breast showed a significantly different overall survival time compared to other sites ($p<0.001$) (Kashi *et al.*, 2010). The same results were also found by Ohta and colleagues (Ohta *et al.*, 2002).

Location of primary tumor	Baker n=114	Globus and Meltzer n=41	Tom n=82	Chason *et al* n=200	Hunter & Rewcastle n=393	Posner and Chernik n=572	Zimm *et al* n=1291	Lagerwaard *et al* n=1291	Nussbaum *et al* n=729	DiLuna *et al* n= 334	Breneman *et al* n= 94	Sansur *et al* n= 193
	%	%	%	%	%	%	%	%	%	%	%	%
Lung	21	46	22	61	34	18	64	56	39	44	60,7	53
Breast	21	2	16	16	19	17	14	16	17	17	7,1	10
Colorectal	7	12	11	4	6	2	3					6
Melanoma	8	7	9	5	6	16	4		11	16	10,7	16
Renal	8	2	1	4	4	2	2	4	6	7	7,1	4
Other	1	10	1	<1	2	22					14,3	15,8
Unknown	4	2	18	1	4		8	8	5			5

Source from (Lassman &DeAngelis, 2003; Breneman et al., 1997; Sansur et al., 2000; DiLuna et al., 2007)

Table 4. Incidence of brain metastases by primary tumor

Histologic subtypes

The brain metastatic tumors recapitulate the pathology of primary neoplasms, which could suggest the PTS in patients who have an unknown PTS (DeAngelis *et al.*, 2008). Some common pathologic subtypes are found in brain metastases: adenocarcinoma (40%-55%); small cell carcinoma (15%-22%); large cell carcinoma (15%-20%); melanoma (10%-

25%); squamous carcinoma (6%-23%); renal cell carcinoma (15%-20%); and other (10%-20%) (Kim *et al.*, 1997; Breneman *et al.*, 1997; Maor *et al.*, 2000; Kim *et al.*, 2008b). Based on the response of the tumor to the standard fractionated radiotherapy, tumor histology is categorized into the radioresponsive, which includes adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma; and the radioresistant which consists of melanoma, sarcoma, renal carcinoma, and thyroid carcinoma. The histological subtypes significantly influence the possibility of survival. Kim and colleagues found that the median survival rate of NSCLC compared to other histologic subtypes, alone or in combination, was 6.5±0.70 months and 10.1±2.33 months, respectively (p=.0401) (Kim *et al.*, 2008b). Maor and colleagues found that the rate of brain tumor recurrence was significantly higher in patient with radioresponsive histology versus radioresistant histology (P = 0.01) (Maor *et al.*, 2000).

The size of brain tumor

It is usually defined by volume or by diameter. The volume is classified into 3 levels: less 5 cm^3, 5-13 cm^3, or greater than 13 cm^3. The diameter is classified into 2 levels: less than 3 cm or bigger than 3 cm. The size of tumors is known as a prognostic factor influencing the survival time of patients with brain metastasis (Kim *et al.*, 1997; Weltman *et al.*, 2000). A study of Sheehan and colleagues found that median survival times after brain metastasis diagnosis was 20.5 months for those with tumor volumes less than or equal to 1.8 cm^3 and 18 months for those with volumes greater than 1.8 cm^3 (Sheehan *et al.*, 2005). It is an important factor used to determine the maximum tolerated doses of single fraction radiosurgery. Study of Shaw and colleagues defined that the maximum tolerated doses were 24 Gy, 18 Gy, and 15 Gy for tumors in diameters of less than 2 cm, 2.1-3 cm, and 3.1-4 cm, respectively. The size of the tumor is taken into account for deciding appropriate treatment options, for example, SRS is not appropriate for a tumor of more than 3 cm, because of the increased risks of radiation to surrounding areas and of swelling (Patchell *et al.*, 1998; Smith and Lee, 2007). In this case, resection or WBRT are preferable. However, due to the nature of brain metastasis, the majority of tumors are observed to be of a small volume (Kim *et al.*, 1997; Williams *et al.*, 2009).

Location of metastases

Brain metastases are widely distributed throughout the brain, and are most often found in supratentorial sites. In the cohort studied by Stark and colleagues, 68.0% of 348 brain metastases in 177 patients were located in supratentorial sites and 32.0% in infratentorial sites (Stark *et al.*, 2005). In 93 single brain metastatic patients in a study by Farnell and colleagues, there were 65 tumors (70%) located in supratentorial and 27 tumors (29%) in infratentorial sites (Farnell GF, 1996). More detailed locations were described by Pan and colleagues, in a study of a series of 191 patients with 424 brain metastases, 148 tumors were in the frontal lobes; 86 in the parietal lobes; 75 in the cerebellum; 65 in the occipital lobes; 43 in the temporal lobes; 17 in the brainstem; and 20 in the thalamus (Pan *et al.*, 2005). The location can also be classified by the functional brain regions, such as in the study by William and colleagues, 39% lesions were in non-eloquent, 32% in near-eloquent, 29% in eloquent regions (Williams *et al.*, 2009). Location of brain metastases was found to be one of the independent and significant prognostic factors of survival in a study by Meier and colleagues which reviewed 100 patients with melanoma brain metastases (Meier *et al.*, 2004). William and colleagues found that the lesions located in functional brain regions (the eloquent cortex) have a significantly increased risk of treatment-related complications (HR, 2.5; 95% CI, 1.6-3.8; $p<0.001$) (Williams *et al.*, 2009).

Extracranial disease

Extracranial metastasis is considered to be stable when the tumor has been clinically controlled for 6 months or longer prior to the detection of cerebral metastases (Farnell GF, 1996). Brain metastases are often observed in parallel with extracerebral metastases, the more common sites have been found to be pulnionary 86 (57%); hepatic 43 (29%); peritoneum 37 (25%); bone 19 (13%); and none 27 (18%) (Farnell GF, 1996). Vuong and colleagues found 58.8% of all cerebral metastatic patients had extracranial metastases, ranging from 1 to 7 sites. The most common sites were bone, which accounted for 22.2% of the total concurrent extracranial metastatic sites; lung, which accounted for 19.0%; and liver, which accounted for 18.3% (Vuong *et al*, 2011). The presence of extracranial metastasis was previously defined as a factor significantly affecting survival (Kim *et al.*, 1997; Gaspar *et al.*, 1997; Kondziolka *et al.*, 2005; Rades *et al.*, 2007) and the number of extracranial metastatic sites is negatively correlated with survival (Arteaga *et al.*, 1988; Cho *et al.*, 2008; Paralkar *et al.*, 2008).

Tumor recurrence

Tumor recurrence is considered in terms of local and distant recurrence. Local brain tumor recurrence is defined as a reappearance of the treated brain tumor and is the variable used to identify the efficacy or failure of the treatment to control the brain metastasis. Distant brain tumor recurrence is defined as an occurrence of a new brain metastasis elsewhere in the brain (Schöggl *et al.*, 2000). For instance, tumor recurrence, local or distant, in patients with a single brain lesion was observed in 30-85% of the patients initially treated with surgery (Sundaresan *et al.*, 1988). The local tumor control rate was reported to be 45-85% for stereotactic radiosurgery. The majority of recent studies reported that local control rates for stereotactic radiosurgery were over 76% (Flickinger *et al.*, 1994; Chitapanarux *et al.*, 2003; Varlotto *et al.*, 2003; DeAngelis *et al.*, 2008). The recurrence rate is related to the duration of survival, which is highly dependent on the nature and the course of the systemic disease, such as the histology of primary tumors. Mindermann studied a series of 101 patients with 253 brain metastases and found that the recurrence rate for malignant melanoma is 67%, for renal cell carcinoma 30%, for lung cancer 19%, for breast cancer 18%, for unknown primary tumor 17%, for gastrointestinal tract cancer 14%, and for other cancers 12% (Mindermann, 2005). The recurrence of brain metastases was well established as having a significant association with overall survival (Kondziolka *et al.*, 1999b; Chang and Adler, 2000).

Number of brain metastases

The number of brain metastases could be the basis of an important distinction. A large number of observations in the setting of SRS and of SR found no significant impact on the OS of patients. However, no less studies found that an increasing number of brain metastases have been associated with poorer survival rates, for example, the series of brain metastatic patients studied by Kondziolka and colleagues, Kim and colleagues, Nieder and colleagues, Weltman and colleagues (Kondziolka *et al.*, 2005; Kim *et al.*, 2008b; Nieder *et al.*, 2000; Weltman *et al.*, 2000). The more detailed study by Diluna and colleagues found that survival was significantly better in patients who had 1-3 metastases (median, 8.5 months) compared to patients with more than 4 metastases (median, 6.3 months; HR, 0.65; P=.003) (DiLuna *et al.*, 2007). Unfortunately, more often patients with multiple brain tumors were observed in the setting of GKS that was found in 55-70% of brain metastases underwent GKS (Maor *et al.*, 2000; Mindermann, 2005; DiLuna *et al.*, 2007; Kim *et al.*, 2008b; Williams *et al.*, 2009). In addition, the number of brain metastases was found in the setting of surgery plus WBRT or SRS to be a factor associated with the probability of tumor control. Pollock demonstrated that the tumor control rate decreases from 64% for one tumor, to 51% for two lesions, and to 41% for three tumors (Pollock, 1999).

Time from primary tumor diagnosis to the development of brain metastases

Time from primary tumor diagnosis to the development of brain metastases holds prognostic value, particularly for breast and melanoma primaries, with long intervals being favorable (Sheehan *et al.*, 2003; Fife *et al.*, 2004; Sheehan *et al.*, 2005). However, the interval time between primary tumor diagnosis and brain metastases is also different depending on the PTS, for example at the time of small cell carcinoma diagnosis 10% of patients already have at least one brain metastasis, after 2 years the incidence of brain metastasis is up to more than 50%, and as many as 30% to 80% of those patients could develop brain metastasis during the course of their disease (Fleck *et al.*, 1990; Pöttgen and Stuschke, 2001). A study with the cohort of n = 2,724 patients combining all different types of cancer, including carcinoma of the breast, colon, kidney, and lung as well as melanoma, conducted by Schouten and colleagues in order to find the incidence of brain metastases occurring during the particular time durations of 1 month, 1 year, and 5 years, demonstrated that brain metastases occurred in 7.8% of the lung cancer patients after just 1 month and 14.8% after 1 year; with a cumulative incidence of 16.3% after 5 years; and 8.5% of the total cohort suffering brain metastases after 5 years (Table 5) (Schouten *et al.*, 2002). The time interval between primary cancer diagnosis and brain metastasis was rather different among previous observations of different PTS, such as one by Distefano and colleagues, which found that the median time from breast cancer to brain metastasis is 34 months (DiStefano *et al.*, 1979); another by Kim YS and colleagues which found that the mean time of NSCLC to brain metastasis was 9 months (range, 0–73 months) (Kim *et al.*, 1997); and another by Wronski and Arbit which found that the median time between diagnosis of colorectal carcinoma and diagnosis of brain metastasis was 27.6 months (mean, 38.7 months) (Wroński and Arbit, 1999). A study by Bouffet and colleagues on brain metastases from solid malignant tumors in children found that the median time from the diagnosis of the primary tumor to the brain metastases was 15 months (range, 9–84 months) (Bouffet *et al.*, 1997). In addition, the time from tumor diagnosis to treatment is also found to be significantly influential for OS (RR, 1.70; P =.003) and local tumor control (RR, 1.59; P =.047) (Rades *et al.*, 2007).

Site	No. of patients at risk	No. with BM	1 Month		1 Year		5 Years	
			% Event free	% CI of BM	% Event free	% CI of BM	% Event free	% CI of BM
Breast	802	42	95,9	0,4	91,6	1,0	68,8	5,0
Colon/rectum	720	10	95,8	0,1	71,8	0,6	50,3	1,2
Kidney	114	12	91,2	1,7	64,0	5,2	48,6	9,8
Lung	938	156	80,1	7,8	34,5	14,8	14,7	16,3
Melanoma	150	12	98,7	0,7	91,3	4,0	78,7	7,4

Source: (Schouten et al., 2002)

Table 5. Cumulative incidence of brain metastasis and event-free brain metastatic interval

Treatment strategies

Treatment strategies for CNS metastases have been found to have significantly different effects on the survival of CNS metastatic patients, which will be described in detail later.

Grading

In the WHO scale of neurological functions, based on general conditions, the neurological function of patients is assessed with a 5-point WHO/Zubrod scale. It is also called the Eastern Cooperative Oncology Group (ECOG). Scale 0 denotes a patient who is in perfect health, that is, asymptomatic; scale 1 is with symptoms but almost completely independent; scale 2 is bedridden but only for less than 50% of the daytime; scale 3 is bedridden for more than 50% of the daytime; scale 4 is completely bedridden or dependent; and scale 5 denotes death (Vecht *et al.*, 1993).

The Glasgow Coma Scale (GCS) includes a variety of clinical factors such as eye response, motor response, and verbal response and is used to assess the level of consciousness of patients in the neurosurgical intensive care unit and elsewhere. Coma is a state of unarousable unresponsiveness it is defined as (1) not opening eyes, (2) not obeying commands, and (3) not uttering understandable words. The normal state merits a GCS score of 15, and lower scores are obtained as the level of consciousness deteriorates (Table 6) (Tindall, 1990; Kim *et al.*, 2009).

Categories	Score
Eye opening (E)	
Opens eyes spontaneously	4
Opens eyes to voice	3
Opens eyes to pain	2
No eye opening	1
Best motor response (M)	
Obeys commands	6

Localizes to pain	5
Withdraws to pain	4
Abnormal flexor response	3
Abnormal extensor response	2
No movement	1
Best verbal response (V)	
Appropriate and oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
No sounds	1

Table 6. The Glasgow Coma Scale

The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. Its scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities; 100 is "perfect" health and 0 is death. KPS may be used to determine a patient's prognosis or decide upon an appropriate treatment methodology (Table 7). It is considered a factor significantly affecting the survival rate of patients with brain metastases (Karnofsky and Burchenal, 1949; Sheehan *et al.*, 2003). Rades and colleagues found that improved chance of survival was associated significantly with a KPS score between 90 and 100 (versus a KPS score between 70 and 80) (Rades *et al.*, 2007). The same findings were also found in studies by Kondziolka and colleagues, Sheenhan and colleagues, Weltman and colleagues (Weltman *et al.*, 2000; Kondziolka *et al.*, 2005; Sheehan *et al.*, 2005). Combining some different prognostic factors such as age, PKS, number of CNS metastases, extracranial metastases, Sperduto and colleagues introduced an index to assess the prognostic grading (Table 8) (Sperduto *et al.*, 2008).

Score	Categories	Score	Categories
100	Normal, no signs of disease	40	Disabled, requiring special care and help
90	Capable of normal activity, few symptoms or signs of disease	30	Severely disabled, hospital admission indicated but no risk of death
80	Normal activity with some difficulty, some symptoms or signs	20	Very ill, urgently requiring admission and supportive measures or treatment
70	Caring for self, not capable of normal activity or work	10	Moribund, rapidly progressive fatal disease processes
60	Requiring some help, can take care of most personal requirements	0	Death
50	Requiring help often, requiring frequent medical care		

Source: (Karnofsky and Burchenal, 1949)

Table 7. The Karnofsky Performance Status

Score	0	0.5	1.0
Age	>60	50 - 59	<50
KPS	<70	70 - 80	90 - 100
Number of CNS metastases	>3	2 - 3	1
Extracranial meastases	Present		None

A score of 0, 0.5 or 1 is assigned to each of 4 categories and the sum of these four categories is the patient's score, ranginf from 0 to 4. *Source from (Sperduto et al., 2008)*

Table 8. Graded prognostic assessment (Sperduto Index)

RPA stands for recursive partitioning analysis, which was initiated by the Radiation Therapy Oncology Group (RTOG). Three prognostic classes were based on KPS, PTS, presence of extracranial system metastases, and age (Table *9).* The RPA classes have been found to be valid and reliable as a stratification factor for clinical trials (Pandita et al., 2007; Tappe *et al*., 2008) and an important prognostic factor affecting the overall survival of patients with brain metastases (Weltman et al., 2000; Pandita et al., 2007; Rades et al., 2007).

KPS	Status of primary tumor or extracranial metastasis	Age (years)	**Class**
< 70	+/-	All	**3**
≥ 70	+	All	**2**
	-	≥65	**2**
		<65	**1**

Source from (Pandita et al., 2007)

Table 9. Recursive Partitioning Analysis classification

Diagnosis and treatment

Brain metastases are pathologically and radiographically diagnosed and confirmed. Nowadays, modern imaging technologies including CT-scanner or MRI have a major impact especially on spinal and intracranial tumors. With CT-scanner or MRI, tumors appear as a contrast-enhancing solid or ring-enhancing mass in the brain parenchyma, usually with surrounding edema (Kim *et al.*, 1997). Smaller lesions can be detected, allowing earlier intervention than that was possible in the past (Cromwell Hospital, 2008).

Comparing the benefits of specialized and non-specialized MRI, the study of Engh and colleagues, which purposed to characterize the detection of additional intracranial metastases in cancer patients at the time of SRS using a specialized high-resolution MRI protocol of stereotactic MRI technique using the Spoiled Gradient Echo sequence, found that up to 29.3% of patients were detected with additional metastases. This finding shows the high prevalence of cryptic intracranial metastases when non-specialized MR techniques with a 5 mm slice, 1 mm gap single-dose contrasted T_1-weighted MRI are used, resulting in a significant increase in the detection rate of cryptic brain metastases. The high-resolution, fine-cut MRI with double-dose MRI contrast is a valid method to plan therapy for metastatic brain cancer (Engh *et al.*, 2007).

WBRT was traditionally the first-line treatment in the management of brain metastases with solitary or multiple tumors. It could typically lead to prolonged survival period of 3-4 months (Borgelt *et al.*, 1980; Cairncross *et al.*, 1980; Byrne *et al.*, 1983; Fadul *et al.*, 1987), compared to approximately 1-2 months without treatment (Cho *et al.*, 2000). During the last decades, the treatment of brain metastases has undergone a considerable evolution. In particular, the advances of technologies have not only contributed to the diagnosis but also to the treatment of brain metastases. Currently, a comprehensive approach to the management of a brain metastatic patient is targeted towards:

(1) Reducing the mass effect and the increased intracranial pressure;

(2) Providing treatment for medical complications, such as seizures, venous thromboses, and side effects from medication;

(3) Prolonging survival and quality of life;

(4) Providing follow-up care to consider the systemic disease and end-of-life directives.

These approaches are divided into two main categories, supportive and definitive, which refer to 2 major strategies of treatment: symptomatic (corticosteroids) and therapeutic (WBRT; radiation sensitizers; WBRT plus chemotherapy; prophylactic cranial irradiation; SRS; WBRT with or without SRS; SRS with or without WBRT; surgery; surgery with or without WBRT; chemotherapy using newer agents that achieve CNS penetration) (Nguyen and Deangelis, 2004; DiLuna *et al.*, 2007). Which therapeutic option or which options could be combined for the treatment of each individual patient must take into account prognostic factors such as age, KPS, PTS, concurrent extracranial diseases, and number of lesions, etc (Kashi *et al.*, 2010). From the literature, it is apparent that different combinations of these treatments have been applied in the management of brain metastases. However, the appropriate combination is still controversial and the prognosis for brain metastasis has remained poor (DiLuna *et al.*, 2007).

Supportive care

Supportive care is important for managing the symptoms of brain metastasis by providing treatment for medical complications and the side effects of medication. The mechanism of action of corticosteroids is not even exactly understood, but they are believed to stabilize the leaky blood-brain barrier of the surrounding and inner areas of metastatic lesion. It reduces the surrounding vasogenic edema, reduces the increasing of intracranial pressure and reserves global, focal neurologic deficit. Therefore, corticosteroids are used in the first therapy for brain metastatic patients as anticonvulsants, and anticoagulants (Nguyen and Deangelis, 2004).

Seizure is a common symptom of brain metastasis, occurring in 10-20% of patients at presentation of brain metastasis (Mason, 2003; Mikkelsen *et al.*, 2010). It requires anticonvulsant medications such as phenytoin, carbamazepine, oxcarbazepine (Trileptal), and phenobarbital inducing cytochrome P450 (Nguyen and Deangelis, 2004).

Anticoagulants are required as the first choice for brain metastases. Deep venous thromboses are common medical complications of brain metastases, and present in 22-45% of brain metastatic patients. However, the potential for hemorrhage into an intracranial lesion should be carefully monitored (Nguyen and Deangelis, 2004).

In addition, supportive care can improve cognition, mood, and quality of life of brain metastatic patients by using medications such as methylphenidate and donepezil (Meyers *et al.*, 1998; Shaw *et al.*, 2006), and prevent acute radiation toxicity due to an increase in edema, which manifests as headaches, nausea, and vomiting (Nguyen and Deangelis, 2004).

Definitive care

Chemotherapy

Historically, drug penetration into the lesion was not reliable due to the main obstacle of the blood-brain barrier. Chemotherapy traditionally played a limited role in the treatment of brain metastasis. Recently, with the development of newer drugs that improve the penetration into the lesion, the role of chemotherapy in the treatment of brain metastasis is fully defined. It provides a significant survival benefit in certain cases, and some advantages in terms of clinical safety and efficacy. Chemotherapy is recommended for the patients after the options of surgery, WBRT, and SRS have been exhausted. However, the success of chemotherapy largely depends on the primary tumors. For the primary tumors of lymphoma, SCLC, germ-cell tumors, breast cancer with high chemosensitivity the response rate is higher than with others. For instance, breast tumors have a response rate of approximately 50% to some agents (cisplatin, etoposide, cyclophosphamide, methotrexate, and 5-fluorouracil). The small-cell lung cancer tumors have a 33%–53% response rate to agents such as teniposide (Vumon), cyclophosphamide, topotecan (Hycamtin), carboplatin (Paraplatin), etoposide, and vincristine. Non–small-cell lung cancer has response rates of 27%–45% with agents like vinorelbine, gemcitabine (Gemzar), cisplatin, and etoposide (Alexander *et al.*, 1995).

Whole brain radiotherapy

WBRT is a radiotherapy which uses high energy light beams (X-rays or gamma rays) or charged particles (electron beams or proton beams) to affect both normal and tumor cells, as the normal cells are believed to be more capable of repairing themselves and the tumor cells, on the other hand, will die or eventually shrink (Cromwell Hospital, 2008). It has been the most common therapy and a mainstay of definitive treatment of brain metastasis for the last five decades (Kashi *et al.*, 2010), with the main purpose of extended palliation for patients (Nguyen and Deangelis, 2004). In particular it is the most favorable for those who have a poor survival prognosis (Rades *et al.*, 2008) as it is standard in cases of multiple brain metastases with poor clinical conditions and which are rapidly deteriorating (Nguyen and Deangelis, 2004).

There are short (20 Gy in 5 fractions/1 week) and longer programs with higher doses (30 Gy in 10 fractions/2 weeks; 40 Gy in 20 fractions/4 weeks; etc). Even so, the WBRT schedule has no significant impact on survival. A study by Rades and colleagues compared the short and long programs in terms of the survival prolongation of 1,085 patients treated with WBRT, in which 387 patients received a short program of 20 Gy, 698 patients received a long program of 30 Gy (527 patients), and 40 Gy (171 patients). The survival outcomes for each were not significantly different ($p = 0.415$) (Rades *et al.*, 2008). Similar outcomes are also found in other studies by Gelber and colleagues, Kurtz and colleagues, Borgelt and colleagues (Gelber *et al.*, 1981; Kurtz *et al.*, 1981; Brown *et al.*, 2008). However the 30 Gy dose resulted in a better response rate (77.8%) and symptomatic relief (63%). Additionally, the higher level of radiation may surpass the maximum dose the brain can tolerate. The typical doses are now 30 Gy in 10 fractions or 37.5 Gy in 15 fractions over 3 weeks (Hazuka and Kinzie, 1988; Chao *et al.*, 1954; Richards *et al.*, 2007; Chang and Adler, 2000).

The response rate is also predicted based on the level of radio-sensitivity of the primary tumor, for instance: NSCLC and breast cancers have intermediate radio-sensitivity, whereas renal cell tumors, sarcomas, and melanomas are relatively radio-resistant (Nguyen and Deangelis, 2004). Although the outcome of WBRT is poor, which when used alone has a mean survival rate ranging from 2.2 months to 4 months, it continues to be a standard and efficacious treatment in the management of brain metastasis (Auchter *et al.*, 1996; Lassman and Deangelis, 2003; Tappe *et al.*, 2008) and the combination of surgical resection and adjunction WBRT could be preferred and become standard treatment on brain metastases to reduce local recurrences (Maor *et al.*, 2000; Chang and Adler, 2000). However, WBRT could cause radiation toxicity, which is usually revealed by some signs of acute toxicity such as headache, nausea, and vomiting within hours of treatment or delayed complications of chronic toxicity such as cognitive effects that occurred after several months. The corticosteroids could be used to eliminate this toxicity (Maor *et al.*, 2000; Nguyen and Deangelis, 2004).

Surgical Resection

In the late 1950s and early 1960s, surgery of brain metastasis had a very high rate of mortality, up to 38% (Simionescu, 1960; Richards and McKissock, 1963). It was not even typically added to the management of brain metastasis until the late 1980s. Since the evolution of surgical techniques in the middle 1980s, there have been a number of modern imaging technology developments, including preoperative imaging with CT-scanner or MRI, which are able to detect smaller lesions; ultrasonography, which is widely used to detect deep-seated lesions, allowing earlier intervention than was possible in the past; and image-guided surgery, such as CT and MRI-guided computer-assisted surgery, neuronavigation, endoscopic-assisted neurosurgery which all enable the surgeon to have better visualization to ensure the clip is correctly placed in aneurysm surgery. The surgical techniques have had a significant impact in making some previously unresectable metastases resectable, and image-guided surgery has become routinely used in elective resection of brain metastasis (Tronnier *et al.*, 2001; Cromwell Hospital, 2008).

The goal of surgery is a gross-total resection of the tumor (defined as the removal of 95% of the tumor), but the additional goals of reducing the tumor size (piecemeal procedure) and relieving the mass effect could be considered in some special cases (Cromwell Hospital, 2008: Suki *et al*., 2009), that has been confirmed to play an important role in local control of brain metastasis. In a study by Patchell and colleagues, surgery was added to WBRT in 25 patients compared to WBRT alone in 23 patients, which resulted in the significant difference in local recurrent rates of 52% versus 20%, respectively (p=0.02) (Patchell et al., 1990). It could provide immediate relief of neurologic signs and symptoms due to a mass effect. It causes an especially significant improvement in the survival rate compared to WBRT. However, surgery is not beneficial for all patients with cerebral metastases, for example it is rarely offered to patients who are predicted to have a poor outcome with multiple brain metastases, especially in the melanoma, that is associated with multiple rather than single brain metastases (Samlowski et al., 2007; Kondziolka et al., 2000); or patients with a large lesion or a lesion that has proximity to critical structures like the brain stem or optic chiasm. The surgery needs careful consideration of the prognostic factors to be determined medically suitable for both surgery and recovery. By RPA (Table 9), the class I patients are good candidates for surgical resection, while class III patients are not likely to be candidates (Cromwell Hospital, 2008). In additional, surgical resection is recommended for patients who have a single brain metastasis with unknown diagnosis, or when the lesion immediately threatens to the life of a patient (Nguyen and Deangelis, 2004).

Surgical complications are defined as those occurring within 30 days after surgery. They were divided into 3 categories of neurological, regional, and systemic complications. The neurological complications are defined by the neurological deficit. The regional complications are those occurring due to the wound in the cranium or the brain surface, but not directly causing a neurological deficit. The systemic complications are those resulting from extracranial disease. These complications are also classified into major or minor varieties depending on their persistence. The major is defined as those lasting over 30 days or requiring aggressive treatment, while the minor is those lasting less than 30 days and not threatening to the life of the patient. Death is attributable to the neurological disease if the systemic disease is stable; to systemic disease if the neurological disease is stable; and to the combination of neurological and systemic disease when both are progressing (Sawaya *et al.*, 1998; Vecil *et al.*, 2005).

In conclusion, with the evolution of imaging and intra-operative guidance technologies surgical resection continues to be one of the leading methodologies in the treatment of brain metastases.

Stereotactic radiosurgery

The concept of radio-surgery was introduced in 1951 by Professor Lars Leksell, a neurosurgeon in Lund, Sweden. It was a result of the study of stereotactic instruments for image guided intervention into the deep parts of the brain, which had started since the end of Second World War. The first Gamma Knife Prototype was made in 1967 and the first patient was treated at the Karolinska / Sophiahemmet Hospital in Stockhom, Sweden in 1968. Then this was improved with computer assistance for a dose planning program to be the second prototype in 1974. This still had mechanical constraints and difficulty in the treatment of larger targets, so more convenient irradiation for larger target volumes was increasingly required. In 1988, the Model B Gamma Knife with a different configuration of the radiation sources to facilitate its loading was introduced. During this period, with the rapid development of computer technology the 'Gamma Plan' was introduced with more user-friendly dose planning programs. Further development of dose planning systems occurred in 1996, when image fusion software made it possible to blend CT and MR images for optimal visualization of the target area, and then in 1998 the detection of gray scale differences in CT and MR Images was made possible (Cromwell Hospital, 2008).

Based on the principle of radiation therapy, which uses high energy rays aimed at a tumor from many angles in a single treatment session, the radiation therapy procedure was developed using Specula Equipment to position the patient and precisely deliver large radiation doses to a tumor and not to normal tissue, in order to treat different kind of cancer, specially brain tumors and other brain disorders. Then, SRS a technology with a highly conformal form of radiation therapy that delivers a high dose in a single treatment to the target volume while sparing adjacent normal tissues was developed (Hazard *et al.*, 2005). It is used to treat intracranial lesions and vascular malformations as an addition to or replacement of WBRT and microsurgery. SRS can be delivered by hardware and software appended to standard linear accelerators (Linacs) or by dedicated systems such as Gamma Knife, which has been proposed as a more accurate and user friendly technology (Griffiths *et al.*, 2007).

The pathology of brain metastatic tumors after SRS

The morphologic features of pathologic lesions appearing after SRS have three basic histological responses which are acute type post-radiosurgery tissue reaction, sub-acute type post-radiosurgery tissue reaction, and chronic type post-radiosurgery tissue reaction. A pathological study by Szeifert and colleagues of 26 specimens reported that 8 of 26 specimens have this kind of reaction that occurs at post-radiosurgery intervals from 1 month to 17 months (median, 4 months); the subacutetype histologic response was found in 18/26 specimens and occurred at post-radiosurgery intervals from 5 months to 59 months (median, 16 months); the chronic type histological responses was observed at post-radiosurgery intervals from 9 months to 33 months (median, 17 months) (Szeifert *et al.*, 2006). Chang and colleagues studied the change in the tumor 3 months after undergoing SRS, and found that 52% of the metastases decreased in size, 8% disappeared, 31% had stabilized in size, and 9% of treated metastases had increased in size. This results in an overall tumor response rate of 91% (Chang *et al.*, 2000).

The acute type was characterised by a sharply demarcated coagulation necrosis in the parenchyma and stroma of the metastasis, and generally was centered within the target volume encompassed by the 50% isodose line. At the periphery of the lesions, there is usually a slight-to-moderate cellular accumulation that contains pycnotic apoptotic elements and an inflammatory reaction, mostly polymorphonuclear leukocytes, and in the center there is homogeneous eosinophylic fibrin strands mixed with tissue debris. Glios around the target volume was not remarkable, nor was the existence of acute vasculopathy with endothelial destruction, different degrees of fibrinoid necrosis in the vessel walls and in the center of the high dose irradiated area of the target volume. The subacute type of the lesion featured necrosis in the center and granulation tissue infiltrated with inflammatory cells in the surroundings, and phagocytotic activity with the expression of macrophages with loaded cytoplasm. There is a immunohistochemical reaction with the demonstration of CD68 (PGM1) positivity in a large majority of these macrophages, and CD31 positivity also presented. Gliosis appeared to a mild to moderate extent and demarcated the periphery of the postradiosurgery target volume. Vasculopathy was present within the irradiated area, by different degrees of endothelial destruction and subendothelial spindle-shaped cell proliferation that narrows the lumen. The chronic type is characterised by almost hypocellular, gliotic, or collagen-rich scar tissue undergoing various degrees of hyaline degeneration, calcification, or even ossification instead of coagulation necrosis. The lesion is infiltrated by a moderate to intense inflammatory cellular reaction, which consisted mainly of lymphocytes. Immunohistochemical reactions occur with a prominent presence of CD3-positive T lymphocytes. Vasculopathy with various degrees of endothelial damage and subendothelial spindle cell proliferation and perivascular fibrosis or scar tissue formation are present frequently and that narrows the lumen. Particularly, there is a specimen that had undergone both acute and sub-acute reactions found on pathologic examination (Szeifert *et al.*, 2006).

Indication for SRS

The goals of SRS in the treatment of brain metastasis is to provide local tumor control, palliate neurological symptoms, prolong survival time and reduce morbidity and mortality rates from neurological causes (Kim *et al.*, 1997; Sheehan *et al.*, 2003).
The prognosis of brain metastases may also take into account the score index for radiosurgery (Table 10), which is an alternative prognostic scoring system based on patients undergoing SRS, which considers 5 categories of age, KPS, systemic disease status, lesion numbers and largest lesion volume. Each scale emphasizes the close association between clinical variables and outcome (Kashi *et al.*, 2010).

	0	**1**	**2**
Age (years)	≥60	51-59	≤50
KPS	≤50	60-70	80-100
Systemic disease status	Progressive disease	Partial remission or stable disease	Complete clinical remission or no evidence of disease
Number of brain lesions	≥3	2	1
Largest lesion volume	>13 cm3	5–13 cm3	<5 cm3

Source: (Weltman et al., 2000)

Table 10. Score Index for Radiosurgery in Brain Metastases

With the distinction of its noninvasive nature, SRS may avoid many of the risks associated with open surgical removal. The precise identification of target volume is delivered by a single, high-dose fraction of ionizing radiation in sharply focused beams of radiation beyond the boundary of the identified target. The healthy brain tissue is not affected and can absorb a relatively safe dose of radiation. The radiation can reach any part of the brain, regardless of eloquent or deep-seated brain regions such as motor/sensory cortex, insula cortex, Wernicke's and Broca's areas, thalamus, and even brainstem (Kondziolka *et al.*, 2000; Suki D, 2007; Cromwell Hospital, 2008). It can be an important treatment option for both single but also multiple brain metastases (Chang *et al.*, 2000) on an outpatient basis and in a single session with local anesthesia (Cromwell Hospital, 2008). Regardless of extracranial disease status, for up to 3 lesions in a rather clinical condition of KPS greater than 70, SRS is favorable option (Cho *et al.*, 2000).

SRS could avoid the problem of radioresistence in some certain PTS of brain metastasis such as sarcoma, melanoma, and renal cell carcinoma. These can be treated by SRS with the same local tumor control rate as others treated by SRS (McDermott and Sneed, 2005; Ranasinghe and Sheehan, 2007; Brown *et al.*, 2008).

SRS was developed at the results of some certain limitations of SR, neurosurgeons pursued a supplementary approach to control single and multiple brain metastases, and thus SRS was developed. In comparison to SR, SRS has a powerful local treatment modality especially for small, multiple and deep metastases. Additionally, SRS combined with WBRT would provide better regional control. Due to its less invasive nature and apparent effectiveness, in a relatively short time SRS has emerged as an important noninvasive option in the neurosurgical armamentarium against brain metastasis and as an alternative form of local therapy, and been chosen increasingly frequency over SR (Cromwell Hospital, 2008; Smith and Lee, 2007). In addition, SRS is more efficient comparing with craniotomy, achieving the optimal treatment in more complex cases. Some authors have even suggested that SRS may supplant craniotomy as the new gold standard (Flickinger and Kondziolka, 1996). With less potential for radiotoxicity, SRS can be repeated to treat intracranial tumor recurrence months to years after the initial treatment in order to prolong the survival time of a brain metastatic patient (Cromwell Hospital, 2008; Chang and Adler, 2000). In a RCT by Kondziolka and colleagues (1999), 48% of the patients underwent repeated SRS and one patient had as many as 7 procedures over a survival period of 10 years (Kondziolka *et al.*, 1999a) (Table 11).

But, one obvious disadvantage of SRS is the lack of histological confirmation of diagnosis, while resection on the other hand provides both the treatment and the opportunity for diagnosis. Therefore, resection—or at least biopsy sampling—should be considered for any patient without a clear diagnosis and resection is still a mainstay in the treatment of brain metastases (Smith and Lee, 2007; Cromwell Hospital, 2008). It cannot be used to treat tumors larger than 3 cm, because there is an increased risk of radiation damage to surrounding areas and of swelling. In such cases, the tumor may be surgically removed immediately to relieve the pressure on surrounding tissue, rather than left to shrink away slowly. SRS is not a preferential option when lesions are located in close proximity to critical structures like an optic nerve or pituitary gland, which would be devastated by the radiation (Ikushima *et al.*, 2000; Nakayama *et al.*, 2004). There would be a concern about the potential of increasing the surrounding edema, especially in the large lesions, for which resection treatment is favored (Nguyen and Deangelis, 2004; Ranasinghe and Sheehan, 2007).

Surgery	Radiosurgery
Advantage:	
Allows histilogical diagnosis;	Minimally invasive;
Removes mass effect;	No hospitalization;
Improves local control treament of recurrence;	Cost effective treament of recurrence;
Able to treat large lessions	Treats surgically inaccessible masses
Disadvantage:	
Invasive;	No histological diagnosis; Limited to small tumors limited to 1 - 3 metastases;
Require hospitalization;	
Limited to 1 - 3 metastases infection	Longer time for resoltion of mass effect

Source: Neurosurg Focus © 2007 American Association of Neurological Surgeons

Table 11. Comparison of advantages and disadvantages of SRS and SR

The combination of WBRT and SRS

The treatment option of SRS in addition to or without WBRT for brain metastasis is slightly controversial. However, WBRT and SRS could decrease the possibility of intracranial tumor recurrence in general, as SRS is basically a focused treatment that controls the potential risk of distant tumors outside the previous irradiated regions and decreases the chance of local tumor recurrence after SRS (Kondziolka *et al.*, 2000).

Compared to WBRT alone, the improvement in local control offered by SRS is far better. Supporting that, Kondziolka and colleagues conducted a study to examine local control in patients with two to four metastases who underwent either WBRT alone or WBRT and SRS. The survival difference between the two groups was not statistically significant because the study was stopped after 60% accrual. But the interim analysis showed a dramatic advantage in SRS, as the median time to local failure was 6 months (95% CI, 3.5-8.5) in patients who received WBRT alone and 36 months (95% CI, 15.6-57) in patients who received both WBRT and SRS ($p< 0.001$). The life time gained median of patients who received WBRT alone was 7.5 months, while the patient who received WBRT plus SRS lived 11 months ($p=0.22$). Survival did not depend on histology or the number of tumors, but was related to the extent of extracranial disease ($p=0.02$) (Kondziolka *et al.*, 1999a). The median survival time for untreated intracranial metastases was approximately 1 month (Paul and James, 1994) and on the basis of historical studies it has been found that the medical treatment of brain metastasis with glucocorticoids alone improves survival by less than 3 months; the addition of WBRT improves it by 3 to 6 months (Smith and Lee, 2007). The overall length of survival was significantly longer in the surgical group versus the radiation group (median, 40 weeks versus 15 weeks; P < 0.01), and the SR patients remained functionally independent longer than the radiation group (median, 38 weeks versus 8 weeks; P < 0.005) (Patchell *et al.*, 1990).

Andrews and colleagues conducted a study from January 1996 to June 2001 with 333 patients with single brain metastases from 55 participating RTOG institutions, in which 167 were treated with WBRT plus SRS and 164 were treated with WBRT alone. Median survival time of 6.5 versus 4.9 months, respectively p=0.039 (Andrews *et al.*, 2004).

In order to compare SRS with WBRT and SRS alone, a randomized controlled trial study was done by Aoyama and colleagues with a total of 132 patients showed that the combination of WBRT and SRS did not improve the survival time of those patients, the median survival time and the 1-year actuarial survival rate for WBRT and SRS were 7.5 months and 38.5% (95% CI, 26.7-50.3%) respectively, and 8.0 months and 28.4% (95% CI, 17.6-39.2%) respectively for SRS alone (P=.42). But brain tumor recurrence was more frequent in the SRS alone group: the 12 month brain tumor recurrence rate was 46.8% in the WBRT and SRS group and 76.4% for the SRS alone group (P<.001) (Aoyama *et al.*, 2006).

Comparison of SRS and SR

The treatment options for patients with a very limited number of brain metastases are controversial. The question remains, which of SR+WBRT and WBRT+SRS or SR versus SRS is superior with respect to treatment outcomes. Two retrospective studies by Gelber and colleagues, Kurtz and colleagues comparing OP+WBRT versus WBRT+SRS for single brain metastasis have been done, both suggesting better local control of the treated metastases but not of significantly improved survival for WBRT+SRS (Gelber *et al.*, 1981; Kurtz *et al.*, 1981). The study of O'Neil and colleagues also confirmed that there was no significant difference in patient survival (p = 0.15) between SR and SRS, but the 1-year survival rate was 56% for the SR patients and 62% for the SRS patients (O'Neil *et al.*, 2003).

The size of the brain metastasis has a big influence to the choice of treatment modality. Local control of SRS for the larger tumors is compromised because of the need to limit the radiation dose prescribed (Patchell *et al.*, 1998; Smith and Lee, 2007), to make sure that the minimum amount of radiation is sufficiently delivered to every tumor cell and the tumor margin, while minimizing the radiation dose to the surrounding brain parenchyma. So, the general goal, in order to achieve the effective local control and the survival benefit of SRS, is to include the entire gross tumor volume within the prescribed radiation dose. The modern SRS systems can contour isodoses to the tumor volume precisely, but the large tumor volume results in a higher integral radiation dose to the surrounding brain and that may cause radiation toxicity. To avoid that, the prescription should generally be lower, which is why the ability to achieve local control is compromised (Smith and Lee, 2007; Shaw *et al.*, 2000). So, it would be better to treat the larger tumors with a mass effect by SR if the patient is young, has a high KPS and has good systemic disease control. SRS should be used if tumors are small, multiple, deep or have a minimal mass effect (Smith and Lee, 2007; Patchell *et al.*, 1998). Regarding the influence of the size of the tumor on local tumor control, some studies have been conducted, such as those of Shaw and colleagues; Kihlstrom and colleagues; Chang and colleagues, etc… Shaw and colleagues conducted a dose escalation study to outline maximum tolerated doses in patients undergoing SRS after WBRT or fractionated external-beam radiation. The study variable was stratified by the size of tumor into groups of less than 2 cm, 2 to 3 cm, or 3 to 4 cm. The result was found that the maximum tolerated doses of single fraction radiosurgery were defined as 24 Gy, 18 Gy, and 15 Gy for tumors less than 2 cm, 2.1-3.0 cm, and 3.1-4.0 cm in maximum diameter. He concluded that the maximum tolerated dose was not reached for tumors larger than 2 cm (Shaw *et al.*, 2000). Some studies also found differences in local tumor control based on size of the tumor, for example, Kihlstrom and colleagues reported a 78% response rate in tumors 2 cm or smaller compared with a 50% response rate in tumors 10 cm or greater (Kihlstrom *et al*, 1993); Selek and colleagues reported that the 1-year local control for all patients treated with SRS was 49%, and among the patients initially treated with SRS alone, the 1-year local control was better for patients with tumors ≤ 2 cm than with tumors >2 cm: 75.2% vs. 42.3% ($p < 0.05$) (Selek *et al.*, 2004). Chang and colleagues found that local control rates for 1 year was 86% and for 2 years was 78% for tumors less than 1 cm in diameter compared with 56% and 24% for tumors of larger diameters (Chang *et al*., 2003).

Furthermore, the success of local control is also influenced by the PTS. Supporting to that, Mehta and colleagues conducted a study to evaluate volumetric response rates based on the primary tumor histological characteristics and found complete response to treatment in 100% of lymphomas, 67% of melanomas and sarcomas, 50% of NSCLCs, 33% of breast cancers, and 11% of renal cell carcinomas (Mehta *et al*., 1992). Chang and colleagues conducted a retrospective study on the influence of histopathological diagnosis on the outcome of radioresistant brain metastases treated with SRS, with a total sample size of

264 brain metastases and a median tumor volume of 1.6 cm^3 (range, 0.06 - 27.5 cm^3) in 189 patients who were consecutively treated with SRS between August 1991 and July 2002. The study reported that the median overall survival was 7.5 months (range, 0.16-52 months), stratified on the basis of histopathological diagnosis of brain metastases it revealed a median survival time of 9.1 months for renal cell carcinoma, 6.7 months for melanoma, and 9.1 months for sarcoma. The actuarial 1-year rates of overall survival for patients with renal cell carcinoma, melanoma, and sarcoma were 39.7, 24.7 and 22.2% respectively (P= 0.035). The incidence of neurological death was lower among patients diagnosed with renal cell carcinoma, at 31%, than among patients with melanoma, at 66%, or sarconoma, at 60% (P< .001). He concluded that SRS is less effective in treating melonoma or sarcoma brain metastases than in treating renal cell carcinoma brain metastases (Chang *et al.*, 2005). In addition, brain metastasis site influences the prescription dose as well, especially as the optic nerve and brainstem are more sensitive to radiation-induced edema than the frontal lobe, so the prescription dose must be reduced to protect such structures (Flickinger *et al.*, 2000).

The failure of SRS was examined in a study by O'Neill and colleagues the local tumor control failure rate of SR was 58% while none of the SRS cases had local failure (O'Neill *et al.*, 2003).

The complications of SRS were reported to include peritumoral edema, radiation-induced necrosis, tumoral hemorrhage, and radiation-induced neoplasia. Chang and colleagues found that 17 brain metastasis patients out of 264, equivalent to 6.4%, showed hemorrhage on neuroimaging at a median follow-up time of 2.5 months (range, 0.03-7 months) of treatment with SRS, and 8 of 17 hemorrhagic metastases required the hemorrhage corrective surgery; 10 of 264 metastases (3.8%) had significant peritumoral edema, half of them requiring resection too; 8 of 264 metastases (3%) had pure necrosis on histopathological examination at a median follow-up time of 9.6 months (range 1.6-22 months) (Chang *et al.*, 2005). But according to Suki and colleagues who studied a literature review of the complications of SRS in patients with brain metastasis from 1995 to 2005 through MEDLINE, the analysis of brain metastases' representation, description, and location is inadequate as a predictor of SRS-related complications (Suki D, 2007).

Cost-effectiveness of SRS

There are four major therapeutic approaches used to manage brain Metastasis: observation with steroids, radiotherapy alone, SR with postoperative radiotherapy, and SRS with radiotherapy. Based on historical studies, medical treatment with gluco-corticoids alone yields a life expectancy of less than 3 months; the addition of WBRT, a traditional treatment, improves survival to 3 to 6 months (Markesbery *et al.*, 1978; Borgelt *et al.*, 1980); aggressive local treatments such as resection and radiosurgery in combination with WBRT can achieve median survival times of 9 to 12 months in some patients (Patchell *et al.*, 1990; Andrews *et al.*, 2004), depending on some different factors such as age, PTS, etc. For example, in the research of Noordijk, age is a strong and independent prognostic factor: patients older than 60 years had a hazard ratio of dying of 2.74 (p=0.003) compared with younger patients (Noordijk *et al.*, 1994).

Rutigliano and colleagues produced a paper titled 'The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors' to analyze the economic efficiency of different treatments by comparing the results of SR and SRS treatment as reported in the medical literature between 1974 and 1994. The results revealed that SRS had a lower uncomplicated procedure cost ($20,209 versus $27,587), a lower average complication cost per case ($2,534 versus $2,874), and a lower total cost per procedure ($22,743 versus $30,461); was more cost-effective ($24,811 versus $32,149 per LYS); and had a better incremental cost-effectiveness ($40,648 versus $52,384 per LYS) than SR (Rutigliano *et al.*, 1995).

Mehta and colleagues conducted a study titled 'A cost-effectiveness and cost-utility analysis of SRS versus SR for single-brain metastases' to review all patients who underwent SR or SRS for single-brain metastases between January 1989 and July 1994, which involved 46 SR and 135 SRS procedures. The results showed that both SR and SRS yielded superior survival and functional independence comparing to WBRT alone, with minor differences in outcome between the two modalities; resection resulted in a 1.8-fold increase in cost, compared to SRS. The average cost per week of survival was $310 for radiotherapy, $524 for SR plus radiation, and $270 for SRS plus radiation. The research concluded that SRS appears to be more cost-effective (Mehta *et al*., 1997).

Cho and colleagues conducted a retrospective study titled 'Socioeconomic Costs of Open Surgery and Gamma Knife Radiosurgery for Benign Cranial Base Tumors' with 174 benign cranial base tumor patients (with tumors of less than 3 cm in diameter), in which 94 patients were treated with SR and 80 patients with SRS. The socioeconomic costs includes direct cost of intensive care unit, ward cost, operating room cost, and outpatient visiting cost; and indirect costs of loss of workdays, length of hospital stay, surgical complications and mortality. It was found that SR has a higher socioeconomic cost (US$34,453+/-97,277) than SRS (US$10,044 +/- 7,481), P < 0.01. SRS has significantly higher CEA (US$3762/QALY) than SR (US$8996/QALY), P < 0.01. The reasons for this difference lie in the socioeconomic cost of SR resulting from the indirect costs of workdays lost and mortality. SRS is associated with shorter hospital stay, fewer workdays lost, fewer complication and reduced mortality, so it results in less socioeconomic loss, and better cost-effectiveness (Cho *et al.*, 2006).

Wellis and colleagues analysed and compared the effective direct costs of microsurgical treatment of intracranial pathology potentially amenable to SRS as they arose between 1998-1999 in 127 patients with various diagnoses such as meningiomas, acoustic neuroma, brain metastases, and arteriovenous malformations less than 3 cm in diameter, who were treated with SR or SRS. The results showed that the average costs of surgery, the intensive care unit, and inpatient and ancillary services, etc. were 15,242 euro for SR and 7,920 euro for SRS. SRS is a more cost-effective treatment for brain metastasis compared to SR. The author suggested that of course, the decision of choosing SR or SRS as treatment for a particular patient should not be determined by economics, but rather that the cost, access, and resource management must be included in professional discussions of treatment algorithms, because these are increasingly important (Wellis *et al.*, 2003).

SRS using Gamma knife is different in terms of CEA versus a modified Linear Accelerator (Linac), according to Griffiths who estimated the incremental cost of Gamma Knife versus a modified Linac to be AUD209 per patient. However, 'this result is sensitive to variations in assumptions. A second analysis proportioning capital costs according to SRS use showed that Gamma Knife may cost up to AUD1,673 more per patient (Griffiths *et al.*, 2007). Ohinmaa show that the cost per patient for Gamma Knife was estimated as Cdn$11,237 compared with Cdn$10,807 for Linac, with an incremental cost per patient of Cdn$430 (Ohinmaa, 2003).

Appendix: Primary brain tumors

Primary cerebral malignancies are among the most disabling and lethal types of cancer, basing on data of some developed countries, generally accounting for approx 1.4% of all cancers and 2.3% of all cancer-related deaths, and associated with severe disability and a high risk of death. According to the Surveillance, Epidemiology, and End Results Program database, in the USA between 1973 and 2001 its incidence rate varied from 4 to 10 per 100 000 in the general population; an overall age-adjusted incident rate of 6.1 cases per 100 000 person years (Yang M *et al.*, 1991; El-Zein R, 2005; Deorah *et al.*, 2006). In Canada, the incidence rates of all ages during 1983-1985 were 5.38 and 7.31 per 100 000 in males and between 3.74 and 4.91 per 100 000 in females (Yang M *et al.*, 1991). The age-adjusted incident rates were significantly different according to sex: 7.4 cases compared to 5.0 cases per 100 000 persons per year in males and females, respectively (RR: 1.48, 95%; CI: 1.45–1.51); and according to age: among children (<20 years old), young/middle age adults (20-65 years old), and the elderly (>65 years old) the incidence rates were 2.5, 5.5, and 17.5 per 100 000 person per year, respectively (Deorah *et al.*, 2006). There is a clear increase in the higher ages: the rates are 4 per 100,000 up to the age of 12 years; 6 per 100,000 up to the age of 35 years; 18 per 100,000 up to the age of 55 years; and 70 100,000 up to the age of 75 years. The relative risk among the elderly compared to the young and the middle-aged was 3.18 (95% CI 3.09–3.22) (El-Zein R, 2005; Deorah *et al.*, 2006).

The treatment management of this disease has improved in the last decades in USA. The five-year survival rates were 21% in the 1970s, 27% in the 1980s, and 31% in the 1990s, p< 0.001 (Deorah *et al.*, 2006). The survival rates of primary brain tumor patients of less than 65 years of age are reduced with the longer survival periods. From 1 to 4 year period, the rates of survival were 57%, 45%, 41% and 37% respectively. When all ages are combined, the median survival period is about 9 months and less than 25% survive for more than 5 years. Many of those who do are left with permanent disabilities (Yang M *et al.*, 1991).

In children of Germany, CNS tumors accounted for 19.4% of all malignancies. The probability of a child of up to 15 years old suffering from a CNS tumor is approximately 0.04%, equal to 1 per 2500 children. A higher probability occurs in boys than girls at a ratio of 1.2:1.0. Astrocytomas represent the most common type with 41.7% of all CNS tumors, followed by medulloblastomas (18.1%), ependymomas (10.4%), supratentorial primitive neuroectodermal tumors (6.7%), and craniopharyngiomas (4.4%). Regarding the site of CNS tumors, tumors occurring in the cerebellum (mostly at the vermis or the fourth ventricle) are the more common, accounting for 27.9% of all tumors, followed by 21.2% of all tumors in the cerebrum, 13.8% in the brainstem (mostly in the pons), 13.1% in the diencephalon, and 11.8% in the infratentorial brain. However, if the brain is considered as two areas, the supratentorial and the infratentorial, the ratio is nearly 1:1 for all CNS tumors. The survival rates after 5 and 10 years are 64% and 59%, respectively, in which the best prognosis is for children with craniopharyngioma (the 10-year survival rate is 87%), followed by astrocytomas (the 10-year survival rate is 73%) (Kaatsch *et al.*, 2001).

Gliomas

These arise from the gliacyte of the nervous system; as the most common primary brain tumor, they comprise more than 40% of all CNS neoplasms; and the peak of the incidence rate is around the age of 60 years. Gliomas are derived from astrocytes, oligodendrocytes, or ependymal cells, and are named with the putative cell types of their origin as astrocytomas, oligodendrogliomas, and ependymomas (El-Zein R, 2005).

Astrocytomas account for the majority of brain tumors and in children are the most common brain tumors, accounting for 40-45% of all NCS malignancies (Arndt *et al.*, 2007; IARC, 1998). Astrocytomas are mostly benign. However, depending on the location, it can interfere with vital sensory functions and frequently recurs and progresses. Sutton and colleagues found that 18% and Dirven and colleagues found that 19% of pediatric patients experience a recurrence after resection (Sutton *et al.*, 1996; Dirven *et al.*, 1997). In adults PA is rarely observed but is almost never benign, has a considerable recurrence rate and is an aggressive cause of death. The recurrence rate after the first macroscopic total resection is 2% versus 16% after a subtotal resection (Stüer *et al.*, 2007).

Oligodendrogliomas are uncommon primary intracranial tumors, which account for 5–7% of all intracranial tumors. They are located commonly in the cerebrum, especially in the frontal or temporal lobes, and are more often observed in adults (7-12%; median age is 42 years). They tend to grow slowly. The median survival period is 105 months. Oligodendrogliomas are diffuse glial tumors which traverse into the cerebral spinal fluid and are then capable of metastasizing and becoming more difficult to surgically remove. They are graded from 1 to 4, depending on its malignancy and rate of growth (Hess *et al.*, 2004; El-Zein R, 2005).

Ependymomas comprise approximately 4–6% of all brain tumors and occur more often in children and young adults up to the age of 20 years, in which 30% occur before the age of 3 years old, and account for 5-10% of all pediatric CNS tumors. Around 90% are intracranial and other 10% are intraspinal. In children, these tumors are more aggressive than in adults. In adults, it is relatively rare, accounting for about 2-5% of all intracranial neoplasm (Reni *et al.*, 2004; Korshunov *et al.*, 2004; El-Zein R, 2005).

Ependymomas originate from neuroectoderm and arise from ependymal cells which line the ventricles of the brain and the central canal of the spinal cord, the filum terminale, the choroid plexus, or the white matter adjacent to the highly angulated ventricular surface. It spreads from the brain to the spinal cord via the cerebrospinal fluid, and causes notable swelling of the ventricle or hydrocephalus. It also can be caused by the migration of fetal ependymal cell residue from periventricular areas in the brain parenchyma (Centeno *et al.*, 1986; Oppenheim *et al.*, 1994; El-Zein R, 2005).

Intracranial ependymomas are histologically classified into low-grade or high-grade/ anaplastic. Despite its appearance of being histologically benign, it is determined as a major prognostic factor. Low-grade ependymomas can display very aggressive local behavior, and anaplastic ependymomas have a worse outcome. In adults, the average 5- and 10-year OS rates are 57-67% and 40-50% respectively. Its PFS rates were 33-43% and 20-25% respectively. In adults, younger age is associated with longer survival (Shu *et al.*, 2007; Metellus *et al.*, 2008; Reni *et al.*, 2004). In children, the average 5- and 10-year OS rates were 66.2% (95% CI, 50.1–78.2%) and 56.3% (95% CI, 39.1–70.3%) respectively. The average 5- and 10-year PFS rates were 40.7% (95% CI, 26.6–54.3%) and 30.9% (95% CI, 17.3–45.5%) respectively (Shu *et al.*, 2007).

Meningiomas

Regarded as benign tumors, they originate from the cells of the endothelial side of the meninges surrounding the brain. Meningiomas account for 10–19% of all brain tumors. The tumors often comprise a large proportion of the cranial base, so it is named a "anatomic malignancy" (El-Zein R, 2005).

Medulloblastomas

These are malignant tumors, derived from primitive or poorly developed cells, and constitute 3–5% of all brain tumors. They occur at all ages but the most common malignancies are observed in children, which represent up to 25% of all brain tumors in children, with the peak incident at ages 3 to 8 years. Because of its location and its association with the fourth ventricle, it is often accompanied by metastases to the ventricular system and the neuroaxis through the cerebral spinal fluid (25–45%). Up to 5% metastases have already occurred at the time of diagnosis (El-Zein R, 2005).

Gangliogliomas

Generally this tumor is benign containing both neurons and glial cells, with rare malignant progression of the glial component. They usually occur in the temporal lobes and cerebral hemispheres. Gangliogliomas account for approximately 1% of all CNS tumors. They are observed in patients of all ages, but more commonly diagnosed in young adults (< 30 yr) and children (Johannsson *et al.*, 1981; El-Zein R, 2005; Pandita *et al.*, 2007).

Schwannomas (Neurilemomas)

Originated from Schwann cell and often to be benign tumors, which usually occur in the head and neck region (trigeminal, facial, vestibular, vagus nerves; parotid, thyroid, vocal cord, floor of mouth, orbit and infra-temporal fossa), and most often originate in the cranial nerves, which are responsible for hearing and balance. They are usually located nearby the cerebellum (Bayindir *et al.*, 2006; Haas-Kogan *et al.*, 1999), such as in the acoustic neuroma of the eighth cranial nerve. However, the tumor can also occur in other cranial nerves such as III, IV and VI (Kim *et al.*, 2008a). Accounting for approximately 8% of primary brain tumors, deriving from peripheral nerve sheath they can develop a malignant course with metastases early (El-Zein R, 2005).

Chordomas

It is relatively rare and as midline tumor in the CNS, about 0.5% in the primary intracranial brain tumors. That typically arises along the neuraxis, mainly occur in the sacrococcygeal area (50%) or the basisphenoidal region (30-40%). Chordomas usually appear in 30-50 years of age people, men were observed more often than in women. It is amenable to treatment but stubbornly recurs over a period of 10-20 years (Rubinstein, 1972; El-Zein R, 2005).

Chapter 3. Extracranial metastatic patterns at the occurrence of brain metastases

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ABSTRACT

Purpose: Extracranial metastases and their frequency by sites have been described as prognostic factors for survival of patients with brain metastasis. However, these factors need to be identified and described in more detail in a large series of patients.

Methods: Using routine data from the largest German health insurance fund, 5,074 patients with brain metastasis who were diagnosed and treated in 2008 were analyzed to identify the frequency and distribution of extracranial metastatic sites concurrent with brain metastasis in relation to age, gender, and tumor type.

Results: Brain metastases were observed in males more frequent than in females (56.4%; 43.6%, respectively. P<0.001), and were most often from lung (51.2%), breast (12.3%) and unknown (7.5%) primaries. Extracranial metastatic sites were observed in 58.8% of patients; the number of sites was from 1 to 7, with a mean of 1.11. For the 16 most common primary sites the range was from 0.13 to 1.91. In 11 of these 16 sites, lungs were the most common concurrent metastatic site. Lung cancer, breast cancer, non-Hodgkin's lymphoma, and testicular cancer most commonly metastasized to bone, and bladder cancer to kidneys.

Conclusion: Different primary tumors have different frequencies and patterns of extracranial metastatic sites concurrently with brain metastasis. The lung is the most common metastatic site of most primary tumors, bone for a few tumors, and kidneys for bladder cancer. For the unknown primary tumor type, screening for these most common metastatic sites must be intensified, in particular when molecular assessment is not available.

Keywords: Extracranial metastasis, neoplasm metastasis, epidemiology

Introduction

Brain metastasis is the most common CNS neoplasm, occurring clinically in 20-60% of cancer patients during the course of their disease (Aronson *et al*., 1964; Delattre *et al*., 1988; Morris *et al*., 2004). On autopsy, brain metastasis has been found in 55-85% of patients (Chason *et al*., 1963; Amer *et al*., 1978; Walker *et al*., 1985; Johnson and Young, 1996). Brain metastasis often causes serious clinical problem for the patients, limits survival, and worsens the quality of life (O'Neill *et al*., 2003; Ranasinghe and Sheehan, 2007). To prolong the survival of those patients, a vital factor that should be carefully considered and managed is the concurrence of extracranial metastasis and its activity. The presence of extracranial metastasis is known as an independent prognostic factor for the survival of patients with brain metastases (Jeremic *et al*., 2000; Kondziolka *et al*., 2005; Rades *et al*., 2007; Itoh *et al*., 2003). In addition, the number of extracranial metastatic sites is negatively correlated with survival (Arteaga *et al*., 1988; Cho *et al*., 2008; Paralkar *et al*., 2008).

Different primary tumor types metastasize with different frequencies and at different sites, so identifying the metastatic pattern would be useful in order to identify the primary tumor (Pilgrim, 1969; Disibio and French, 2008; Fidler, 2003). This is more important for patients with brain metastasis, because the primary tumor is unknown in 5-40% of patients presenting with the symptoms of brain metastases (Bartelt and Lutterbach, 2003; Khansur *et al*., 1997; Salvati *et al*., 1995), which should be described in detail in a large series of patients for better understanding.

The primary goal of this study was to provide a descriptive epidemiology including the frequency and distribution of extracranial metastatic sites occurring concurrently with brain metastasis in relation to age, gender, and primary tumor type.

Material and methods

Data sources

Patients with main diagnosis or secondary diagnosis of brain metastasis (C79.3) and admitted between January 2008 and December 2008 were searched from Wissenschaftliches Institut der AOK (WIdO) database which has data from AOK, the largest health insurance fund association in Germany, serving approximately 30% of the German population (AOK, 2010). Five-thousand and seventy-four different patients had a total of 10,140 inpatient stays during 2008 (range per patient within 2008: 1-8 hospital inpatient stays). For those patients with more than one stays, we selected the first stay within that year, irrespective of whether C79.3 was coded as main or secondary diagnosis, i.e. whether it constituted the main reason for the inpatient treatment, which it was the in 1,418 (28%) of these cases. Another 2,691 patients (53%) had a main diagnosis of malignant neoplasm (C00-C97, excl. C79.3) and the 965 remaining patients (19%) had different main diagnoses. Of those different main diagnostic patients, 481 patients (49.8%) returned to the hospital for treatment of their malignant disease in the same year. The interval (mean ± SD) between the initial hospital stay and the treatment for the malignant disease was 44.7± 52.5 days.

Methods

The primary tumor types were categorized according to the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) (WHO, 2001a). The classification included 36 specific tumor types including an extra category for cancer of unknown primary (C80).

The number of extracranial metastatic sites generated by all primary sites were quantified and categorized into 30 categories using the International Classification of Disease, 10th Edition (ICD 10) with 26 categories (C77.0-C77.9; C78.0-C78.9; C79.0-C79.8), in which the C79.8 was in more detail categorized into five sub-categories (C79.81, C79.82, C79.83, C79.84 and C79.88) following the ICD-10-GM (DIMDI, 2007) (Table 12). Patient age was categorized into 6 age groups 0-19 years (G1); 20-39 years (G2); 40-49 years (G3); 50-59 years (G4); 60-69 years (G5); 70 years and older (G6).

ICD10	Current extracranial metastatic site of	ICD10	Current extracranial metastatic site of
C77.0	Lymph nodes of head, face and neck	C78.7	Liver
C77.1	Intrathoracic lymph nodes	C78.8	Other and unspecified digestive organs
C77.2	Intraabdominal lymph nodes	C79.0	Kidney and renal pelvis
C77.3	Axillary and upper limb lymph nodes	C79.1	Bladder and other and unspecified urinary organs
C77.4	Inguinal and lower limb lymph nodes	C79.2	Skin
C77.5	Intrapelvic lymph nodes	C79.3	Brain and cerebral meninges
C77.8	Lymph nodes of multiple regions	C79.4	Other and unspecified parts of nervous system
C77.9	Lymph nodes, unspecified	C79.5	Bone and bone marrow
C78.0	Lung	C79.6	Ovary
C78.1	Mediastinum	C79.7	Adrenal grand
C78.2	Pleura	C79.81*	Mammary gland
C78.3	Other and unspecified respiratory organs	C79.82*	Genital organ
C78.4	Small intestine	C79.83*	Pericarditis
C78.5	Large intestine and rectum	C79.84*	Heart
C78.6	Retroperitoneum and peritoneum	C79.88*	Other specified sites

(* *ICD10-GM*)

Table 12. Coding of extracranial metastatic sites

For statistical reasons, the frequency of primary cancer site with concurrent extracranial metastasis and the mean of concurrent extracranial metastatic sites by primary site were calculated only for those primary sites which had more than 30 cases in the study sample. Sixteen primary sites out of 36 categories met this threshold (Table 13).

Data analysis was performed by use of SPSS 16.0 statistics software. Number of extracranial metastatic sites in relation to primary tumor type, sex, and age groups was analyzed as mean value plus and minus standard deviation. An ANOVA test was used for analyzing those mean values. The results were considered statistically significant for P-values ≤0.05.

Results

There were more males then females in the patient cohort, 56.4 and 43.6%, respectively (P<0.001). The number of patients per primary site varied from 2,597 cases of lung cancer to only two cases of malignant immune proliferative disease. Primary sites with the highest proportion are lung cancer (51.2% of the sample population), followed by breast (12.3%), cancer of unspecified primary sites (7.5%), kidney and renal pelvis (4.0%), and melanoma of the skin (3.9%) (Figure 6). The most common primary tumors acting as sources of brain metastases, by sex, were lung cancer and cancer of unknown primary in male patients; lung cancer and breast cancer in female patients (Figure 7).

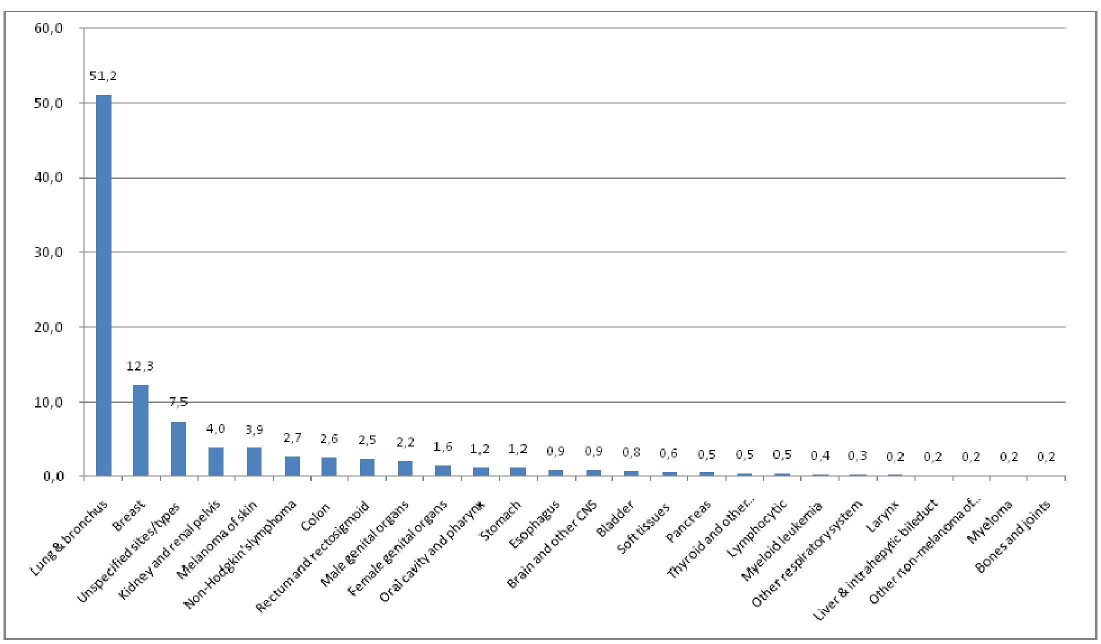
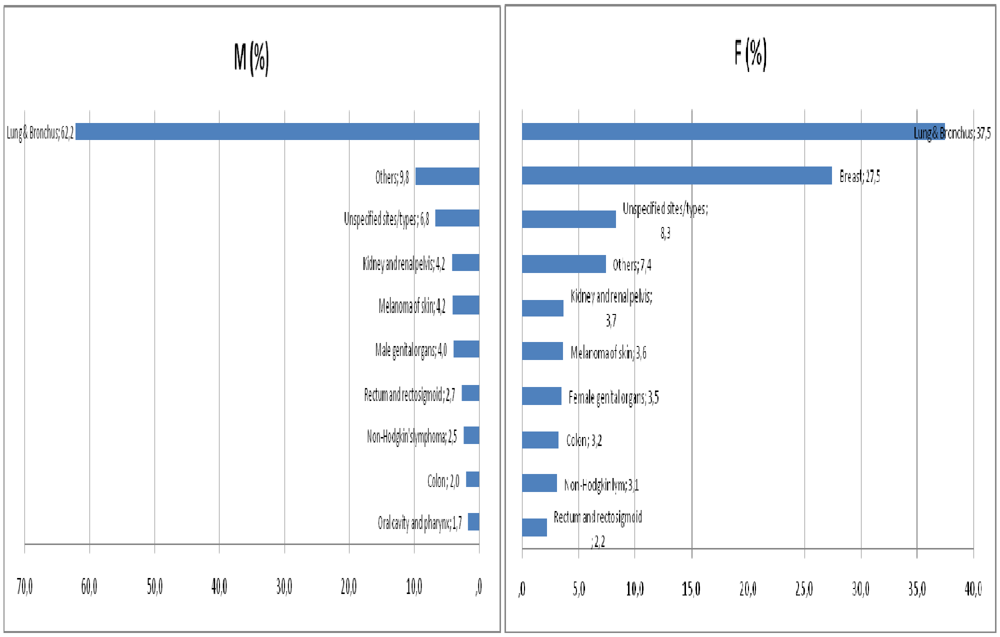


Figure 6. Patients with brain metastases - Frequency of primary tumor site specifications in descending order



(NB: 100% = to all patients with brain metastases)

Figure 7. Distribution of primary tumor types in patients with brain metastases by sex

Extracranial metastatic sites were observed in 58.8% of all patients; the range from 1 to 7. The mean number of extracranial metastatic sites across all patients was 1.11 with a range from 0.13 to 1.91 for the 16 most common primary sites (totaling of >96% of all cases) (Table 13). A relatively large number of extracranial metastatic sites was observed for melanoma of the skin, stomach, rectum and rectosigmoid, and breast cancer. The number of concurrent extracranial metastatic sites was relatively low for non-Hodgkin's lymphoma, brain and other CNS, and bladder cancer. Female and male patients had a similar number of extracranial metastatic sites for most tumor types, except for cancer of soft tissues, for which the mean number of extracranial metastatic sites was significantly higher for male than for female patients ($P<0.05$). Significantly different mean numbers of extracranial metastatic sites among the six compared age groups were observed for kidney and renal pelvis cancer, lung cancer, cancer of unspecified primary sites, and non-Hodgkin's lymphoma ($P<0.05$). Among those sites, the mean of number of extracranial metastases was highest for lung cancer patients in the age group of 20-39 years (mean = 1.73), followed by age group of 50-59 years of patient with kidney and renal pelvis cancer (mean = 1.65) (Table 13).

Primary tumor sites	**Mean**	**SD**	**95% Confidence Interval (CI)**		**Sex**			**Age groups**						
					M	**F**	**P-value**	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**	**P-value**
Melanoma of skin	1.91	1.63	1.68	2.14	2.06	1.70	0.12		2.27	2.59	2.10	1.91	1.61	0.06
Stomach	1.43	1.31	1.10	1.76	1.41	1.50	0.81				1.64	1.20	1.21	0.24
Rectum and rectosigmoid	1.37	1.33	1.13	1.60	1.21	1.60	0.10				1.61	1.40	1.20	0.52
Breast	1.36	1.19	1.27	1.45	1.00	1.36	0.54		1.35	1.55	1.35	1.45	1.21	0.22
Kidney and renal pelvis	1.35	1.17	1.18	1.51	1.40	1.27	0.41			1.56	1.65	1.31	1.16	0.00
Colon	1.29	1.14	1.09	1.48	1.38	1.22	0.44				1.73	1.35	1.18	0.29
Soft tissues	1.25	1.24	0.82	1.68	1.92	0.79	0.01							0.43
Oral cavity and pharynx	1.13	1.19	0.83	1.43	1.14	1.08	0.86			1.20	1.44	0.87	0.75	0.31
Male genital organs	1.11	0.91	0.94	1.28		n/a				1.00	1.10	1.08	1.00	0.64
Lung & bronchus	1.09	1.18	1.04	1.13	1.10	1.06	0.51		1.73	1.12	1.23	1.09	0.96	0.00
Esophagus	0.98	1.26	0.62	1.34	1.05	0.40	0.28				1.10	0.75	0.85	0.17
Female genital organs	0.97	1.30	0.68	1.26		n/a					1.53	1.04	0.66	0.13
Unspecified sites/types	0.71	1.16	0.60	0.83	0.83	0.60	0.04			0.90	0.93	0.70	0.56	0.00
Bladder	0.68	0.93	0.40	0.97	0.75	0.44	0.39							0.27
Brain and other CNS	0.30	0.59	0.12	0.48	0.21	0.47	0.19							0.29
Non-Hodgkin's lymphoma	0.13	0.39	0.06	0.20	0.16	0.10	0.36		0.75	0.24	0.08	0.05	0.13	0.00
Total	**1.11**	**0.02**	**1.07**	**1.14**	**1.11**	**1.11**	**0.91**	**0.45**	**1.59**	**1.27**	**1.27**	**1.11**	**0.96**	**0.00**

Notes: n/a not applicable, empty field = fewer than 10 patients

*Table **13.** Mean numbers of extracranial metastatic sites in patients with brain metastases for the 16 most common primary tumor sites in general and by sex and age groups*

Primary tumor sites	All primary tumor sites		Lung & bronchus		Breast		Unspecified sites/types		Kidney and renal pelvis		Melanoma of skin		Non-Hodgkin's lymphoma		Colon		Rectum and rectosigmoid	
Oder of Metastatic site (Me-site)	Me-site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%
First	C79.5	22.2	C79.5	20.8	C79.5	32.8	C78.0	23.2	C78.0	39.0	C78.0	24.2	C79.5	66.7	C78.0	35.5	C78.0	36.3
Second	C78.0	18.9	C78.7	18.0	C78.7	22.2	C79.5	20.2	C79.5	24.3	C78.7	15.5	C78.0	11.1	C78.7	30.1	C78.7	25.0
Third	C78.7	18.2	C77.1	15.5	C78.0	18.8	C78.7	19.9	C78.7	8.8	C79.5	10.3	C79.4	11.1	C79.5	15.1	C79.5	10.7
Fourth	C77.1	8.9	C78.0	12.9	C78.2	5.5	C79.7	4.8	C77.2	4.0	C79.2	7.9	C77.1	5.6	C78.6	4.2	C77.1	4.2
Fifth	C79.7	6.0	C79.7	9.9	C77.3	3.5	C77.1	4.0	C78.8	2.9	C78.8	5.3	C79.0	5.6	C77.2	3.0	C77.2	2.4
Sixth	C78.2	3.6	C78.2	4.1	C79.2	2.4	C77.2	2.6	C78.2	2.6	C77.8	5.0			C78.2	3.0	C78.2	2.4
Seventh	C77.2	2.1	C77.8	2.1	C78.6	1.8	C77.9	2.6	C77.1	2.2	C79.88	4.5			C77.1	2.4	C79.7	2.4
Eighth	C77.8	2.1	C77.9	1.8	C79.88	1.6	C79.2	2.6	C79.0	1.8	C79.7	3.9			C77.0	1.2	C77.5	1.8
Ninth	C79.2	2.1	C78.1	1.6	C78.1	1.3	C79.88	2.6	C79.2	1.8	C77.3	3.4			C77.8	1.2	C78.6	1.8
Tenth	C79.88	1.8	C79.88	1.6	C77.1	1.1	C77.8	2.2	C77.9	1.5	C78.6	2.9			C79.0	1.2	C79.0	1.8

(continued)

Primary tumor sites	Male genital organs		Female genital organs		Oral cavity and pharynx		Stomach		Esophagus		Brain and other CNS		Bladder		Soft tissues	
Oder of Metastatic site (Me-site)	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%	Me-Site	%
First	C79.5	54.1	C78.0	25.0	C78.0	32.9	C78.0	17.4	C78.0	30.0	C78.0	26.1	C79.0	46.2	C78.0	42.9
Second	C78.0	13.1	C78.7	14.5	C77.0	15.7	C78.7	15.1	C79.5	20.0	C78.7	21.7	C78.0	23.1	C79.5	28.6
Third	C78.7	9.8	C79.5	14.5	C79.5	11.4	C79.5	15.1	C77.8	7.5	C79.5	13.0	C79.4	15.4	C77.2	10.7
Fourth	C77.9	3.3	C78.6	13.2	C77.1	5.7	C77.2	10.5	C78.7	7.5	C77.2	8.7	C79.5	7.7	C78.7	10.7
Fifth	C77.2	2.5	C77.2	6.6	C78.7	5.7	C77.8	9.3	C77.0	5.0	C77.0	4.3	C79.88	7.7	C77.9	3.6
Sixth	C77.5	2.5	C78.2	3.9	C77.2	4.3	C78.6	9.3	C77.1	5.0	C77.1	4.3			C79.7	3.6
Seventh	C78.2	2.5	C79.7	3.9	C79.2	4.3	C79.2	4.7	C77.3	5.0	C77.8	4.3				
Eighth	C77.8	1.6	C77.1	2.6	C79.7	4.3	C79.7	4.7	C77.9	5.0	C78.6	4.3				
Ninth	C78.6	1.6	C78.1	2.6	C78.2	2.9	C79.0	3.5	C79.88	5.0	C77.5	2.2				
Tenth	C79.0	1.6	C79.0	2.6	C78.8	2.9	C77.1	2.3	C77.4	2.5	C78.1	2.2				

Table 14. Frequency of extracranial metastatic sites in patients with brain metastases, in total and for the 16 most common primary tumor sites

The three most common metastatic sites involved concurrently with brain metastases were bone metastases (C79.5), lung metastases (C78.0), and liver metastases (C78.7), which accounted for 22.2, 19.0 and 18.3% of the total concurrent extracranial metastatic sites, respectively. Lung (C78.0) was the most common metastatic site for 11 out of 16 primary tumors. The primary tumors that were most frequently associated with concurrent bone metastases (C79.5) and brain metastasis were non-Hodgkin's lymphoma, male genital organs, breast, and lung cancer with 66.7%, 54.1%, 32.8%, 20.8% of these patients, respectively; concurrent kidney metastasis was most frequent in cancer of the bladder (46.2%) (Table 14).

Discussion

Because we used administrative data retrieved from the largest health insurance fund association, the results of this study may be generalized to the whole German population. It seems reasonable to compare the results of patients with brain metastasis as obtained from our study with the distribution of primary tumors, age, and gender in the cohort of all cancer patients in Germany (N=436,500; Estimate by Federal Cancer Surveillance Unit at the Robert Koch Institute). The distribution of our study population with regard to gender seemed similar to the distribution among all German cancer patients. In our series, 56.4% of the patients were males, and 43.6% were females, compared to 52.8% and 47.2% for all German cancer patients.

The distribution of primary tumors differed a lot between our series of patients with brain metastases and all German cancer patients. Cancers of male genital organs were the most common primary tumors in male cancer patients in Germany, but were quite rare in our series of patients with brain metastases (27.5% vs. 4.0%) (RKI, 2008). On the other hand, lung cancer, which was the most common tumor type in male patients of our series, was less common in all German cancer patients (62.2% vs. 14.3%). Similar findings were observed for female patients. In our series, 37.5% of the female patients had lung cancer, but only 6.4% of all female German cancer patients. In the entire cohort of German cancer patients, the incidence of colorectal cancers was relatively high for both female (17.5%) and male (16.2%) patients. In our series of patients with brain metastasis, the corresponding rates were 2.0 and 3.2%, respectively.

These findings lead to the conclusion that lung cancer has a higher tendency to metastasize to the brain compared with to other primary tumors. In contrast, only very few patients with prostate cancer or colorectal cancers had developed brain metastases. These findings can be explained by the fact that the development of metastases may be affected in three ways, by invasion of the primary tumor into surrounding tissues, by tumor cell distribution through the blood-stream, or by tumor cell distribution through the lymphatic system via lymph nodes. Each type of cancer may follow specific routes of metastatic spreading. However, the common way of metastatic spreading into the brain is via the blood-stream. Lung cancer is well known for following this route to metastasize to the brain (Berge and Toremalm, 1975; Aoyama *et al*., 2006; Santarelli *et al*., 2007). In contrast, colorectal cancers metastasize most commonly through lymphatic routes and portal venous vessels to the liver (Wroński and Arbit, 1999).

In our study, brain metastases occurred concurrently with extracranial metastasis in 58.8% of the patients. This finding is in accordance with previously reported small case series (max. 120 patients) from Germany and the US reporting incidence of concurrent extracranial metastasis between 45% and 68% of brain metastatic patients (Engenhart *et al*., 1993; Joseph *et al*., 1996; Breneman *et al*., 1997; Mori *et al*., 1998). The calculated mean number of extracranial metastatic sites involved concurrently with brain metastasis was 1.11 per patient, resulting in a total average number of metastasic sites (both extracranial and intracranial) per patient of 2.11. This result is consistent with previous results. Disibio and French reported in their study of 4,012 autopsies of cancer patients an average of 2.48 metastatic sites per each patient (Disibio and French, 2008). Hess *et al*. investigated a series of 4,399 cancer patients including 11 primary tumor types and found an average of 1.91 metastatic sites per patient (Hess *et al*., 2006). Our study's finding that bone, lung, and liver are the most frequently affected extracranial metastatic sites is also consistent with previously published data (Kebudi *et al*., 2005; Hess *et al*., 2006; Disibio and French, 2008).

The strength of our study is the large sample size (*N*=5,074) which provides sufficient statistical power for one half of the primary tumor types causing brain metastases with respect to the evaluations performed in this study. The evaluations were performed in order to investigate possible associations between sex and age groups of each primary tumor with regard to extracranial metastatic sites involved concurrently with brain metastases. The study demonstrates that some primary tumors – including melanoma of skin, stomach, rectum and rectosigmoid, and breast cancer – have a relatively high tendency to develop extracranial metastases at multiple different sites concurrently with brain metastases. Other tumors, for example kidney and renal pelvis cancer, lung cancer, cancer of unspecified primary sites, and non-Hodgkin's lymphoma had a tendency to develop concurrent extracranial metastases at multiple sites more predominantly in younger than in older patients.

Some limitation of this study should be noted. These include (1) the mixing of brain metastases which occurred at different times during the course of progressive disease, because we used cross sectional data; and (2) use of routine data from an insurance fund. However several studies, e.g. in the US, the UK and Switzerland, have demonstrated that the routine data are generally as valid as clinical records – possibly with slight under-coding of secondary diagnoses (Quan *et al*., 2002; Kiyota *et al*., 2004; Aylin *et al*., 2007; Luthi *et al*., 2007); they can provide valuable information as it reflects real-world settings and larger study population (McKee *et al*., 1999); in addition, recently the validity of diagnoses in administrative claims data has recently been confirmed for patients with brain metastases (Eichler and Lamont, 2009). On the other hand, there are worries that systems relying on diagnosis-related groups (DRGs) for reimbursement have an incentive for upcoding (Busse *et al*., 2006) that may distort the quality of data. In the German DRG system, this incentive is, however, very weak because the relative weights are re-calculated every year. Accordingly, in 2007 wrong coding of secondary diagnoses or the main diagnosis are minor issue in disputes between hospitals and third-party payers – and they led to reduced reimbursement in one of six disputed cases only (Thieme, 2008). Regarding brain metastases in particular, the German DRG system sets no incentives for upcoding as neither number nor location leads to different DRG codes and thus reimbursement.

Conclusion

The findings of this large retrospective study of 5,074 patients demonstrate that different primary tumors have different frequencies and patterns of metastatic disease with regard to extracranial metastatic sites involved concurrently with brain metastasis. While bone metastases were most frequent overall, 11 out of 16 primary tumor sites were most frequently associated with concurrent lung metastases. In bladder cancer patients, the most common concurrent metastatic site were the kidneys, and in breast cancer, lung cancer, non-Hodgkin's lymphoma, and testicular cancer patients, it was bone. Because of these particular patterns, screening for lung metastasis, kidney metastasis, and bone metastasis should be intensified for the unknown primary tumor type, particular when molecular assessment is not available.

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PART III. HEALTH CARE SERVICES AND HOSPITAL FINANCE

Chapter 4. Mental health in Vietnam: Burden of disease and availability of services

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Abstract

Purpose: Despite the accomplishments, the economic and social reform program of Vietnam has had negative effects, such as limited access to health care services for those disadvantaged in the new market economy. Among this group are persons with mental disorders. This paper aims to understand the burden of mental disorders and availability of mental health services (MHS) in Vietnam.

Methods: We reviewed both national as well as the international literature about the burden of mental disorders and MHS in Vietnam. This included academic literature (Medline, Pubmed), national (government) reports, World Health Organization (WHO) reports, and grey literature.

Results: The burden of mental disorders in Vietnam is similar to that of other Asian countries and occurs across all population groups. MHS have been made one of the national health priorities and more efforts are being made to promote equity of access by integrating MHS into other health care programs and by increasing MHS capacity. However, it is not yet sufficient to meet the care demand of persons with mental disorders. Challenges remain in various areas of MHS, including: lack of mental health legislation, human resources, hospital beds, shortage and diversification of MHS.

Conclusion: Although MHS in Vietnam have considerably improved over the last decade, mainly in terms of accessibility, the care demand and the illness burden remain high. Therefore, more emphasis should be put on increasing MHS capacity and on human resource development. In that process, more representative epidemiological data and intervention research is needed.

Keywords: mental health service, mental disorders, illness burden, Vietnam

Introduction

Beginning in 1986, Vietnam initiated an economic and social reform program called Doi Moi. The main policies of this program were de-collectivization of agriculture, trade liberalization, attracting foreign direct investment and privatization of state-owned enterprises. Thus far, Vietnam has made considerable progress in the economic and social well-being of the population. These accomplishments were the subject of remarks by the World Bank: '*Vietnam's poverty reduction and economic growth achievements in the last 15 years are one of the most spectacular success stories in economic development*' (World Bank, 2008). Nevertheless, the Doi Moi program has also had some negative side effects, such as larger disparities in access to social and health services among different geographical regions and income groups. These negative effects have been found especially among those who are less successful in the new market economy (Beresford, 2008; WHO, 2005b; Adams, 2005). Accessibility to health care services is partly hampered by official and unofficial payments for health services and pharmaceuticals, and private out-of-pocket spending may represent as much as 75% of total spending on health care (Witter, 1998; World Bank, 2004; Dao *et al*., 2008); Increase in drug and alcohol use, as well as other social stressors have been found to be consequences of the Doi Moi (Hoblyn *et al*., 2009; Volkow, 2009; Martin *et al*., 1996; Boyle and Offord, 1991). Moreover, Vietnam had to live through three major wars in the last century, which has had an impact on both the burden and provision of MHS in Vietnam.The aim of this paper, therefore, is to understand the burden of mental disorders and availability of MHS since the implementation of the Doi Moi policies.

Methods

We reviewed national as well as international literature regarding MHS and mental disorders in Vietnam by searching academic literature on PubMed, Medline using the following key words or combinations of key words: mental disorder, epilepsy, psychiatry, mental health (service) and Vietnam. Unfortunately, the body of academic literatures is still very limited. To fill in this gap, we also searched for grey national and international literature, including government reports, WHO reports and mass media, using Google and Google Scholar.

Results

Mental disorders in Vietnam

Mental disorders make a substantial contribution to the illness burden in all countries. According to the World Health Organization's World Mental Health Survey Initiative conducted in 17 countries, the highest lifetime prevalence of mental disorder (DSM-IV) occurred in the USA (47.4%) and the lowest in Nigeria (12.0%). The Asian countries had relatively low prevalence ranging from 13.2% in China, 14.4% in Iran to 18.0% in Japan (Kessler *et al*., 2007; Fakhari *et al*., 2007). In Vietnam, mental disorders have not been adequately researched. A national representative epidemiological survey on 10 common mental disorders in the period 2001-2003 showed that the 10 most common mental disorders combined had a prevalence of approximately 14.9% of the population. Estimating from this result about 12 million people are in need of MHS. The most prevalent of these are alcohol abuse (5.3%), depression (2.8%) and anxiety (2.6%) (Table 15) (NPHNo1, 2002).

The propagation of illegal drugs from rural and mountainous areas to urban areas led to a dramatic increase in drug abuse from 78 drug addicts per 100,000 population in 1994 to 208 per 100,000 in 2004 (Nguyen and Scannapieco, 2008). Regarding alcohol abuse, 16.3% of the men were at-risk of becoming dependent on alcohol (defined here by a daily average of >2.4 standard drinks); 7.9% were alcohol dependent and 1.97% were harmful users (Giang *et al*., 2008). Minh and colleagues found that 66.7% of men between the age of 25 and 44 years consumed more than 3 standard drinks per day in the previous month, notably higher rates than men aged 45-64 years (59%) and men aged 65-74 (53.4%) (Minh *et al*., 2008). Supporting results, one study using AUDIT (defined as an AUDIT score greater than 7 in men and 5 in women) noticed that prevalence of alcohol consumption-related problems were 25.5% for men and 0.7% for women (Giang *et al*., 2008).

Mental disorder	**ICD**	**Prevalence**
Alcohol abuse	F10.1	5.3%
Depression	F32	2.8%
Anxiety	F41	2.6%
Juvenile behavioural disorder	F91.0	0.9%
Old age amnesia	F00-F04	0.9%
Slow mental development	F70-F73	0.6%
Cerebro cranial trauma	F07.2	0.5%
Schizophrenia	F20	0.5%
Epilepsy*	G40	0.3%
Drug use	F11	0.3%

*Source: Unpublished report of National Psychiatric Hospital No 1 submitted to Vietnam Ministry of Health. * Since epilepsy is part of the management of mental health care provision in Vietnam, it is approached as a 'mental disorder' although the ICD classifies it as disease of the nervous system.*

Table 15. Prevalence of 10 common mental disorders.

Depressive disorders have the second highest prevalence among mental disorders (NPHNo1, 2002). A more recent national community-based study among 14-25 years old showed that 32% of them experienced sad feelings about their life in general, 25% felt so sad or helpless that they could no longer engage in their normal activities and found it difficult to function, and 21% felt disappointed about their future, 0.5% reported to have made a suicide attempt and 2.8% tried to deliberately injure or harm themselves. The highest suicide attempt rate was reported for young males, particularly among 18-21 year olds, which stood at 6.4% for those living in urban areas and 4.1% for those living in rural areas (MOH, 2005). Similar results were also found by Huong and colleagues who found prevalence rates of 8.9% for life time suicidal thoughts, 1.1% for suicide plans and 0.4% for suicide attempts. They concluded that suicidal thoughts are associated with similar negative psychosocial risk factors, lifestyle and emotional problems as in Western and other Asian countries (Huong *et al*., 2006). Additionally, Fisher and colleagues reported that 33% of women who attend general health clinics in Ho Chi Minh City were depressed, and that 19% of them explicitly acknowledged experiencing suicidal ideation. A nationwide survey showed that 20% of mothers of 1 year olds suffer from depression or anxiety rates possibly relevant to 8% to 16.9% maternal deaths (within 42 days of postpartum) by suicide (Fisher *et al*., 2004; WHO, 2005b).

Epilepsy has a rather ambigious status in Vietnamese health care from an international perspective. Since epilepsy is treated and managed within the mental health system, it is approached and regarded by policy makers as a mental disorder, although the ICD-10 classifies it as a disease of the nervous system. As a result it has an influence on the demand for MHS and subsequently the planning of these services. It therefore needs to be discussed here. The prevalence of epilepsy estimated by Le and colleagues is about 7.5 per 1000 population (active epilepsy is 5.5/1000) 33.9% of whom are between 10 and 20 years of age (Le *et al*., 2007); While another study by Tuan and colleagues found a lower prevalence of 4.4 per 1000 population (95%, CI 3.8-5.0). These results are similar to other Asian countries but lower than African and Latin American countries (Tuan *et al*., 2008).

The awareness of the population with regard to mental disorders is rather limited. This may explain why stigmatization and discrimination pose a large problem. According to Hoi (director of Maihuong day care Hospital in Hanoi) 'whenever people think about mental illness, they will certainly think about madness and strange behavior' (Hong, 2008) or as Weiss commented 'The stigma associated with mental health concerns in Vietnam is even greater than in Western countries' (Weiss, 2007). This assertion is partly supported by findings of Tuan that of the 67.0% of the respondents who had heard about epilepsy, 10% of the respondents thought that it is a form of insanity, and 36.3% of the respondents would object to their child being friends with somebody suffering from epilepsy. Moreover, 67.4% assumed that people with epilepsy should be denied a job (Tuan *et al*., 2007). It seems that the situation has improved since the implementation of the NHTP (discussed below) with a CBMHP as one of its pillars. Yet about 50% of the population still have limited awareness about this issue according to an estimate by a director of a leading mental health hospital (Hong, 2008).

Mental health care provision in Vietnam

Policy and legislation

Although Vietnam does not have an explicit mental health law, the 1989 Law on Protection of People's Health recognizes and affirms that all people have an equal right to health care and treatment. It protects certain rights of the mentally ill by explicitly stating the conditions in which a doctor must get a relative's consent before beginning treatment and conditions in which involuntary treatments are permitted.

Mental health policy has since 1998 been declared as one of the main targets of the NHTP (WHO, 2001b). The specific goal of this program was to improve MHS by increasing and strengthening community-based mental health care (Vietnam Gov, 1998). Other key aspects of the program were detection, treatment and community reintegration of an estimated 50,000 persons with schizophrenia (Vietnam Gov, 2001). Since 2002, two additional mental disorders, i.e. depression and epilepsy, were added to the NHTP as part of an initiative on non-communicable disease prevention and control for the period 2002-2010. The goal is to reduce the prevalence rate and mortality rate of epilepsy as well as to prevent epileptics from hurting themselves or their environment, in addition to reducing the number of depressed patients and suicides due to depression (Vietnam Gov, 2002). In parallel with the NHTP, the Vietnamese government launched a policy to give funds to provinces or cities to enable them to provide a minimum support of 65,000 VND (about US$3.60) per month for the mentally ill living alone or in poor families. People with mental disorders who choose to live in a homecare center receive a minimum support of 140,000 VND (US$7.70) per month. As result of this decentralized policy approach, the actual amount that provinces or cities pay out may be higher and depends on the public budget of the respective province or city (Vietnam Gov, 2004).

Organization of mental health services

Mental health care is provided by a catchment area system built upon Vietnam's 4 tier system (central, province, district and commune) with two major types of services i.e community-based and hospital-based.

The CBS is provided by more than 700 outpatient mental health facilities. These facilities include 30 outpatient departments of central and provincial level mental health hospitals, about 35 mental health departments that belong to the provincial center for social disease control and prevention or provincial mental health dispensaries, and 642 mental health divisions of each district preventive health center. In addition, apart from being one of the primary health care providers, 6278 commune health stations (per total of 10,750 communes equal to 64%), function as gatekeepers to the health care system and have gained an additional role in mental health care. This new role has been found through integration of mental health into other community-based health care programs (GSO, 2009- In: Education, health, culture and life). The CBS is responsible for mental health promotion, scanning, early detection and managing the treatment of mental disorders in the community. Moreover, emphasis is put on patient follow-ups and implementation of the CBMHP at the community level. This service has been implemented in 64% of communes and in 100% of provinces and cities. Therefore, the community based mental health program is now providing approximately 60-70% of the population with free access to essential psychotropic medicines for some prioritized mental disorders such as schizophrenia, depression and epilepsy (where they have availability of at least one psychotropic medicine of each therapeutic class of anti-psychotic, antidepressant, mood stabilizer, anxiolytic, and antiepileptic medicines). For those not living in a commune covered by the program, free access to these medicines is possible as well but requires more effort, as patients will have to go to a provincial mental health dispensary or go to another commune where the program is available. Alternatively, they can pay for these medicines. Basic medication is relatively affordable. One day anti-psychotic medication and antidepressant medication cost about 33% (US$ 0.38) and 13% (US$ 0.16) of one day's minimum wage respectively (WHO, 2006a).

The hospital service is provided by 2 central mental health hospitals, 31 provincial mental hospitals, 23 psychiatric departments in the general provincial hospitals, 2 day care hospital/clinics, and 1 child/adolescent inpatient clinic. The two central mental health hospitals are authorized by the Ministry of Health to plan, manage, coordinate, monitor and conduct quality assessment of all MHS in Vietnam. The number of beds for mental health patient amounts to 5000, or 6.08 beds per 100,000 population, compared to 151.3 total hospital beds per 100,000 population. The hospital bed occupancy rate in mental health hospitals stood at 122.9% in 2004. Although the number of mental health hospital beds was increased by 6% (300 beds) in the period 2000-2004 and by even 16% in the period 2004-2008, the occupancy rate remained at 122.6% (MOH, 2004a; MOH, 2008d). Approximately 4% of beds in mental hospitals are reserved for children and adolescents only (WHO, 2006a; MOH, 2004b). To put these numbers in perspective, both the mental health bed rate in general and the mental health bed rate for children and adolescents of Vietnam is rather low compared to Thailand (13.8 beds/100,000 of population; 9% of total mental health beds) and China (6.79/100,000; 5%) but higher than in the Philippines (5.57/100,000; 2%)(WHO, 2006b; WHO, 2006c; WHO, 2007).

Human resources

The human resources working in both the CBS and the hospital-based service included only 286 psychiatrists, counting those who had at least six months of mental health training, which equals 0.35 psychiatrists per 100,000 population (in 2004) (all psychiatrists work for mental hospitals, as no psychiatrist works for outpatient facilities). In the same year, the rate for general physicians working in mental health facilities (730) was 0.90 per 100,000 population. Even when general physicians are included, the rate of doctors in mental health was still small compared to the total country rate of 61 medical doctors per 100,000 population in 2004 (WHO, 2006a) and to the more recent (2008) number 67 medical doctors per 100,000 population (GSO, 2010- In: Education, health, culture and life).

Country	Psychiatrist	Doctors (not specialized)	Nurse	Psychologist	Social worker	Occupational therapist	Other health Worker
Vietnam	0.35	0.90	2.10	0.06	0.15	0.005	0.80
China	1.40		3.20				1.50
Thailand	0.66	0.17	3.81	0.26	0.74	0.20	1.45
Philippines	0.42	0.17	091	0.14	0.08	0.08	1.62

Source: WHO-AIMS report on mental health system in Vietnam. WHO.2006; WHO AIMS reports Vietnam, the Philippines, Thailand and China (only Hunan province)

Table 16. Number of human resources working in mental health care in Vietnam and selected countries from the region per 100,000 populations (2004).

The total number of psychiatrists and doctors working in the mental health field is on the same level as the other countries nearby and higher than Thailand and Philippines. If only taking into account the proportion of actual psychiatrists, the rate is much lower than in neighbouring countries (Table 16). In terms of other mental health professionals, there were 2.1 per 100,000 (1,700) nurses working in the mental health field, compared to 81.9 per 100,000 nurses in all fields in 2004 (103.4 per 100,000 in 2008) (WHO, 2006a; GSO, 2010- In: Education, health, culture and life). Furthermore, also in 2004, there were 50 psychologists, 125 social workers, 4 occupational therapists and 650 other mental health workers (WHO, 2006a).

Regarding the development of human resources, mental health is now facing a huge problem. Psychiatry is among the least preferred post-graduate specialities in the country. Of the 2,500 new medical graduates per year, none studied psychiatry and only about 30 chose psychiatry as a speciality in post graduating training. In 2004, there were no psychiatric nurses, psychologists, psychiatric social workers, occupational therapists or mental health workers who graduated with a minimum of one year training in the mental health area.

Inpatient and outpatient care

Outpatient mental health care is mainly provided by the CBS, whereas inpatient mental health care is provided by the hospital-based service. At the present time, the focus of the system is still on hospital-based rather than CBS. However, this focus is rapidly shifting. In 2004, outpatient facilities treated a total of 46,070 patients (56.9/100,000 population), 39% of whom were female and 17% children or adolescents (WHO, 2006a). By 2008, this number had almost tripled to 126,600 patients (150/100,000 population) (MOH, 2008d). In 2004, less than 20% facilities of the CBS could offer psychosocial intervention. The hospital service treated 57,500 patients, equal to 71 patients per 100,000 population (Table 17), with an average of 35 hospital days per patient. The daycare facilities treated about 3,000 patients (3.7/100,000 population), an average of 40 days per patient per year. The most common mental disorders upon hospital admission are schizophrenia, schizotypal and delusional disorders (60%), mood (affective) disorders (15%), as well as neurotic, stress-related and somatoform disorders (15%). About 60-70% of them received a psychosocial intervention. Involuntary hospital admission make up 1% of all cases, and about 2-5% of patients in mental hospitals were restrained or secluded at least once (WHO, 2006a).

In total, about 132 people per 100,000 population in 2004, which equals about a quarter of the proportion of people treated in the Chinese MHS in the same year (Table 17), and a rough estimate of 250 people in 2008 per 100,000 population, were treated by the outpatient and inpatient MHS in Vietnam, roughly equal to 10-15% of these persons had one of the prioritized mental disorders in Vietnam (schizophrenia, depression, and epilepsy).

Country	No of user/100,000 population treated in hospital network	No of user/100,000 population treated in community-based program
Vietnam	71	56.9
Philippines	13.6	135
Thailand	158	n/a
China	35.5	454

Source: WHO.2006

Table 17. Number of treated mental patients in Vietnam and selected countries from the region (2004).

Discussion

Although research on prevalence of mental health disorders in Vietnam is increasing, there is still a need for comprehensive epidemiological studies on the prevalence of mental disorders. Available evidence indicates that mental disorders are very common conditions and their prevalence rates are similar to those of other Asian countries. They also occur across all population groups.

There are efforts to promote equity of access to MHS through an integrated approach supported by the CBMHP (part of the NHTP). The network providing MHS includes specialized psychiatric hospitals, psychiatric departments in general hospitals, psychiatric department in pediatric hospitals (all providing inpatient and outpatient care), psychiatric day care hospitals; psychiatric clinics for children and adolescents, clinics especially reserved for forensic mental disorders as well as outpatient mental health facilities. Essential psychotropic medicines are available in all clinical facilities from health commune stations up. However, the MHS system is not completely built yet as it does not cover all people and as a result still reveals accessibility problems. Activities of the program are still rather limited and mainly focus on mental health promotion, prevention, screening, early detection and managing the treatment of mental disorders in the community through monthly check ups and provision of drugs for schizophrenia, epilepsy and depression. In contrast to this, the controlling of risk factors, rehabilitation and health education (knowledge, attitude, practice, behaviour) of the population have thus far not been targeted and strengthened. In addition, programs for home care, as well as children and adolescent mental health care are lacking.

Although, the number of mental hospital beds was increased in the last decade, there is still a substantial gap with the demand for such services. This is in contrast to some Western countries, where the number of mental hospital beds are declining and care is provided if possible at the primary level, rather than institutionalizing patients. Even though there is a focus on secondary and tertiary care in Vietnam, this does not mean that these services are always abundant and accessible. Some mental health hospital services are very limited in terms of quantity, especially day care and hospital care exclusively for children and adolescents. An explanation is that MHS for children in Vietnam are limited due to the prioritization of other health problems, such as infectious diseases and malnutrition (McKelvey *et al.*, 1997).

Our review found that the rate of patients accessing MHS is increasing but still low compared to other countries. That may partly be explained by the fact that many people with mental health needs may access private health care providers or other specialized health care service rather than MHS. This is plausible since Vietnam has a sizeable private health care sector, mainly consisting of outpatient clinics. Yet data on mental patients in the private sector is lacking or anecdotal. Stigmatization of mental illness is also an important issue (Thuan *et al.*, 2008).

The Vietnamese MHS is challenged by a lack of human resources. When compared to other Asian countries in the region, the proportion of physicians working in the mental health field in Vietnam is fairly average, but the proportion of psychiatrists is below the proportion of countries such as China and Thailand. This is the result of insufficient training of psychiatrists. Hence, the largest future challenge for the Vietnamese mental health care field is to attract mental health workers. However, training of primary care staff, e.g. psychiatric nurses, is limited and complicated by the absence of psychiatric/mental health topics in the nursing curriculum and the lack of psychiatric nursing textbooks and periodicals in Vietnamese (Goren, 2007).

Conclusion

The provision and accessibility of MHS in Vietnam was considerably improved over the last decade. However, the care demand of persons with mental disorders has not yet been met and the illness burden remains high. The CBMHP needs to be expanded to include more mental disorders and cover more people. In addition, the capacity of MHS needs to be increased by diversifying specialized services and by educating and training more human resources. Lastly, our review signals the need for more representative epidemiological data and intervention research in mental health services. This will be the key to address the challenges facing Vietnamese MHS effectively.

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Chapter 5. Determining the impacts of hospital cost-sharing on the uninsured in Vietnam

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Abstract

Objectives: This study was to identify the status of different hospital financing sources and their impact on the uninsured.

Methods: A panel dataset of 84 public general hospitals (2005-2008) with large cross-section data was used to calculate hospital unit costs by applying multiple regression models. The number of individuals at risk of catastrophic health expenditure (CHE) was estimated.

Results: Average user fees (UF) of outpatient visits and inpatient bed days are US$4.13 and US$20.27; while actual full costs (AFC) are US$8.41 and US$36.66, respectively. These unit costs are 2.5 times higher in hospitals at the central versus the provincial level. UF for surgical inpatient bed days are 3.6 times that of internal treatments (US$47.50/12.87) and AFC 5.0 times (US$101.72/20.08). UF accounted for 44.6-77.9% of the AFC, the rest was provided by direct government support (DGS). One inpatient of either internal or surgical treatment at any hospital level immediately pushed near-poor individuals at risk of CHE, and one surgical inpatient treatment at any hospital level exceeded the 20% threshold of the average annual income per capita.

Conclusion: Almost half of hospital AFC is paid by DGS, the rest by UF. However, UF has become a great financial burden on the uninsured, driven them into poverty and maintained inequities in hospital service utilization between the rich and the poor. Increasing UF could be advised to reduce DGS, and the savings spent on subsidizing insurance to ensure that more of the population is insured, especially the near-poor individuals/households.

Keywords: cost-sharing, hospital unit cost, user fee, Vietnam

Introduction

The Socialist Republic of Vietnam is currently in the process of implementing major health care reforms. One major element of these reforms is a shift from a centrally planned system where health care services were provided to the population free of charge, to the decentralized and contracted SoHI model. The introduction of hospital cost-sharing under the mechanism of a fee-for-service scheme was started in 1989 (World Bank, 1993; Hung, 2000; Tuong *et al*., 2000). The main objectives of this new hospital financing scheme, as stated by the Government, are improved financial capacity and sustainability of these health care institutions resulting in higher quality and reliability of care. There have been major achievements, such as NHT development, better health care service provision, increasing financial support for hospital performance and relief of the financial burden on the government (Dao *et al*., 2008; Thuc, 2008). However, in the process of ongoing reform, a mix of payments for health care services consisting of contributions from the state budget, TPP, and OOP payments developed, which resulted in a major controversy. Objections to the reform include that it might reduce necessary utilization by the poor, who may not be able to afford the health care services; and the role of the government in supporting population access to hospital services is unclear as there is no clear policy to demarcate responsibility between the state, health insurance and service users (Tuong *et al*., 2000; Dao *et al*., 2008). The question remains of how much of the hospital service costs are now covered by the user fees and what are the impacts of this on the service users, in particular those who are uninsured and have to pay by OOP. This question will be explored and answered in this paper by looking at the costs of two main hospital services, namely outpatient visit unit costs and inpatient stay unit costs.

The paper will provide the reader with some background on the health care system in Vietnam and the current health care reform program, the methodology and some basic results, focusing on those aspects most relevant for the policy-makers. The paper will conclude with some discussion and policy implications for the more efficient use of government support in respect to relieving the burden of hospital cost-sharing on the uninsured.

Background

The current health care system was established in the northern part of Vietnam by the late 1950s, then in the south after reunification in 1975. The health care system was formed according to the four administrative levels of the state. These are, firstly, the central level, then the provinces, which are in turn divided into districts and communes. At the central level there are 41 hospitals (18 general and 23 specialized); at the provincial level there are 340 hospitals (124 general and 216 specialized); and there are 609 district general hospitals. One health commune station exists in each commune at the grassroots (Weaver and Deolalikar, 2004; Sepehri *et al*., 2005; MOH, 2008a).

The official line of control is through the People's Committee at the national, provincial, district and commune levels. The Ministry of Health is the highest authority in the health sector, then provincial health bureaus are in turn responsible for the formulation, execution and control of the related health services of the central and provincial hospitals. The district hospitals and health commune stations have been under the control of provincial health bureaus since the reforms of 1993 (Flessa and Dung, 2004; Sepehri *et al*., 2005).

The above four-tier health care services system also acts as a referral network in a pyramid health care system. At the grassroots, health commune stations are responsible for the majority of primary care provision including preventive health medicine, ambulatory, and inpatient services for slight or mild illness. In theory, more severe illness is referred to the hospitals at the top of the pyramid. But in reality, levels are bypassed depending on the severity of the illness and location of the patients. The central and provincial level hospitals, besides the main task of treatment and care for the patient, also have the responsibility for medical research; providing official training for medical and nursing students in collaboration with medical universities and offering medical professional support, and doing on-the-job training for staff from the lower levels of the system (Ensor, 1995; Flessa and Dung, 2004).

As in most countries in Central-Eastern Europe and Central Asia, after the collapse of the Soviet Union in the late 1980s, the country faced a socio-economic crisis due to a sudden cut of foreign aid, and free health care provision to the whole population was no longer available. The state budget is only sufficient to support for public health facilities in some main categories of salaries, administrative management, equipment, maintenance, consumables, and a small number of hospital fee exemptions for the very poor or vulnerable groups of patients (Dixon, 2004; MOH, 2006a; Rodrigo, 2009). The rest has been covered by the so called 'User Fee', which was issued by the Vietnamese Government in the Ordinance of Private Medical and Pharmaceutical Practices and the Policy on Hospital Partial Fees. The user fee was first introduced in 1989 for inpatient services, with a partial hospital fee, then expanded to all in- and outpatient services. It allows hospitals to collect a fee, according to a FFS scheme, for certain services including consultation, drugs, consumables, blood infusions, diagnostic procedures, operative procedures, and hospital bed utilization (MOH, 2006a). The ranges of these services' fee were issued by the Ministry of Health, with the basic threshold determined for each relevant administrative level. The local authorities take it as a basis to specify the precise fee for each service, in relation to the technical capacity of their hospital and their local community's ability to pay (MOH, 2008b; Dao *et al*., 2008; Tuong NV *et al*., 2000). The hospitals at the central level normally receive more investment and are better equipped with technology; and being the highest level in the referral hierarchy, they logically receive patients with more severe illnesses. Consequently, the highest level of the central hospitals has a higher cost rate compared to provincial or district hospital levels for the same service (Flessa and Dung, 2004). In short, funding to hospitals is a combination of two main sources: state budget (bed-norm based provision) and user fees (MOH, 2008b). The state budget was, as in most developing and some industrialized countries, previously transferred to the hospitals in the form of line-item allocations from government health authorities, the rate of provision depending on the wealth of each province (Barnum *et al*., 1995; MOH, 2006b). There are two main sources of user fee payments: TPP and OOP payments. SoHI is a major part of TPP, it covered 49% of the population in 2007, of which SHI (the benefits provided to employees) covered 9%, health care for the poor (HCFP) 18%; free health care for children under 6 years of age 11%; and voluntary health insurance 11% (Ekman *et al*., 2008). OOP payments are made by those with no health insurance. The HCFP was established in 2002 following 'Decision 139' to provide free health insurance for the poor who were defined as those with a total income per year under 2,400,000VND in rural and 3,120,000VND in urban areas (by PPP in 2002, equal to US$405; US$527, respectively) (UNdata, 2010; Gov, 2002). The HCFP was rather successful in achieving positive outcomes with a positive impact on increasing overall health care service utilization; reducing OOP expenditure for health care of the poor and the risk of catastrophic OOP spending (Axelson *et al*., 2009; Wagstaff A, 2007). However, aside from the defined poor households who were provided free health insurance, the near-poor households are now of the greatest concern for the government in regard to health insurance provision. The government made a policy to provide 50% of the health insurance premium for the near-poor, but 90% of them are not yet covered, while the remaining 10% belong to the statutory health insured groups (Thiet, 2011; Phuong Thao, 2011). The near-poor are defined as having an income between 201-260,000VND/head/month in rural and

261-338,000VND/head/month in urban areas (in the estimation of the average annual income of the near-poor by PPP, in 2008 it was equal to US$420 per head for both urban and rural groups) (MOLISA, 2008). The near-poor are roughly estimated to account for 14% of the population (Thuong DN, 2011). This group is now at the higher risk of CHE; Nguyen found that 24% of them have to borrow money to pay for outpatient treatment, compared to 20% of the poor and 12% of others (Nguyen, 2008).

Following the accounting regime of the public administrative units (all public hospitals are non-profit organizations) the annual expenditure of all revenue received from different sources for hospital operation was previously externally governed. In August 2006, greater financial autonomy was issued to hospital management that allowed the hospital to be freer in reallocating resources across line-items as needed for efficient management and to ensure the continuity of technical activities and quality of health care services; and to allow hospitals to use the previous year's excess revenue in the following year, mostly to supplement employees' incomes (Barnum *et al*., 1995; MOF, 1996, 2006; van Minh *et al*., 2010). Taking advantage of the financial autonomy policy and FFS (Gov, 2006), hospitals focused more on developing the 'elective' services to generate revenue with either separate wards for 'elective' services or by integrating them in the regular treatment facilities. As a result of this change, and joint ventures or business collaboration between hospitals and other private institutions which could invest in the hospital for mutual benefits, hospitals have had a burst of medical equipment investment, especially in upgrading high technology equipment of diagnostic imaging (MOH, 2008b). Consequently, hospital income has increased, and user fees have become the main source of hospital funding, increasing from 24% in 1994 to 52% in 1998, 60% in 2004 and 61% in 2005 (Sepehri *et al*., 2005; Dang, 2007; MOH, 2008c).

Methods

Data set:

The data used in this study are facility-based data of routine annual reports, extracted from the annual hospital statistics, which are collected and administered by Ministry of Health (Department of Medical Service Administration), over 4 years (2005-2008). By regulation, every hospital has to annually submit the hospital statistical report to the Ministry of Health (by electronic mail or on paper). However, each year about 15-20% of the observations were not available the missing reports were those sent by post where the address may have been incorrect or the data administrators were not able to manually enter all data into the database at the Ministry of Health. General hospitals at the central and provincial levels which have submitted a minimum of 4 year reports to the Ministry of Health were selected for this study. The set of available data included 84 general hospitals (76 provincial hospitals, 8 central hospitals) with a total of 336 observations equal to 60% of all observations. Private hospitals were excluded as our purpose is to establish the share of different financial sources for the public hospital unit costs.

A panel dataset was generated with large cross-sectional dimensions including patient flows (outpatient visits, inpatient bed days, internal medicine and surgical inpatient cases); treatment and care procedures; and hospital income, consisting of state budget and user fee; which were all selected for statistical analysis. To balance the value of local currency (VND) by years and to be suitable for international benchmarking, hospital income figures were adjusted by PPP to US dollars (PPP in 2008: 7,688; 2007: 6,484; 2006: 6,158; 2005: 5,919) (UNdata, 2010). Unit costs of hospital service are defined in the current study as unit cost of hospital stay (inpatient bed day) and unit cost of outpatient visits, the inpatient bed days were further categorized into internal medicine and surgical cases (Adam and Evans, 2006; Hutubessy *et al*., 2002).

The hospital annual reports in our current study were compiled in December each year, when the final balance sheets of annual finances were not ready. Based on the fact that all sources in the processing procedures that can contribute to final outcomes are value-added (Flessa, 2009) and on the accounting regime of the public administrative units, hence the projected revenue was substituted for actual costs in analyzing cost units. The actual costs were classified into three different categories: user fees are the first revenue for the hospital facilities, then direct provider cost, and actual full cost (Table 19). Each cost is devoted to its relevant revenue. The hospital revenue from user fee (UF revenue) was collected by the reimbursement of TPP or OOP; and revenue from direct provider cost (DirPC revenue) was the combination of UF revenue, bed-norm based provision of state budget, donation and others (generally called state budget). To estimate the revenue from actual full cost (AFC revenue), based on previous studies, we estimated that the annual depreciation rate of capital investment on equipment and buildings accounted for 8.5% of the actual full cost (Lieu, 2005; Flessa and Dung, 2004; van Minh *et al*., 2010). Hence, from the DirPC revenue, AFC revenue is calculated. The state budget plus the annual depreciation of capital investment accounted for the direct share contributed by the government (the so-called direct government support).

The results of each unit cost were judged in relation to the concept of individuals at risk of CHE, that is, those who have to pay for the hospital services with OOP payments. What is defined in our study as OOP exceeds 20% of an individual's annual income (Axelson *et* *al*., 2009; Gotsadze *et al*., 2009). The income was taken here as the average income per capita in 2008 (11,942,400VND) adjusted to US$ by PPP (equal to US$1,553) (Nguyen, 2008).

Years	Average number of hospital beds			Average number of length of stay			Rate of hospital bed occupancy		
	All	Province	Central	All	Province	Central	All	Province	Central
2005	456	425	725	7.7	7.4	10.4	118.9	117.3	134.8
2006	475	443	777	7.8	7.6	10.1	126.4	125.0	139.7
2007	489	461	752	7.7	7.5	10.0	130.5	128.4	150.6
2008	513	481	815	7.6	7.3	9.6	128.6	126.8	146.4

Table 18. Hospital characteristics by years

Categories	Revenue of User Fee (UF_Revenue)	Revenue of Direct Provider Cost (DirPC_Revenue)	Revenue of Actual Full Cost (AFC_Revenue)
Variable costs: Cost of consultation Cost of drug + consumable + infusion + blood Cost of diagnosed test procedures Cost of operation procedures Cost of hospital bed use	x	x	x
Fix costs 1: Cost of maintenance Cost of salaries/ wages Cost of management/ operation		x	x
Fix costs 2: Cost of depreciation on equipments Cost of depreciation on buildings			x
	$UF\_R = \Sigma_{Variable\ costs}$	$DirPC\_R = UF\_R + \Sigma_{Fixcosts1}$	$AFC\_R = UF\_R + DirPC\_R + \Sigma_{Fixcosts2}$

Table 19. The components of 3 different cost categories

Regression models:

Using the equation of multiple regressions on hospital cost functions to calculate the final hospital unit costs is appropriate to the current study's purpose of providing information for policy analysis rather than forecasting future costs:

$$R_{i,t} = b_o + \sum b_{i,t} X_{i,t} + e_i$$

In which, $R_{i,t}$ stands for the income of hospital i at time t;

b_0: the plane's reference position (intercept), defines the value of R when all $X_i = 0$;

b_i: a regression coefficient of X_i on the total income R_i;

$X_{i,t}$: $X_{1,t}$ is predictor variable of inpatient bed day at time t and

$X_{2,t}$ is predictor variable of outpatient visit at time t;

$e_{i:}$ error term (Grannemann, 1986; Carey, 1997)

Statistic analysis:

The linear regression on the longitudinal/panel data methodology was applied in STATA 10.

Firstly, UF revenue was regressed (fixed-effect) on the outcome variables of inpatient bed days (InpBD), and outpatient visits (OutPV). Then, similar regression was applied for DirPC revenue in the relationship with InPBD and OutPV. Those two models resulted in the ratios of regression coefficient between InPBD and OutPV interactions on UF revenue and on DirPC revenue which suggests cost complementarities between InPBD, OutPV on UF revenue and those on DirPC revenue. These ratios were in turn used to estimate the UF revenue/DirPC revenue allocated relevant to the unit costs of InPBD and OutPV (Table 16).

The number of InpBD was composed of bed days in internal medicine and surgical cases. The Regression Model (fixed-effect) was run for the hospital bed days on two variables of internal medicine and surgical inpatient cases, to find regression coefficient ratios of length of stay for one surgical case (SurInpC) versus one internal medicine inpatient case (IntInpC), that were used to calculate the number of surgical inpatient bed days (SurInpBD) and number of internal medicine bed days (IntInpBD). Those two variables (SurInpBD, IntInpBD) were then regressed on the UF revenue/DirPC revenue to find the ratios of regression coefficients of one SurInpBD and one IntInpBD interaction on the cost of inpatient bed days in regard to UF revenue and to DirPC revenue, respectively. Then, relying on those regression coefficient ratios the cost of internal inpatient bed days and cost of surgical inpatient bed days were calculated (Table 19).

All fixed-effect (within) regression were tested by a Hausman Fixed Random test to make sure the difference in coefficients between fixed-effect (within) regression and random-effect GLS regression is not systematic (Carey, 1997; Adam *et al*., 2003).

Results

From the baseline data:

The income derived from user fees accounted for up to 65.5% of total hospital income (excluding annual depreciation costs on capital investment) (Figure 8). The OOP proportion of total out- and inpatient visits was 46.7%, reduced from 2005 (56.2%) to 2008 (41.8%) (Figure 9). The lengths of stay were almost stable, in the range of 7.3-7.6 days at the provincial hospital level and 9.6-10.4 days at the central hospital level. Although the average number of hospital beds increased from 456 to 513 beds between 2005 and 2008, the hospital bed occupancy rate did not decrease, in fact, it was even 10% higher in 2008 compared to 2005 (128.6%, 118.9% respectively), especially at the central hospital level where the average occupancy rate was up to 150.6% in the year 2007 (Table 18).

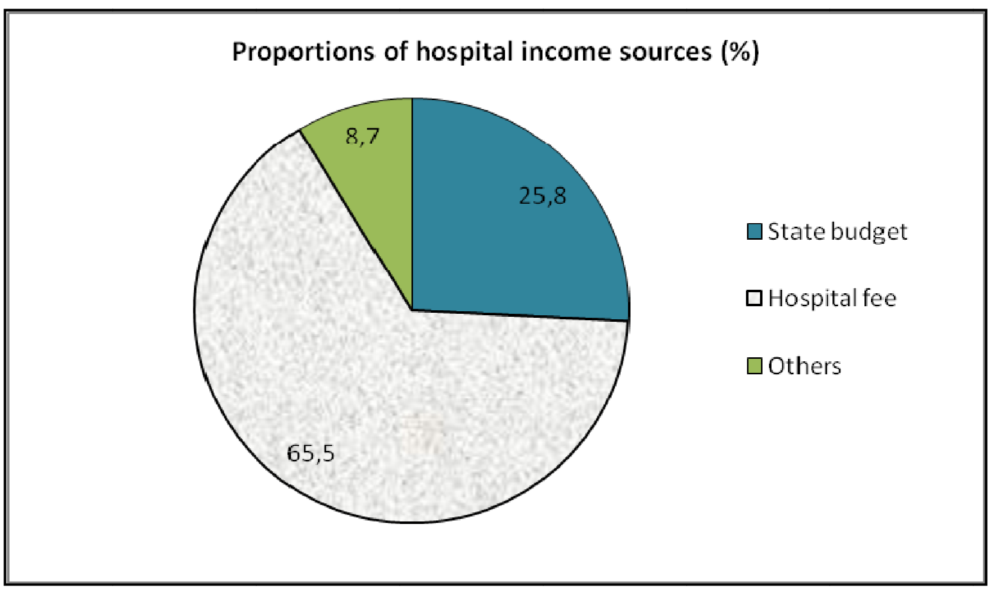

Figure 8. Proportions of hospital income sources (combination of 4 years 2005-2008), not including annual depreciation rate from state budget.

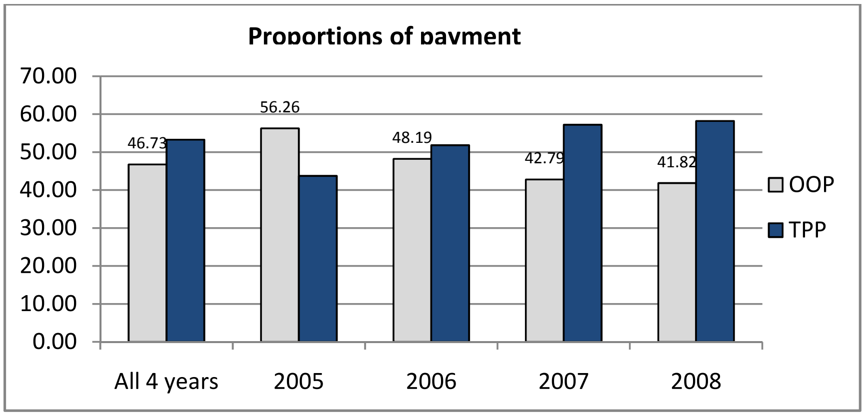

Figure 9. Proportion of hospital service payment sources by year 2005-2008

From Regression Model:

A significant linear regression was found between UF revenue and two predictors of inpatient bed day and outpatient visit (both variables, $p<.001$) and accounted for 63% of the variance in UF revenue ($R^2=.63$). Similar observations were found for DirPC revenue in the relationship with InPBD and OutPV ($R^2=.71$; both variables, $p<.001$). The ratio of regression coefficients between InPBD and OutPV interactions on UF revenue is 75.71/15.42 and on DirPC revenue is 87.69/20.15 (Table 20).

On the UF revenue, the costs of one inpatient bed day and one outpatient visit were US$20.27 and US$4.13, respectively; one surgical inpatient bed day cost US$47.50 versus US$12.87 for an internal medicine bed day. Comparing unit costs between different hospital levels, the hospitals at the central level cost 2.5 times more than the ones at the provincial level (outpatient visits: US$9.22/3.59, inpatient bed day: US$45.28/17.64) (Table 18).

Independent Variables	Revenue of User Fee			Revenue of Direct Provider Cost		
	Coefficient	**SE**	**t / P-value**	**Coefficient**	**SE**	**t / P-value**
	Dep Var: UF-Revenue	R-sq: within = 0.63		Dep Var: DPC-Revenue	R-sq: within = 0.71	
InpBD	75.71	4.46	16.96/ <.001	87.69	4.35	20.15/ <.001
OutpV	15.42	4.26	3.61/ <.001	20.15	4.16	4.84/ <.001
	Dep Var: InpBD	R-sq: within = 0.76				
IntInpC	7.21	.320	22.53/ <.001			
SurInpC	6.29	.624	10.07/ <.001			
	Dep Var: Cost of inpatient bed days R-sq: within= 0.46			Dep Var: Cost of inpatient bed days R-sq: within = 0.40		
IntInpBD	.0000446	.0000091	5.59/<.001	.0000367	.0000091	4.00/ <.001
SurInpBD	.0001646	.0000199	8.27/<.001	.0001859	.0000229	8.11/ <.001

Table 20. Results derive on the regression models

(Abbreviations: InpBD: inpatient bed day; OutpV: outpatient visit; IntInpC: Internal medicine inpatient cases; SurInpC: Surgical inpatient cases; IntInpBD: Internal medicine inpatient bed day; SurInpBD: Surgical inpatient bed day)

Unit costs	Mean of unit costs (US$)			Share of unit costs by user fee to actual full costs (%)
	By User Fee – 95% CI	By Direct Provider Cost – 95% CI	By Actual Full Cost – 95% CI	
Outpatient visit				
All	4.13 [3.76-4.49]	7.76 [7.32-8.20]	8.41	49.10
Prov. Level	3.59 [3.35-3.83]	7.04 [6.72-7.35]	7.63	47.05
Central level	9.22 [6.59-11.85]	14.64 [12.03-17.25]	15.88	58.06
Inpatient bed day				
All	20.27 [18.47-22.08]	33.79 [31.87-35.70]	36.66	55.29
Prov. Level	17.64 [16.46-18.82]	30.63 [29.27-31.99]	33.23	53.08
Central level	45.28 [32.38-58.18]	63.74 [52.38-75.10]	69.15	65.48
Internal medicine inpatient bed day				
All	12.87 [11.81-13.92]	18.51 [17.55-19.46]	20.08	64.09
Prov. Level	11.30 [10.63-11.96]	16.99 [16.33-17.66]	18.43	61.31
Central level	27.78 [20.07-35.48]	32.86 [26.85-38.86]	35.65	77.92
Surgical inpatient bed day				
All	47.50 [43.59-51.40]	93.76 [88.93-98.58]	101.72	46.69
Prov. Level	41.70 [39.25-44.16]	86.10 [82.73-89.47]	93.41	44.64
Central level	102.53 [74.08-130.97]	166.46 [136.03-196.89]	180.60	56.77

Table 21. Means of hospital unit costs and proportion of OOP per actual full cost of each unit cost (combination of 4 years 2005-2008)

On the AFC revenue, one outpatient visit cost US$8.41 and one inpatient bed day cost US$36.66. Inpatient bed days for surgery cost up to US$101.72 compared to US$20.08 for internal medicine (Table 21). The share of user fees of the AFC differed among unit costs. On average, one OOP payment or TPP covered about 50% of the AFC of outpatient visits and 55% of one inpatient bed day. The user fee made up a higher proportion of the AFC of different unit costs at the central level compared to the provincial level, ranging between 56.77 and 77.92% and 44.64 and 61.31%, respectively. The highest share was for an internal medicine bed day at the central level (77.92%) and the lowest share for a surgical inpatient bed day at the provincial level (44.64%).

Impact implications:

In the estimation of the impact of sharing the unit costs of hospital services, one inpatient treatment episode of either internal or surgical treatment at any hospital level immediately made the near-poor individuals who are uninsured and had to pay OOP for the treatment at risk of CHE. Just one surgical inpatient treatment at any levels of central or provincial hospitals exceeded the 20% threshold of the average annual income of the whole population (in 2008) (Table 22).

Hospital unit costs of each hospital level	Cost per day (US$)	Average LOS (days)	Cost of treatment episode (US$)	Cost/annual income of near-poor individual (%)	Cost/average income per head in 2008 (%)
Surgical inpatient treatment case					
Province	41.7	7.4	310.7	74.0	20.0
Central	102.5	10.0	1025.3	244.1	66.0
Internal inpatient treatment case					
Province	11.3	7.4	84.2	20.0	5.4
Central	27.7	10.0	277.8	66.1	17.9

Table 22. The impact of hospital unit cost to the users who has to pay by OOP

Discussion

Information about hospital unit costs are key requirements for many types of decision making, serving as input to assess the relative efficiency of treatment between hospitals, and are essential for budgeting and planning exercises (Adam and Evans, 2006). The unit costs of inpatient bed days and outpatient visits are typically available. Unfortunately, it is rare in Vietnam or in similar contexts in developing countries where the public hospital cost data are mostly nonexistent (La Lewis, 1996). To fill this gap, using a large panel data of 4 consecutive years in 60% of general hospitals in Vietnam, the results of the current study reflect the real picture of Vietnam hospital health care services. The main result found was that generally up to 51% of outpatient visits and 55% of inpatient bed day costs are directly supported by the government (state budget). This indicates a higher proportion of hospital unit costs are covered by the government, compared to 30% of total health expenditure covered by public expenditure on health (MOH, 2008b). The main result in the current study was derived from a series of results on different hospital unit costs, which were found to be consistent with those of previous studies. The results of studies conducted by the Ministry of Health in 2006 (data for 2005) found the total cost per bed day (within 29 inpatient episodes) in provincial general hospitals to be 218,363VND (equal to US$36.8) (MOH, 2006a). Other studies by the Ministry of Health in 2005 (data from 2003 from 30 provincial hospitals) found that one inpatient bed day for surgery treatment (childbirth and appendicitis) cost 195,000VND (equal to US$33), internal treatment cost in the range of 94,000-340,000VND (US$15.8-57.4) (Lieu DH, 2005). At the central level, to our knowledge, there is only one study by Flessa & Dung (2004) which gave results from Bachmai hospital, indicating that one outpatient visit costs US$0.86 and one inpatient bed day US$13.40 (those costs were converted to USD according to the exchange rate, and by

PPP they were equal to US$2.3 for an outpatient visit and US$35.3 for an inpatient bed day), of which the inpatient bed day cost is consistent with our current results (Flessa and Dung, 2004). In comparison with other countries, our result is similar to the unit costs of secondary level hospitals in the much higher GDP per capita countries like Indonesia (cost of inpatient bed day: US$35.1), Equador (US$35.9), and Romania (US$39.0); and higher than those countries which have approximately the same GDP per capita, such as Algeria (cost of inpatient bed day: US$19.28) (Hung, 2000; Adam *et al*., 2003). In comparison to the WHO categorized regions, our result is relatively lower than that of Western Pacific Region B (Vietnam belongs to this region) where an inpatient bed day costs US$63, and an outpatient visit costs US$34. It is similar to the Eastern Mediterranean Region D (Afganistan, Pakistan, Iraq and Sudan, etc) (WHO, 2005a).

In consideration of DGS, for only one inpatient day of surgery at the central level the government has to subsidize up to US$78.07, that is as much as 10 outpatient visits at the provincial level. This support could be crucial for the poor or near-poor who have to pay for hospital services by OOP payment. However, the use of medical services (hospital admission) by the better off is 2.5-4.5 times greater than that of the poor (MOH, 2008b). The insured have almost twice the rate of admission than the uninsured (Sepehri *et al*., 2005), and insurance coverage was higher among those who have a higher ability to pay for health care (Chaudhuri and Roy, 2008). That clearly implied an inequity in the benefits of hospital service utilization among different groups within the population. The richer could pay for the services but actually they gain greater benefit from the direct support of the government, which was originally targeted at the lower income group in the population (Castro-Leal *et al*., 2000; O'Dennell, 2007; MOH, 2008b).

Policy implications: The findings of the paper offer some suggestions for evidence-based policy solutions that will help decrease the prevalence of catastrophic health spending in Vietnam. One of three fundamental concerns of the government in health financing sources is to protect people from the financial consequences of ill health and having to pay for health services (Chan, 2010), aside from the poor who have been provided with free health insurance. The remaining near-poor individuals (roughly estimated, 60% of whom have no health insurance), will be subject to the negative impact of the FFS regime, that is, to be at risk of CHE. The government should shift from direct support to hospitals to the prepaid regime with free health insurance which would provide a larger proportion of the vulnerable group of low income people or households with the benefit of increased access to health care services.

The strength of our study is that the results relied on the panel data of quite a large number of hospitals (60% of the total number of general hospitals) in 4 consecutive years which allowed us to capture the outcome variation among hospitals caused by the differences of unobservable determinants and the correlation between differences of unobservable and observable determinants of behavior (Carey, 1997).

However, the limitations of this article are that, firstly, with the limited information on the health care system, poor quality of hospital statistics, and the multi-stage regressions used to estimate the unit costs, we were only able to relatively calculate some basic unit costs necessary for hospital policy considerations (Weaver and Deolalikar, 2004). Secondly, the output measured here may provide a relatively poor fit, because the two groups of hospitals would have quite different total costs, while the total number of bed days, and also the number of outpatient visits, are the same (Grannemann, 1986).

Conclusion

Almost half of hospital AFC is covered by DGS, the rest is covered by user fees. However, the user fees have become a great financial burden for the uninsured, driven them into poverty and maintained inequities in health service utilization between the rich and the poor. Increasing the rates of user fees could be advised to support the performance of hospitals while reducing the direct support of the government for hospitals. The savings could be spent on subsidizing insurance to ensure that a larger part of the population are insured, especially the near-poor individuals/households.

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Chapter 6. Health care system in Germany

Introduction

Germany is situated in central Europe and shares borders with Denmark, Poland, the Czech Republic, Austria, Switzerland, France, Luxembourg, Belgium and Netherlands (clockwise from the north). It has an area of 357,112 km^2, with a total of 82,002 million inhabitants (in 2008). The average population density is 230 inhabitants per 1 km^2, varying between 72 inhabitants in Mecklenburg Western-Pomerania and 3834 inhabitants per km^2 in Berlin. There are 20 cities with more than 300,000 inhabitants, of which Berlin, the capital of Germany, has the largest population (Statistisches Bundesamt, 2010).

The country is a federal republic, where the Federal Assembly and Federal Council exist outside of federal government, and serve as constitutionally-defined bodies with legislative functions. The Federal Assembly is Germany's parliament, which stands at the centre of the country's political life and is its supreme democratic organ of the state, made up of 622 members. The largest parliamentary group is the CDU/CSU with 239 seats (in 2010). The Council of Elders, that assists the President of Federal Assembly, comprises the Federal Assembly President, the Vice-Presidents and 23 other members. The composition of the Council of Elders, the make-up of the committees and the members appointed as committee chairpersons depend on the individual parliamentary group's strength. There are 16 federal states. Each state has a constitution consistent with the republican, democratic and social principles embodied in the national constitution. The legislative authority principally lies with those 16 states, except in areas where the authority is explicitly given to the federal level. The states can fill in any gaps left by federal legislation or in areas not specified by the constitution. The Cabinet of Federal Government consists of the Chancellor, head of the government and federal ministers, who are chosen by the Chancellor and proposed to the President for appointment or dismissal. The Chancellor is responsible for establishing guidelines for government policy. The federal ministers independently run their departments under the framework of the Chancellor's guidelines.

Germany is a member of the G8 group that consists of the leading industrial countries of Germany, France, the United Kingdom, Italy, Japan, the United States of America, Canada and Russia. Germany has a Gross Domestic Product (GDP) of US$3,352 billion at current prices in 2009 the highest within the 42 European countries, equal to PPP_US$36,850 per capita, above 31 other European countries (for those have available data in German

Statistical Yearbook 2010). However, the unemployment rate is rather high at 8.2% in 2010, and varies between 4.8% and 14.1% (Berlin has the highest rate at 14.1%) in different states. The unemployment rate for men is higher than that for women, at 8.4%, compared to 7.9% (Statistisches Bundesamt, 2010). The living conditions are by law required to be of an equal standard among all states (Busse R, 2004).

Demography and health status

Since reunification in 1989, the Federal Republic of Germany is the combination of former Western and Eastern parts, with a total of 66.6 million and 13.5 million inhabitants, respectively (in 2003). The share of under 14-years-olds in all of Germany decreased from 25% in 1970 to 14.4% in 2000 and 12.6% in 2008, whereas the share of those over 65 years of age increased from 15% in 1991 to 19.2% in 2005 and accounted for 20.4% in 2008 (Statistisches Bundesamt, 2010). This figure will increase up to 30% of the total population (equal to 21-25 million people) by the year 2050 (Statistisches Bundesamt, 2006).

The life expectancy at birth increased from 72.6 years for males and 79.1 for females in the period 1991-1993 to 77.1 years and 82.4 years for males and females, respectively, during the period 2005-2010. But the birth rate decreased from 9.3 to 8.3 per 1000 inhabitants between 1995 and 2008 and the total fertility rate (the average number of children per woman) was 1.3 during the period 2005-2010. The death rate was 10.3 per 1000 inhabitants during the period 2005-2010, which is similar to that of the year 2000 (10.2 per 1000 population) (Statistisches Bundesamt, 2010). The standardized mortality rates rank above the EU-15 average; the higher mortality can be found in most age groups except for infant mortality (4.3 versus 4.7 per 1000 life births) and child mortality (5.3 versus 5.6) (Busse R, 2004).

Indicator	1991	1995	2000	2005	2008
Total population (in thousands)	80,274	81,817	82,259	82,437	82,002
Population aged 0– less than 14 years (% of total)	15.29	15.06	14.40	13.07	12.62
Population aged 65 years and older (% of total)	14.99	15.56	16.65	19.25	20.40
Population growth (annual %)		-0.15	-0.09	-0.18	-0.20
Birth rate, crude (per 1000 population)		9.35	9.32	8.32	8.32
Death rate, crude (per 1000 population)		10.81	10.20	10.07	10.30

Sources: (Statistisches Bundesamt, 2010)

Table 23. Population/demographic indicators, 1991–2007

This background of demographic changes has a major impact on the disease pattern and health care structure of Germany. Recently, the German health care system has been more concerned about diseases related to demographic trends such as chronic-degenerative diseases: obstructive lung diseases, diseases of cardiovascular system (stroke, cerebrovascular disease, ischemic heart disease), urogenital diseases and cancer. This raises more demand for the elderly population's preventative, therapeutic, rehabilitative and nursing care, which include long-term care and services for informal care, hospice and palliative care (Busse R, 2004). The statistic figures in 2008 showed that the highest share of hospital inpatient visits belongs to diseases of the circulatory system (I00-I99), accounting for 2,675,770 of the total hospital inpatient visits of 17,937,101, which is equal to 14.9%. Of these, ischaemia heart diseases comprise 25.5% and cerebrovascular diseases comprise 13.3%. Next to the circulatory system diseases, neoplasm diseases (C00-D48) accounted for 10.4% of total inpatient visits (Statistisches Bundesamt, 2010).

Consequently, demographic changes contribute considerably to the current and projected future rise in health expenditure. Just looking at one example of a disease, stroke costs more than 43,000 euro per one life time year, costing up to 7.1 billion euro in the whole of Germany in 2004, or equal to 3% of total health care expenditure. This disease is expected to considerably increase in the coming years. Taking the example of the state of Hesse, a study by Foerch and colleagues found that stroke is projected to increase steadily from 20,846 in 2005 to more than 35,000 in 2050 (and increase of 168%), the majority of cases will be over 75 years of age (Foerch *et al.*, 2008).

Organizational structure and personnel resources

Organizational structure

Germany is administratively categorized into the federal level (Bund), states (Laender), administrative districts (Bezirke), counties (Kreise), and municipalities (Gemeinden). However, the health care system is structured into the federal level, state level, and corporatist level. There are no sub-level administrative offices, since all political units at these levels have their own autonomous, elected representatives and governments. Therefore, decentralization is of only minor importance in the German health care system (Busse R, 2004).

Federal level

The federal level represents the national level. The main regulatory issues at the federal level are equity, comprehensiveness and the regulation for social service finance and provision. Key actors at the national level are the Federal Assembly, the Federal Council and the Federal Ministry of Health and Social Security (henceforth called the Ministry of Health). The Ministry of Health has five areas (each area is assigned by one Department):

1. Fundamental policy issues, long-term nursing care
2. Central department, European and international health policy
3. Pharmaceuticals, medical devices and biotechnology
4. Health care delivery, SHI
5. Prevention, health protection, disease control, biomedicine

The Ministry of Health is consulted by ad-hoc committees and the Advisory Council for Evaluating the Development in Health Care and is assisted by subordinate authorities regarding the execution of licensing and supervisory functions, scientific consultancy and information services to the population or scientific community; which consists of the Federal Institute for Pharmaceuticals and Medical Devices, the Federal Institute for Sera and Vaccines - Licensing of Sera and Vaccines, the Federal Institute for Communicable and Non-Communicable Diseases, the Federal Centre for Health Education, the Institute for Medical Documentation and Information Federal Insurance, the Federal Insurance Authority and the Federal Authority for Financial Services Supervision, and the Institute for Quality and Efficiency (Nassehi A, 2008; Busse R, 2004).

State level

At the state level, health is a field responded to by different ministries, but most commonly it is in one of four or five divisions in the Ministry of Labor and Social Policy. The health division is further sub-divided into units related to: (1) Public health services, communicable diseases, environmental hygiene, disaster preparedness and civil emergency planning; (2) Health promotion, pharmaceuticals, medical devices, biotechnology; (3) Occupational safety, product safety/consumer protection, prevention of substance abuse, state commissioner for narcotics; (4) Hospitals; (5) Health professions; (6) Psychiatry. The main tasks at the state level are to regulate the inpatient sector, to cover investment costs, to control the capacity planning and quantity of hospital care services and overall costs of the health system, such as the current DRG system.

Corporatist level

The corporatist level consists of representatives of provider federal associations, payer federal associations, and the Hospital Federation.

Providers

SHI accredited physicians are both private practice physicians and hospital physicians, who are accredited to provide ambulance care to SHI patients; and psychologists with a sub-specialization in psychotherapy, and child and adolescent psychotherapists are all organized in regional associations of physicians that are based on obligatory membership and democratically elected representation. There are approximately 149,900 physicians and psychotherapists who are members of physician associations (in 2008). Each state has one association, with the exception of the highly populated state of North Rhine-Westphalia which has two associations. The members of the executive board are elected by an assembly of delegates. Similarly, SHI-accredited dentists are organized in the same way as physicians—that is, through the Federal Association of SHI Dentists. The Federal Association of SHI physicians is known as the umbrella organization and is represented at the federal level which is a quasi-public corporation within the joint self-government system and represents the political interests of SHI-accredited physicians and psychotherapists to deal with the federal government. In addition there are different health professional chambers that can recommend and consult in decisions that affect health professions (Bundesärztekammer, 2009; Busse R, 2004).

German Hospital Federation has been increasingly integrated into decision-making bodies of the SHI structure. It does not have the status of a quasi-public corporation but represents the system of joint self-government through private organizations. The function of this Federation is to represent the interests of hospitals in dealing with other stakeholders and federal government. The 16 state organizations and 12 hospital associations of different hospital types and ownership types such as university hospitals, public municipal hospitals and private for-profit institutions are members of the German Hospital Federation (Busse R, 2004).

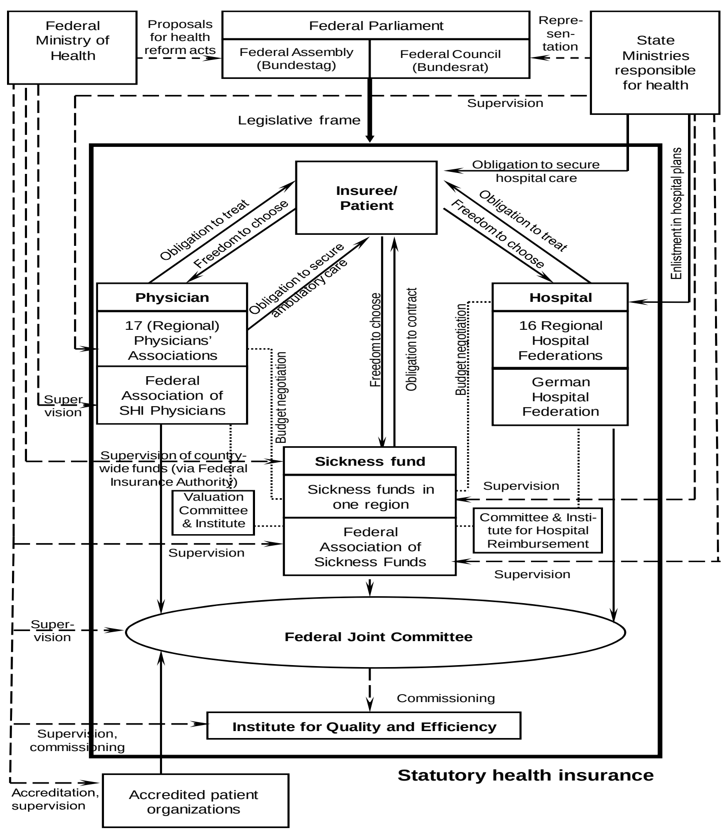
Payers

The payers' side is made up of autonomous sickness funds that are organized on a regional and/or federal basis. The sickness funds/SHI have non-profit status. They are based on the principle of self-governance. The SHI covers about 91% of the total insured people; the remained 9% are insured by private health insurance companies. The distribution of sickness funds and their insured in 2009 was: 15 general regional sickness funds (AOK) covered 34% of the whole health insured people; 8 substitute sickness funds, formerly open to either white-collar or blue-collar workers, covered 34%; 160 company-based sickness funds (BKK) covered 20%; 14 guild sickness funds (IKK) covered 9%; the sickness fund for mining workers covered 2%. By law, sickness funds have the obligation to raise contributions for their members, including the right to determine what contribution rate is sufficient to cover expenditures (up to 2009). SHI is almost exclusively financed by income-related contributions on a pay-as-you-go basis.

Besides the above mentioned legal actors, there are some other actors. They are voluntary organizations, which may be differentiated by their main focus on scientific, professional, political or economic interests and the group they represent, for instance, the charitable organizations like the Red Cross (Nassehi A, 2008).

The health care system adheres to the fundamental facet of the German political system whereby decision-making powers are shared among all states, federal government and legitimized civil society organizations. It was traditionally delegated by governments to a mixture of regulating competencies of different actors at the federal, state and corporatist levels. Setting the functional framework is a federal state monopoly, mainly prepared by Federal Ministry of Health. However, the responsibility of the everyday care in the ambulatory sector is assigned to the Federal Joint Committee. The different actors have the duty and power to define benefits, prices and standards at the federal level, and to negotiate horizontal contracts to manage and sanction their members' behavior at the regional level. The vertical implementation of decisions taken by superior levels is combined with strong horizontal decision making and contracting among the legitimate stakeholders involved in the various sectors of health care (Busse R, 2004).

The major actors and their main interrelationships are shown below in Figure 10:



(source: Busse R, 2004)

Figure 10. Organizational relationships of the key actors in the German health care system

Health care personnel resources

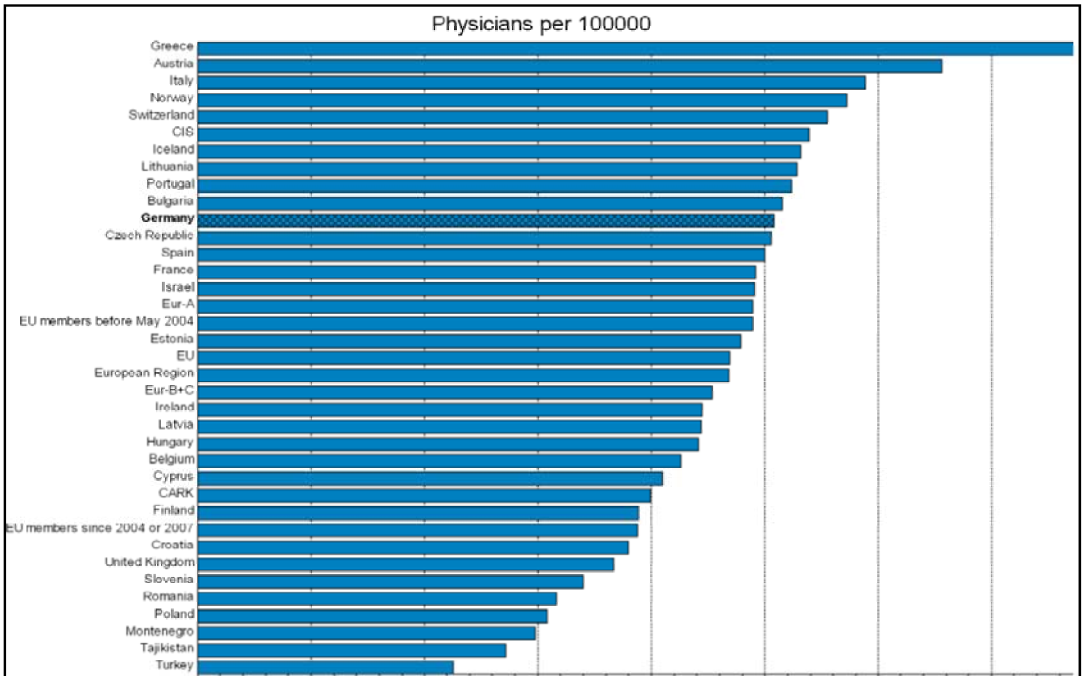
The German health care system is made up of different players, which consist of hospitals, health insurers, medical device manufacturers, pharmaceutical manufacturers and wholesalers, care providers, consulting organizations, pharmacies, spas, etc. These comprise a dynamic economic sector with strong innovative capabilities and considerable economic importance for the country and it is considered an engine for future growth and employment. Providing a great contribution to the employment sector in Germany, it comprises up to 11.6% of total employment (in 2008), with a total of 4.6 million people working (in a combination of full-time and part-time job) in the health sector. The total number is 1.7% higher than the previous year (2007), and 10% higher compared to 2004. An expected 600 000 new jobs can be offered in 2011 (Federal MOH, 2011a).

Indicators	1991	1995	2000	2005	2007	2008
Physicians per 100000	276.39	306.53	326.04	341.13	350.32	355.74
Physicians, medical group of specialties (PP), per 100000	51.36	57.4	66.13	73.67	76.54	77.85
% of physicians working in hospitals	...	...	48.19	49.18	50.13	51.1
General practitioners (PP) per 100000	58.06	66.38	66.22	66.61	66.07	65.42
Dentists (PP) per 100000	...	70.55	73.45	75.58	76.57	77.31
Pharmacists (PP) per 100000	52.02	54.73	58.29	58.28	60.21	60.77
Nurses (PP) per 100000	...	...	958.78	1022.26	1047.86	1067.95
% of nurses working in hospitals	...	...	68.11	63.11	61.17	61.11
Midwives (PP) per 100000	...	...	18.25	20.61	21.88	21.92
Physicians graduated per 100000	...	12.54	11.12	10.7	11.58	12.09
Nurses graduated per 100000	...	...	28.7	28.27	26.81	27.08
Midwives graduated per 100000	...	...	0.72	0.75	0.8	0.71
Pharmacists graduated per 100000	2.47	2.2	2.36	2.21	2.16	2.19
Dentists graduated per 100000	3.06	2.63	2.28	2.01	2.24	...

Source: WHO - European health for all databases (HFA-DB) (WHO, 2011)

Table 24. Health care workforce 1991-2004 (persons per 100 000 population).

In average, the number of physicians in Germany is 355.74 per 100 000 inhabitants, which is the 11th highest among all EU member states (Figure 11). This figure has increased between 4.5% and 10.9% every 5 years. Contributing most to this increasing trend are physicians and medical groups of specialists, and the number of general practitioners has remained rather stable during the last 15 years (Table 24).

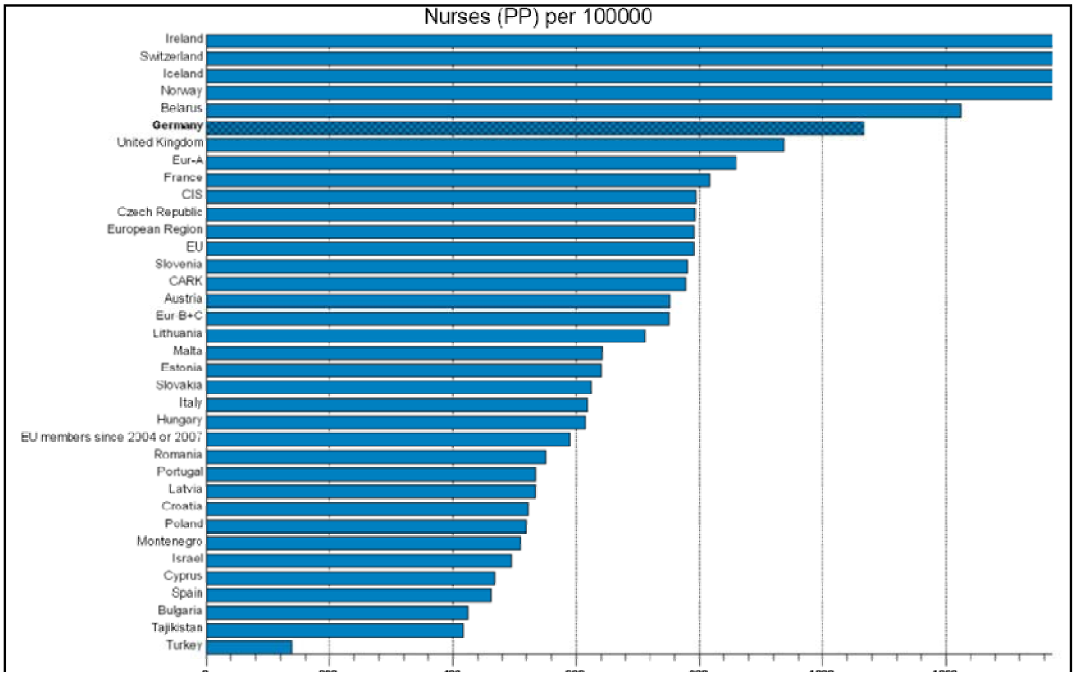


Source: WHO/Europe, European HFA Database, January 2011 (WHO, 2011)

Figure 11. The chart of Physicians in Germany compared to others in EU (2008)

In 2009, with a total of 429,926 physicians, 325,945 were active. Of these 158,223 were working in hospitals, 139,612 in ambulatory care, and about 9,500 physicians were working in public health services and administration or corporatist bodies and the other 18,600 physicians in other areas (i.e. the pharmaceutical industry) (Bundesärztekammer, 2009).

The average number of nurses per 100,000 inhabitants is quite high in Germany compared to other EU member States. It is only lower than 5 other countries: Ireland, Switzerland, Iceland, Norway, and Belarus (Figure 12). An increase in the number of nurses has been observed over the last 10 years: the number was 4.4% higher in 2008 compared to 2005 and 6.6% higher in 2005 compared to the year 2000. The majority of them (61% - 68%) work in the hospital (Table 24).



Source: WHO/Europe, European HFA Database, January 2011 (WHO, 2011)

Figure 12. The chart of nurses in Germany compared to other states in the EU

However, one of the major challenges of the German health care system is a shortage of physicians. Doctors working in hospitals frequently complain about the excessive workload: too much administrative work and documentation tasks, working overtime, doing extended shift work and on-call duties at short notice, lack of internal coordination and communication of working routines. The average working time per week of young physicians is 55.3 hours (in 2003). This workload makes physicians more at risk of suffering from psychological stress than workers in other sectors (Rieser S, 2006; Mache and Groneberg, 2009). In particular, there is a shortage of general practitioners (GPs), especially in the rural areas, where the young doctors do not want to work, the figures show that by the year 2010, approximately 15,600 GPs will be needed to replace the retired physicians. This issue has been dealt with by the Associations of SHI Physicians by attempting to acquire more young physicians for employment in rural areas by offering financial incentives. However, that initiative has had only moderate success. The recruitment of more medical students for employment in rural areas as GPs is a major challenge for Germany (Natanzon *et al.*, 2010). Therefore, one of the reforms to deal with this challenge is the rearrangement of the tasks of physicians. Some particular tasks of physicians could be carried out by non-physician, for example, prescription rights will be partly taken on by nurses and doctor's assistants. This task was assigned by exclusive right to physicians. Non-physicians were only allowed to provide treatment upon referral from a physician. The idea of delegating prescription rights was initiated by the Advisory Council on the Assessment of Developments in the Health Care System, with the purpose of avoiding health care provision shortfalls caused by an increasing shortage of physicians and professional caregivers for seniors and the disabled, in particularly the higher demand for long-term care; and relieving the workload of GPs. To do it, a list of all treatments that could be additionally prescribed by non-physicians will be issued by the Federal Joint Committee (Hoffman C, 2010).

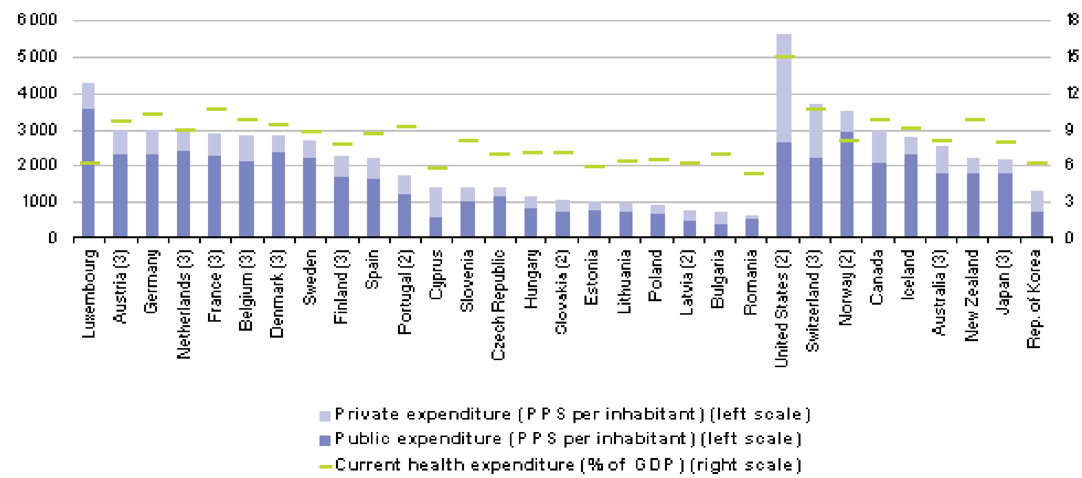
Patient empowerment

There is no specific piece of legislation describing clearly and comprehensively the rights of the patient (the draft is now on the approval process), but they are defined in the various jurisdictions in Germany. They consist of the right to freely choose physicians and hospitals; seek a second opinion; receive qualified and judicious medical treatment according to recognized medical practice standards; determine treatment regime to receive; use sign language or other communication aids in case they are needed to communicate with the physician, and the sickness funds will cover those costs; require all medical procedures to be performed only with their legal consent; get individual advice about insurance benefits from their sickness funds; receive pharmaceuticals or medical products that match the legal quality and safety requirements; have timely, face-to-face information about their proposed treatment; obtain a written record of the most important diagnoses and treatments that they were diagnosed and treated with; see and get copies of their own medical records; have their medical data kept confidential; and to receive compensation in case of medical error, lack of informed consent, or side-effects of medicines or medical devices.

The patient's position in the health system has been improved, since the health reform came into force in 2004. A commissioner of the federal government was introduced to attend to patients' issues, which consist of patients' rights to extensive and independent consultation and objective information by service providers, cost units, authorities in the health care sector and medical care. The commissioner is permitted to participate in all legal, regulatory or other important initiatives in respect to the rights and protection of patients. The focal points of the commissioner are to provide legal information or user-friendly information and contact details of authorized institutions like medication services of the medical council, the consumer counselling centres and counselling facilities of the sickness funds (Schneider *et al.*, 2007).

Health care financing

Health care expenditures

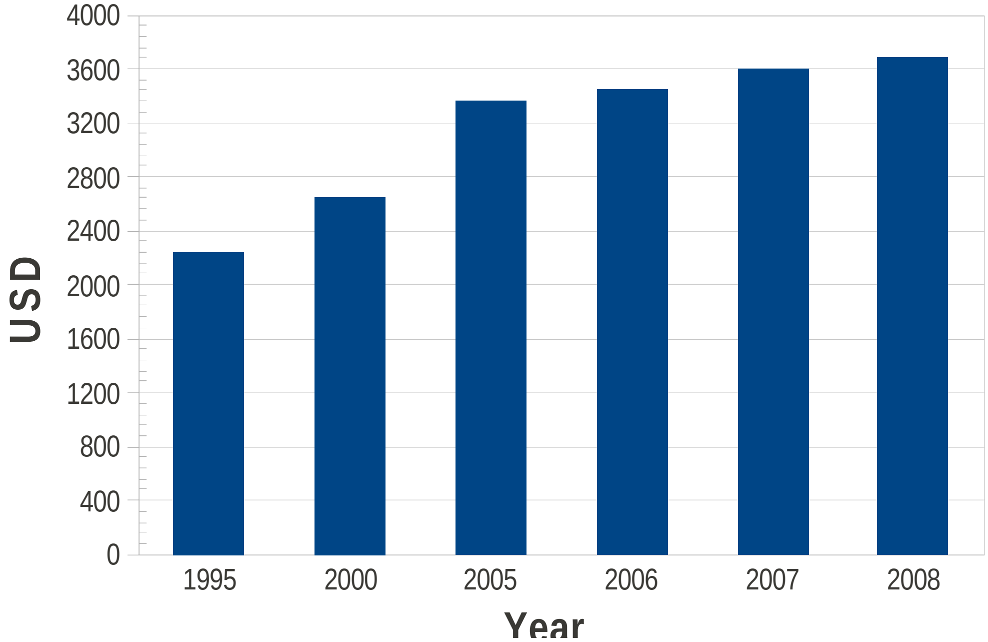


(1) Countries are ranked on the current health expenditure (PPS per inhabitant); Ireland, Greece, Italy, Malta and the United Kingdom, not available.
(2) 2006.
(3) 2007
Source: Eurostat (hlth_sha_hf)

Source: from (European Commission, 2010)

Figure 13. Current health care expenditure, 2008

The health expenditure is the mix of public and private funding. That amounted to around €263 billion - equivalent to 10.5% of the GDP in 2008. The share financed by public expenditure of 77.3%, major share of social security systems comprised 70.2% of the total expenditure, and was made up of 161 billion from SHI (compared to 171 billion in 2007) and 25 billion from private health insurance (European Commission, 2010; Federal MOH, 2011b). While private household out-of-pocket expenditure was 12.3% and private insurance enterprise including private social insurance comprised 9.7%. This dominance of public funding is similar to Romania, the Netherlands, the Czech Republic, Sweden, Luxembourg and Denmark; but different to other countries like Cyprus and Bulgaria where public funding accounts for only 42% and 56%, respectively. The total healthcare expenditure share exceeded 10% of GDP in Germany, which represented almost twice that of Romania, Cyprus and Estonia (below 6% of GDP) (Figure 13). The health care expenditures spent per capital increased by about 42% between 2008 and 1995 (Figure 14).



Source: from (WHO, 2011)

Figure 14. Total health expenditure PPP$ per capital

The functional patterns of health care expenditures show that Germany spent the largest part (53.3%) of current health care expenditure on curative and rehabilitative care services, which is similar to most other European countries; then the second largest function, with average spending accounting for 20.5% of total current health care expenditure, was medical goods dispensed to outpatients; the services related to long-term nursing care accounted for 12.3%, which is rather higher than half of the Member States of the European Commission which spent less than 10% of current health care expenditure (due to the long-term nursing care provided by family members in many Member States and no payment was made for these services), but much less compared to Denmark and Luxembourg who spent up to 21% and 20%, respectively. The proportion of current health care expenditure spent on health care administration and health insurance was 5.4%, and on ancillary services such as laboratory testing or the transportation of patients was 4.7%. The expenditure related to prevention and public health programs was 3.7%, a very small function compared to medical treatment recorded under the heading of curative care. However that is quite similar to most other Member States, among which the expenditure associated with collective services reported under preventive program and the administration of health care systems did not surpass 10% of overall current health care expenditure (Table 25) (European Commission, 2010).

	Services of curative & rehabilitative care	Services of long term nursing care	Ancillary services to healthcare	Medical goods dispensed to out patients	Prevention & public health services	Health administration & health insurance	Not specified by kind
Belgium(1)	50.5	17.0	2.4	17.6	4.1	8.5	0.0
Bulgaria	53.6	0.1	3.6	36.8	4.3	1.0	0.6
Czech Repulic	58.5	3.4	5.6	24.6	2.7	3.5	1.7
Denmark(1)	58.1	21.4	4.7	13.2	1.5	1.2	0.0
Germany	**53.3**	**12.3**	**4.7**	**20.5**	**3.7**	**5.4**	**0.0**
Estonia	55.8	4.2	10.1	24.9	2.8	2.3	0.0
Ireland							
Greece							
Spain	56.4	9.2	5.3	23.5	2.4	3.3	0.0
France (1)	53.7	10.8	5.2	21.2	2.0	1.7	0.0
Italia							
Cyprus	59.3	2.5	9.5	23.9	0.7	4.2	0.0
Latvia (2)	52.9	3.5	8.4	26.0	3.1	6.1	0.0
Lithuania	53.4	7.4	5.6	29.9	1.4	2.3	0.0
Luxembourg	58.3	19.9	5.9	12.5	1.9	1.7	0.0
Hungary	48.9	4.0	4.5	36.5	4.0	1.3	1.0
Malta							
Netherland	53.8	13.4	4.9	17.2	5.1	5.6	0.0
Austria (1)	60.0	13.2	3.1	18.1	1.8	3.7	0.0
Poland	57.7	5.6	5.9	26.9	2.4	1.7	0.0
Portugal (2)	62.3	1.4	8.5	24.7	1.9	1.2	0.0
Rumania	47.5	12.4	4.7	26.6	6.0	2.8	0.1
Slovenia	57.5	8.6	3.0	23.0	3.9	4.0	0.0
Slovakia (2)	44.7	0.4	7.3	39.1	4.5	4.1	0.0
Finland (1)	59.0	12.1	3.0	17.8	5.8	2.3	0.0
Sweden	64.4	7.9	9.4	16.9	3.6	1.4	0.9
United Kingkom							
Iceland	59.4	19.0	2.3	16.0	1.6	1.8	0.0
Norway (2)	50.5	26.4	6.4	13.9	2.0	0.8	0.0
Switzerland	57.7	19.4	3.3	12.3	3.3	5.0	0.0
Australia	70.3	0.3	6.0	18.4	2.1	2.8	0.0
Canada	46.4	14.8	6.3	20.9	7.1	3.8	0.6
Japan	57.9	15.1	0.7	21.5	2.4	2.4	0.0
Rep. Korea	63.5	3.1	0.3	27.3	2.5	3.3	0.0
New zealand	57.0	14.2	4.7	10.9	6.1	7.2	0.0
United States (2)	69.0	6.4	0.0	14.0	3.2	7.4	0.0

Source: (European Commission, 2010)

Table 25. Health care expenditure by function, 2008 (% of current health expenditure).

Payer and payment mechanisms

Before October 1990, the health care system in East Germany was state-owned, and financed by a national budget distributed through several hierarchical levels to health services with a small share of the gross national product. All physicians and other health staff were public employees, and paid an average salary. Patients accessed health services free of charge. The organizational structures more or less followed a primary health care model. The polyclinics were responsible for primary and secondary care in urban areas. However, the health facilities were in poor condition, lacking or with only out-of-date technical equipment, restricted pharmaceutical supplies in domestic products and rarely of international standards, and with considerably long waiting lists. On the other hand, the health care system in West Germany before reunification was private-based and funded within a social security system that has been in existence for more than 100 years. SHI covered more than 90% of the population. The remaining 10%, mainly the self-employed, civil servants and high-income groups, are covered by private health insurance. For those insured by SHI, employers and employees each co-paid half of the premium, which was a fixed percentage of their wages, and family members co-benefited without extra charges. Patients were freely able to access physicians and specialists. Ambulatory and hospital care was separated. Doctors were in private offices or self-employed. They get paid on a fee-for-service basis for those in private office whereas those in hospitals were employees (Häussler, 1993). In the reunification process since 1990, this health care model was adopted for East Germany, therefore the health care system in the East has been totally reconstructed.

Therefore, in the reunified country, the health care system is provided by SoHI, which is the oldest system in the world. Since the 17th century, the statutory sickness fund has been in place, which is based on the principle of solidarity with five types of relief funds in different regions of Germany; such as relief funds for journeymen, relief funds for craftsmen, factory relief funds founded by socially-oriented entrepreneurs, relief funds founded by local authorities of workers or trades, and community relief funds. A health care system reform was made in 1883 by Bismarck which included incremental changes and adjustments, rather than a transformational change, which aimed to establish a comprehensive, social insurance system. The basic principles of Bismarck's system were (1) largely self-governed support funds; (2) both employers and employees were to be presented in the bodies of self-governance in most of the company-based funds; (3) both employers and employees were to partly contribute to company-based funds; (4) introduction of compulsory insurance in many municipalities. In establishing SoHI, the German central government played a crucial role by creating a legal framework. To survive until now German health care system had to modify in many details of the basic structures in order to adapt to the new challenges of health care technological advances, demographic ageing, and increasing unemployment which do not fit to the original model of Bismarck (Breckenkamp *et al.*, 2007).

The advantages of SoHI are that it provides a stable source of revenues, a visible flow of funds into the health sector, and a combination of risk pooling with mutual support. However, it has some problems with insuring informal sector workers and a lack of cost control (Bärnighausen and Sauerborn, 2002). Some typical characteristics of the system are the tradition of self-government of health care provision with representative bodies of physicians and sickness funds, and two separated sectors of administrative divisions, one of which is in-patient care and other ambulatory care (Breckenkamp *et al.*, 2007).

Eighty-six percent of populations were insured by SHI, which covered all health care costs; in additional patients were free to choose physicians, specialists; and doctors tried to provide patients best choice of treatment. Particularly, ambulatory physicians were reimbursed on a fee-for-service basis. This mechanism had stimulated the highest health utilization rates in the world: on average one person had 11 visits to physicians annually, compared to 5.5 visits in the United States (Statistisches Bundesamt, 2010; Himmel *et al.*, 2000). Consequently, health care costs had significantly increased. Two years after reunification, the substantial reforms of the health care system were politically debated. Therefore, since 1992 the reforms have started to stop the constant increase in service utilization by introducing characteristics to the health care system whereby the provider hase a strong position, and the reimbursement system of hospital care has been gradually changed towards a prospective payment system, following the model of the United States (Häussler, 1993). The German health care system has highlighted the financial burden of the health care and has been forced to undertake a series of reforms to shift more financial responsibility to the insured.

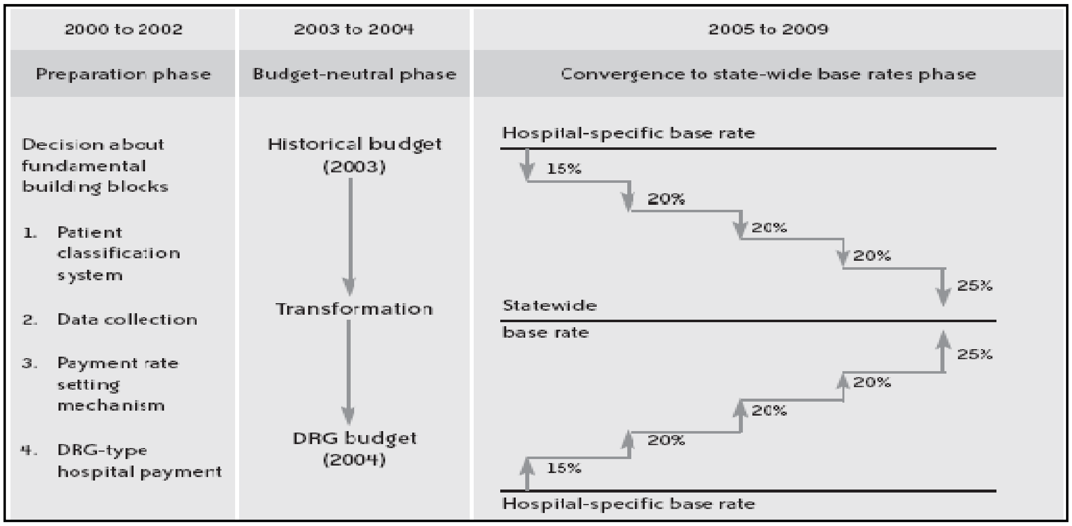
With the intention of cutting down health care costs, there were several adjustments which exclusively focused on cost reduction during the period 1993-2000. That consisted of the obligatory introduction and development of internal quality management systems in hospitals, inter-sectoral contracts between health care providers and sickness funds, introducing a model of optional family doctors and financial incentives for patient staying with the same GPs as their family doctor, introducing a restrictive list of effective drugs replacing the negative list of ineffective drugs on the market. In 2004, some other reforms were introduced, for example, DRG became mandatory for all hospitals; GPs are encouraged to prescribe cheaper drugs and obliged to provide information on the cost of treatment to patients if they demand it; work-related sickness benefits, visit to health spas, cookery courses, and taxi fares to doctors are no longer paid by state health insurance schemes; and patients are required to pay for every GP visit (10 Euro), prescription drugs, and every inpatient day in hospital (10 Euro) (Breckenkamp *et al.*, 2007; Burgermeister, 2003). This practice charge of 10 euro applied for all those insured by SHI over 18 years of age upon the first visit to physicians or dentists each 3 months and was introduced in January 2004. It excludes preventive medical services (cancer screenings, examinations to ensure a normal pregnancy, general health checks for those above 35 years of age, and dental prophylaxis). The fee is paid directly by the insured in cash at the doctor's office and then transferred to SHI by physicians. To avoid a financial burden on the insured from this co-payment, SHI has made the upper limit for the annual payments. That should not exceed 2% of the payer's total annual income for those not insured, 1% for those suffering from chronic diseases and exemption for those who spent over 28 inpatient days per year. Just two years later, the number of physician visits was reduced by 8% (2005 compared to 2003). However, this policy has been highly debated and is controversial. The major concerns are whether it limits the important physician visits, increasing social-economic inequalities. The study by Schneider and colleagues showed that services of the health insurances were of the most concerns to patients (75.6% of all inquiries received by the commissioner were related to this). The health reforms on the introduction of the practice charge, higher surcharges to self-payment for over-the-counter drugs, individual health services, the preventive medical check-ups (not included in the defined spectrum of services of health insurance) resulted in a financial overburden on patients (Schneider *et al.*, 2007). A study of Rückert and colleagues in the setting of 7,769 respondents reported that about 14% of those who had chronic diseases exceeded the maximum co-payment of 1% of total annual income. The avoiding or delaying of a physician visit due to the practice fee in the total cohort was 27% or 18%, respectively. That was strongly dependent on the age of the patient, and significant differences were seen between groups of less than 30 years versus over 70 years of age (OR= 4.83, CI 3.94-5.91, $p<0.001$). Even in the chronic disease group, the delayed and avoided visits were also high, and ranged from 28% to 42%. However, that is significantly lower than that of the group without chronic diseases, which ranged from 40% to 60% (Rückert *et al.*, 2008). The reform was objected to by 63% of Germans (Burgermeister, 2003).

The introduction of G-DRG

The hospital receives a system of 'dual financing' which means infrastructure is funded by the state governments through tax-funded state budgets and operating costs are covered via DRGs by the sickness funds and private fund insurances that shifted from a payment mechanism of historically-based hospital budgets (using per diem charges as the unit for reimbursement), which maintained big problems of inefficiency. Typically, the high proportion of inappropriate hospital days and admission was not surprising in the German health care system, where health care is completely paid for by third party payment (SHI) and hospital reimbursement is predominantly per diem. Doctors were not forced to reduce the length of hospital stays of patients. The rate of inappropriate admission was evident for all specialists: the results of a study by Sangha and colleagues (2002) in the setting of 2,317 patients in a general internal medicine department and 2672 patients in a surgery department in a 400 bed hospital in 1997 showed that 33% of surgery admissions and 6% of internal medicine admissions were judged to be inappropriate; 28% and 33% of consecutive hospital days of surgery and internal medicine patients, respectively, were judged to be inappropriate (Sangha *et al.*, 2002). Dental care was affected by significant problems due to this payment mechanism because until the end of 1970s, there was no co-payment for dental care services for patients. All treatment was totally paid by SHI, which resulted in the overuse of the most expensive treatment for the patients decided by either dentists or patients. The dental care expenditures were raised by up to 14.7% of total health expenditures and 1.15% of GDP in 1980 (Saekel, 2010).

The purposes of the DRG system is to achieve an appropriate and fair allocation of resources; to facilitate a precise and transparent measurement of the case mix and the level of services delivered by hospitals; to increase the efficiency and quality of service delivery in the hospital sector due to the improved documentation of internal processes and increased managerial capacity; and to control costs through a reduction of LOS and bed capacity with the goal of promoting efficiency, quality and transparency in the health sector. Following the fundamental characteristics of the new payment system outlined in the reform legislation, the self-governing bodies consisting of the federal associations of sickness funds, the Association of Private Health Insurance and the German Hospital Federation develop and manage the G-DRG system. Then they founded the Institute for the Payment system in Hospitals (InEK), which is responsible for the technical management of the G-DRG system. The new payment system has been applied currently in 1,700 hospitals (80% of all hospitals) with all types of hospital ownerships (except the psychiatric services) and accounting for 97% of all inpatient discharges.

Up to now, G-DRG has passed through three phases: preparation phase in the period 2000-2002, budget-neutral phase in 2003-2004; and convergence to state-wide base rate phase in 2005-2009 (Figure 15). The detail of each phase is described below:



Source: (Quentin W, 2010)

Figure 15. Three phases of introducing GRD-type hospital payment in Germany

Preparation phase:

Patient classification system: In June 2000, the self-governing bodies decided to adapt the Australian Refined DRGs to the German context. The codes for procedures and diagnoses of Australia were transformed to German procedures (following the procedure classification codes - OPS) and diagnoses (following German modification international code diseases ICD-10-GM) codes for diagnoses. A first version of 664 DRGs was developed at the end of 2002 after the pilot project in 2001. Each DRG is determined by the algorithm of major diagnosis, procedure, secondary diagnoses and patient characteristics (age, sex, weight of newborns). All inpatient discharges were assigned to a specific DRG within those 664 DRGs; the majority of the DRGs are the combination of diagnostic or procedure group, except in the high cost procedures (transplantations or extended intensive cases) each procedure was directly determined by a single DRG. The number of DRGs has been updated annually, resulting in a list of 1200 DRGs in 2010.

Data collection: To develop the new DRG catalogue: about 250 hospitals were selected as a sample by InEK, which must calculate the patient level costs for each patient, then transfer the cost data to a Data Center to check the data then forward it to InEK for calculating cost weights and developing the new DRG catalogue. For the payment: Before payments of sickness funds, the clinical data of discharged inpatients are collected by the hospital and reviewed by medical review boards of sickness funds to detect any fraudulent actions by hospitals, such as inappropriate inpatient discharges or patient classification into higher-paying DRGs.

DRG-type hospital payment: The share of DRG reimbursement accounted for about 80% of total hospital revenues that cover all medical treatment, nursing care, pharmaceuticals, therapeutic appliances, board and accommodation. Since 2010, hospital payment of each patient's DRG is calculated by multiplying the cost weight with a uniform state-wide base rate. A surcharge is added for those patients, who stay above the upper length of the stay threshold. Similarly, the DRG payment is reduced by per diem based deductions for those are discharged earlier than the lower length of stay threshold.

Budget neutral introduction phase

Before the introduction of G-DRG, hospital budgets were divided by the negotiated number of annual patient days to calculate per-diem charges. In the budget neutral transformation phase hospital budgets were divided by the hospitals' case mix to calculate a hospital-specific base rate that varied from ~€2200 (mostly in small rural hospitals) up to ~€3200 (for major hospitals in urban areas) to ensure that the total of DRG-payments would be the same budget as negotiated for previous years.

Some different steps have been taken in the budget neutral introduction phase. In the first year, hospitals started classifying inpatients into DRGs and received historically-based budgets as in previous years. In the second year, hospitals voluntarily group their patients into DRGs and enable to negotiate higher budgets. However, in the third year (2004) all hospitals were mandated to do so.

Convergence phase

In the convergence phase, the state-wide base rates have been gradually adjusted one for each of the 16 federal states since 2005 and the actual base rates were programmed to converge at the state-wide base rates in 2009 and the excessive budget losses are no longer limited, all hospitals are paid by using the state-wide base rate since 2010. However, hospital budgets continue to be negotiated for each year based on the expected case mix volume. It means that the DRG payment rate is increased or decreased by a certain percentage, depending on the accomplishment of the volumes assigned by the negotiation between hospital and sickness funds. If the hospital treated more than the negotiated case volume then the reimbursement rate is reduced by certain percentages and vice versa it is increased if less cases were treated (Quentin W, 2010).

Due to the fact that the sustainability of the German health care system's finances have been threatened by the rise in the health care spending, as a result of demographic changes (ageing population and falling birth rates) causing a shrinking labor force, and medical progress. Consequently, reform of health care in 2010 was particularly dedicated to reorganization of the financing of the health care system (Federal MOH, 2011d). In particular, the German coalition government has implemented major changes in the funding of SHI. Since the health care costs are expected to increase, from January 2011 onwards, the income-related contribution rate will be fixed by law at 15.5% of contributory income: the insured have to pay 8.2% of their income and the other 7.3% is paid by employers. The capped level of 15.5% will be fixed in the future. To fund further future capital needs of sickness funds, the different surcharges can be individually increased depending on each sickness fund's financial power. This reform will introduce competitive elements into the marketing of SHI sickness funds and allow insured persons to compare the price and the benefit package and choose the sickness fund with the best price-performance ratio. In addition, future rises in health expenditure will burden labor costs to the same degree as they would in a system the financing of which is completely wage-based. To prevent the insured from being overburdened by the premium, the insured is eligible for tax-financial social compensation if the average additional premium exceeds 2% of the individual's assessable income. The compensation is indirectly paid out by reducing the income-related contribution rate of the insured persons, and is made automatically by the employer together with the insured persons's wages or by the pension fund with pension payments (Federal MOH, 2011b; Bäumler M, 2010). This reform makes one more important change: the idea of having a second convergence phase towards a nation-wide base rate is abandoned. Consequently, hospitals in different states will continue to be paid at different price levels. In addition, starting in 2012, sickness funds will be allowed to negotiate with individual hospitals in order to obtain discounts for their members (Busse R, 2010).

Over the last 10 years, the standard G-DRGs payment has been successfully developed. The G-DRGs left medical ground in order to achieve optimal economical homogeneity that offers a higher outstanding homogeneity (R^2 of 83.5% in 2009 compared to R^2 of 70.2% in 2004) (Stausberg and Kiefer, 2010). However, these schemes is recently not allowed for strategically operating and managing hospitals in an environment of increasing competition (Lüngen *et al*. 2009); and further adjustments of the G-DRG system especially for cases with extremely high costs are necessary. In particularly, intensive care medicine is extremely heterogeneous and expensive, and can only be partially planned and controlled. The G-DRGs version 2010 has gained complexity and adequate quality of case allocation and G-DRG reimbursement relevant to intensive medical care, with the total of 58 G-DRGs (compared to n = 3 in 2003), but it is unable to cover extremely high-cost cases

(Franz *et al.*, 2010b). A similar problem has been found also in the complex urology cases (Wenke *et al.*, 2009) and severe injury cases (Franz *et al.*, 2009). However, the changes to the G-DRG structure in orthopedics and traumatology, especially in the areas of spinal surgery and surgery of the upper and lower extremities have reached a high level of complexity, but the actual impact of the changes may vary depending on the individual hospital services and only a few DRG users can follow them (Franz *et al.*, 2010a).

Health care service provision

Hospital sector

Hospital care is not organized by the Federal Administration, but rather by a sovereign mandatory regulation of the 16 German states. 89% of the total hospital beds enlisted in state hospital plans plus university hospital beds (9%) made up 98% enlisted in the hospital plans and entitled to investments from the federal state independent of hospital ownership; beds in hospitals additionally contracted by sickness funds made up 1.6% and beds for private insured patients in hospitals without the contracts of sickness funds only 0.6%. Finally, 99% of hospital beds were accessible to SHI-insured patients. The hospital beds per capita and investment per bed vary among federal state depending on political priorities and the availability of finances for hospital investments. The private for-profit hospitals are entitled by the Hospitals Financing Act to depreciate parts of their investment via the sickness funds' reimbursement of recurrent expenditures (Busse R, 2004).

In total, Germany has 2083 hospitals which fall into several different ownership types: publicly-owned hospital, private non-profit and private for-profit hospitals, with a total of 503,360 beds, equal to 6.1 beds per 1000 inhabitants. The number of bed per 1000 inhabitants has been dramatically reduced in comparison to 8.3 in the year 1991 and 6.8 in the year 2000. Of this number of hospitals, the majority are general (or acute) hospitals, which comprises for 1781 out of 2083 hospitals, comprising 92.2% of total hospital beds. The rest belong to psychiatric and neurology hospitals. Regarding the size of the hospital, the most common sizes are between 200-299 beds and 100-149 beds per hospital. However, some trends have been observed as the number of small size hospitals (less than 49 beds) has increased while all other sizes have been reduced over the last 20 years (Table 26).

Size of hospital	Total	>49	50-99	100-149	150-199	200-299	300-399	400-499	500-599	600-799	>800
1991	2411	331	316	316	271	410	265	175	98	104	125
1995	2325	319	308	301	267	417	252	186	87	89	99
2000	2242	361	271	303	276	375	263	142	90	74	87
2005	2139	400	269	291	230	334	225	135	106	65	84
2006	2104	398	273	303	220	328	201	133	94	67	87
2007	2087	407	264	302	208	326	203	131	96	64	86
2008	2083	417	273	297	194	325	201	134	89	67	86

Sources: (Statistisches Bundesamt, 2009)

Table 26. Number of hospitals by size and years between 1991 – 2008

Regarding the ownership of German hospitals, the private non-profit hospitals are the more common, accounting for 37.1%, then private for-profit (31.7%) and publicly-owned (31.1%). However the major proportion of hospital beds belongs to publicly-owned hospitals, comprising 48.3%, then private non-profit, comprising 35.8%. Compared to the years 2000 and 1991, when the hospital sector was predominantly publicly-owned, recently there has been a big trend toward privatization in both the number of facilities and hospital beds while the number of publicly-owned hospital has been gradually reduced (Table 27).

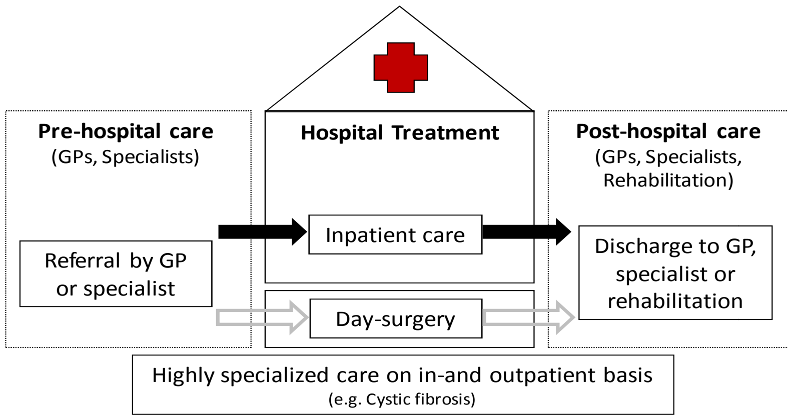
	Public		**Private not-for-profit**		**Private for-profit**		**Total**
	No of Hospitals	**Beds in 1000/ Share (%) of all beds**	**No of Hospitals**	**Beds in 1000/ Share (%) of all beds**	**No of Hospitals**	**Beds in 1000/ Share (%) of all beds**	**No of Hospitals**
1991	-	367/ 61.4	-	207/ 34.6	-	24/ 4.0	-
2000	-	284/ 54.2	-	201/ 38.4	-	39/ 7.4	-
2005	647	249/51.5	712	175/36.3	487	59/12.2	1846
2006	614	237/50.3	692	171/36.2	503	63/13.4	1809
2007	587	230/49.1	678	167/35.8	526	70/15.1	1791
2008	571	225/48.6	673	167/36.2	537	71/15.3	1781
2009	554	223/48.3	661	165/35.8	565	73/16.0	1780

Sources: The figures were calculated based on the data from (Deutsche Krankenhaus Gesellchaft, 2011)

Table 27. Trends in the public-private mix of general hospitals, 1991 to 2009

Besides the general hospitals for secondary care, there is a system of preventative and rehabilitative care institutions, with a total of 1239 institutions with 171,060 beds (2.1 beds per 1000 people in 2008). In comparison to general hospitals, ownership is very different: publicly-owned institutions comprise 18%, non-profit 26%, and for-profit 56%; and the bed shares are 17%, 16%, and 67% respectively. In total, 91% of those institutions were able to provide care to SHI-insured patients (through being contracted by the sickness funds) (Statistisches Bundesamt, 2010).

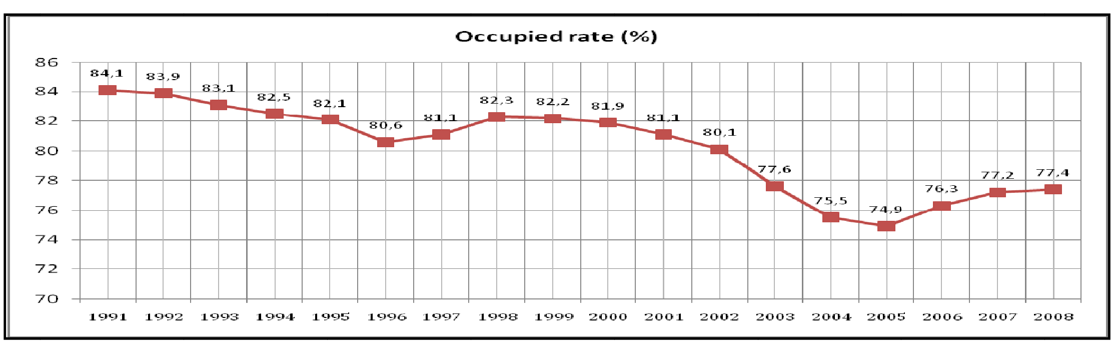
Traditionally, the hospital system in Germany focused on inpatient care services. There is a big gap in integration between inpatient and outpatient care (ambulatory care). However, since 2004 hospitals have been made responsible for more outpatient care provision, which requires highly specialized care on a regular basic and opportunities to participate in integrated care models to become more active in ambulatory care (Busse R, 2004) (Figure 16).



Source: (Busse R, 2010)

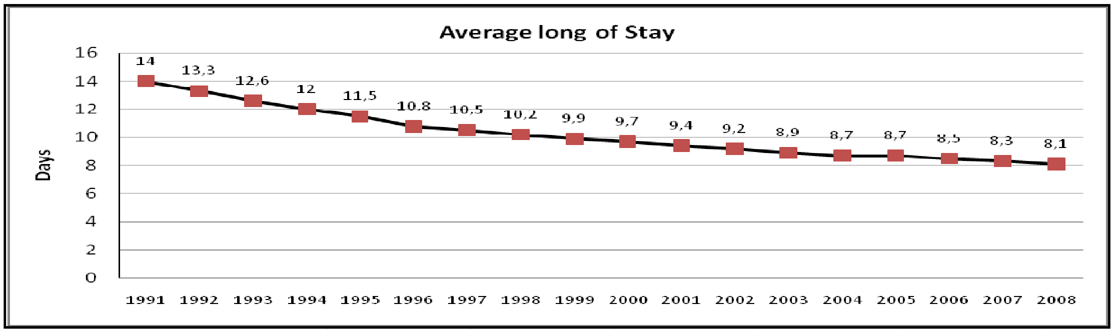
Figure 16: Typical episode of care across sectoral borders

The hospital system in Germany provides about 17 million inpatient visits per year with an average length of hospital stay of 8.1 days per inpatient visit. That was gradually reduced from 14 days in 1991 to 9.7 days in 2000 (Figure 18). The hospital occupancy rate has been rather stable during the last few years at 77%, higher than in the year 2005 (74.9%) but much lower than in the last decade (Figure 17).



Source: (Statistisches Bundesamt, 2009)

Figure 17. Hospital occupancy rate by years



Source: (Statistisches Bundesamt, 2009)

Figure 18. Average days of hospital stays

Primary health care

Alongside the hospital sector there is an independent primary health care system that consists of ambulatory care services, general practitioners/ family doctors, general internists, and pediatricians, which are all private, for-profit and office-based services, accounting for up to 49% of all office-based physicians. The majority of them work in solo practice, only 31% are in group practices. However, in group practices they only share the office space, not patients or patients' health care files. Previously, physicians did not work in the hospital system and vice versa: only doctors who did not work in the ambulatory sector work in hospitals. All different procedures, medical care and patient management were done exclusively by physicians, only 6% of the practices employed a nurse. The medical assistants in the physicians' practices are only responsible for administrative work and very limited clinical tasks such as blood pressure taking, giving injections, and analyzing blood samples. The idea of developing nurse practitioners and expanding the role of non-physicians to provide care for the patient was rejected by 56% of doctors (Peters-Klimm *et al.*, 2009).

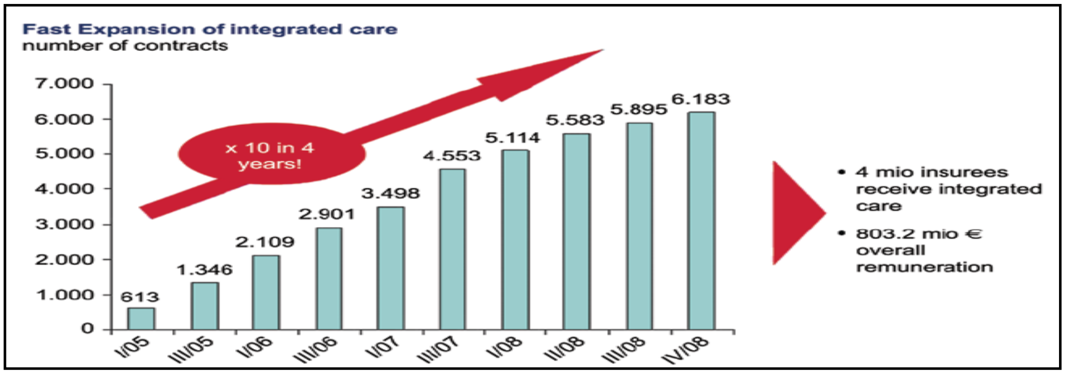
Before 2000, primary health care was neglected. Health care provided by solo practices were often not coordinated. There was no one responsible for the gatekeeper function. People were free to choose their primary care providers. The cooperation between primary care and other sectors is a challenge in Germany, and health care is often not coordinated, especially between ambulance and hospital care services. When patients were in need of inpatient treatment, primary care physicians referred them to hospitals. However, the integration of information systems between office-based physician and hospitals was not good, and only 14% of physician had electronic hospital records. Generally, 14 to 30 days after a patient was discharged from the hospital, the primary care physician could receive the report. The health information technology in the primary care practice in Germany lagged far behind other developed countries such as the Netherlands, UK, and Australia. Challenges were also revealed in the poor integration between the health care system and community services such as long-term care, social services, self-help, family and lay caregivers or patient groups.

The weakness in primary care has been well recognized. Since 2000, the German government has tried to improve this weakness by introducing a number of reforms, with a variety of managed care tools, structures and cooperation between primary care providers and other sectors. The role of primary care has been strengthened to have a more integrating function, acting as patients' navigators through the health care system by adding more services such as the gatekeeper function, disease management programs, integrated care contracts, medical care centers and community medicine nurses. Some other reforms regarding quality improvement, cost control, care coordination have also been pursued (Schlette *et al.*, 2009).

In term of the primary care provided by GPs, there is no difference in the access to GPs between urban and rural areas. However there is a significant discrepency concerning to specialist visits. The result of a study of Koller and colleagues in the setting of patients with dementia, showed that persons living in urban areas have a significantly higher chance (about 43%) to visit specialists (neuro-psychiatrists) compared to those living in rural areas. Of those patients, after the incident of diagnosis of dementia in 2004-2006, 52.8% of the patients living in urban areas versus 42.8% of those are in rural areas had at least one contact with a neuro-psychiatrist ($p<0.001$) (Koller *et al.*, 2010).

Integrated care contracts

The health care reform in 2000 established the legal basis for health insurance funds and providers which can enter the selective integrated care contract. Under the contracts, integrated care is provided in provider networks, which are managed by independent management organizations. The initiative was very slow in the beginning, but it gained momentum fast during 2005 and 2008, from just over 600 contracts in early 2005 to 6000 contracts at the end of 2008, and four million patients being treated (Figure 19). Since 2007, with the Statutory Health Insurance Competition Strengthening Act there are further integrated care opportunities. Long-term care can be integrated by providers (consists of medical professionals and non-medical professionals) and can become the main contractual partner to health insurance funds. Since then, the integrated care contracts have been focusing on population-oriented integrated care. The population-oriented integrated care implies a more comprehensive concept of health care, more proactive, and more patient-centered health care for a defined population. Within this model a multidisciplinary group of providers is responsible for both curing illness and maintaining and improving the health status of the defined population (Schlette *et al.*, 2009).



Source: (Schlette et al., 2009)

Figure 19. Fast expansion of integrated care contracts

Gatekeeping models

Since the new government was elected in September 1998, first-line medical care has been discussed and recognized as rather unpopular in Germany. Therefore the gate-keeper was introduced with the intention of reducing costs while maintaining or improving quality of care by encouraging first-contact care, increasing coordination and continuity of services, and reducing duplicative or inappropriate care (Himmel *et al.*, 2000).

One of the gatekeeper roles of GPs is to assist in accessing hospital care. This was started in 2004, as a first step of patients towards GPs. GPs decide whether patients need a referral to specialists or hospital care, and allow referral receivers to refer further if needed or refer back after the consultation. Otherwise, the patient has to pay an additional fee if they do not consult their GP first and directly access specialist or hospital care. Since this was introduced the number of patient referrals to hospitals initiated by GPs has increased tremendously. A study by Rosemann and colleagues found that referrals to specialists initiated by GPs were more often seen in orthopedics, cardiologists, surgeons and radiologists. These referrals were appropriate in 91% of the cases and with clarity of referral purpose (95%), except for some critical issues in the information provided in the patients' medical history (61%) and prescriptions (48%). Referred patients were satisfied (83%) and their experiences were more positive after being referred with GPs' initiation ($p<0.001$) (Rosemann *et al.*, 2006).

Disease management programs

DMP consist of diabetes type 1, diabetes type 2, coronary heart disease, breast cancer, asthma and chronic obstructive pulmonary disease (in 2009). This DMP model has been adopted based on the managed care models in the USA since 2002, which requires clear definitions for documentation, evaluation and treatment guidelines and the incentives for payers, providers and patients. The payers get the funds from a separate high-risk structure compensation scheme for DMP-enrolled patients which was improved from the existing scheme of risk equalization based on average spending by age and sex. The sickness funds receive an additional lump sum from the risk equalization scheme for each enrolled person. The physicians involved in DMP can receive a lump sum payment for coordination and documentation activities. DMP-enrolled patient no longer pay the out-patient fees or co-payments. They are cared for by primary care physicians overtime and can be referred to specialists by physician if needed (Schlette *et al.*, 2009).

The diabetes DMP was introduced as one of the DMP in Germany nationwide in 2003. It was determined as a compulsory requirement by the Germany Ministry of Health that sickness funds contract with primary care physicians. Primary care physicians take part in 90% of these programs (Schlette *et al.*, 2009). Patients are voluntary but participating doctors are obliged to keep within the conditions of the programs to provide care to enrolled patients with diabetes (Szecsenyi *et al.*, 2008). Diabetes DMP is a systems-based, multifaceted, patient-centered and primary care-based intervention that integrates the perspectives of health care providers and patients within primary care settings. It has significantly reduced the mortality rate of those enrolled compared to those do not enroll in program (Miksch A, 2010).

Besides the DMP, due to a great number of diseases which could be prevented to avoid concomitant health care expenditure, German health care reforms have focused on the introduction of different programs in the framework of strengthening disease prevention:

(1) A National Action Plan: It has been developed in order to prevent the lack of physical activity and malnutrition, to drastically reduce diseases which are related to factors of unhealthy lifestyle, a one-sided diet and a lack of physical activity, in order to make it possible for children to grow up healthier, for adults to have a healthier lifestyle and enjoy a better quality of life, and greater productivity for everybody.

(2) Life has Weight: This initiative recognizes the big problem of eating disorders and the serious diseases (such as anorexia, bulimia) associated with eating disorders in German

society, which affect 20% of children and adolescents between 11 and 17 years of age (Robert Koch Institute, 2005). Since 2007, the initiative "'Life has Weight – Together Against Slimming Mania" has been launched in order to transport a positive body image to young people and strengthen their self-esteem. Alongside awareness-building among the public and various prevention measures, the program primarily depends on voluntary commitment, with an important counterpart in this endeavor being the fashion and modeling industry.

(3) Primary palliative care: This aims at reducing hospital expenditure and improving patients' quality of life at the end of life, especially for patients of cancer, who comprised up to 90% of patient cared for by hospices and palliative care units in 2008. The legislation of specialist palliative care in the community was established as part of the 2007 health care reforms. The care is provided by a specialist team with varying degrees of specialist support from consultations to full palliative care, which enable more people to stay at home in the last period of their lives (Schneider *et al.*, 2010).

(4) Long-term care: The Federal Ministry of Health is responsible for some tasks: (1) the legislative process that consists of drawing up and monitoring the bills of law and ordinances; (2) monitoring the finances of the Long-Term Care Fund; (3) for the corresponding statistics. The long-term care insurance funds offer their services on a statutory basis and ensure appropriate long-term care for the insured in the form of statutory benefits and services. The long-term care services are provided by care facilities which are under municipal, non-profit or private ownership cooperation and fulfill the requirements. The federal states are responsible for providing efficient long-term care structures and financing investment for the care providing facilities. However, the ongoing operating and nursing care costs are to be paid by the persons in need of long-term care or their financing institutions (Federal MOH, 2011e).

Medical care centers

Medical care centers are defined as inter-professional institutions, to provide ambulatory care services. Medical care centers are run by independent management companies, headed by physicians, with a mix of registered general practitioners and specialists under one roof who are paid on the basis of an item of service. The aim of establishing the centers is to improve the quality of care, accessibility and service, infrastructure and organizational structures, and pursue greater cooperation between general practitioners, specialist and hospitals; to improve integration between institutions; and to reduce health care costs. It is similar to the state-owned policlinics which existed as part of primary health care in the former East Germany, where the facilities and laboratories were shared, alternative treatment and prevention strategies were coordinated, with well-monitored referrals. Unfortunately, that was removed in 1995 after the reunification of Germany as it was not appropriate to the concept of independently contracted doctors in the West Germany. This restructure of East Germany was simply undertaken to be in line with West Germany. It had to change from state-controlled public group practices in the DDR to private individual practices (Schlette *et al.*, 2009; Meusel *et al.*, 2005).

Community medicine nurses

Nurses or doctors' assistants had a little role in health care provision, in normal practices they mainly supported physicians in administrative work including arranging appointment for patients, answering telephone calls, preparing and providing patient files. The role of the nurse was limited for many different reasons: the nursing curriculum in school focused more on administrative works than medical knowledge, therefore they do not feel competent enough to consult about the disease, or provide treatment to patients. Besides, GPs did not believe that practice nurses could have sufficient medical knowledge to be more involved in health care provision.

However, these ideas about the nurse's role are changing with the changes in technology and society; the tremendous decrease of GPs in the near future; the fact that more and more German physicians have left for other countries where they find better working environments, such as the UK and Scandinavian countries; and especially with the introduction of DMP which boost the need of medical assistant in primary health care. In the program, practice nurses are more involved in giving patient advice and managing disease by protocol (Bäumler M, 2010) which has caused their roles and relationships with physicians to improve. Some GPs appreciated that once a doctor's assistant adopted the new case management role, it lead to transient competition; and their relationship with patients were remained stable or improved consistently (Peters-Klimm *et al.*, 2009).

Quality management

Hospital quality assurance

The development of quality assurance has made great progress in Germany which has been appreciated as a comprehensive system of comparative hospital quality data. No other country has undertaken such a big project (Gemeinsamer Bundesausschuss, 2004). It has been an integrated part of the health professions with a long tradition of methodology development for quality assessment, in order to maintain agreed-upon standards, to optimize the provision of health care by identifying inadequate health care provision and positive influences on morbidity and mortality of the population. As already highlighted, the health care reform of Germany since the 1990s has urgently needed to control health care costs, therefore the quality assurance has a more prominent role in the aspect of cost effective assessment. This has been either maintained so far, or strongly enhanced in the latest reform of health care legislation in 2003 with the act on the modernization of the health care system. Quality of health care is one of the objectives to ensure for the cost containment (Breckenkamp *et al.*, 2007). The main actors involved in quality management at the federal level consist of the Federal Association of Sickness Funds (the central organization), Federal Chamber of Physicians (responsible for qualification of physicians), Federal Association of SHI physicians, Cooperation for Transparency and Quality in Hospitals (KTQ) joined by Hospital Federation and Nursing Council (mission is to strengthen transparency in the performance of hospitals), Federal Joint Committee (the highest decision making body in the SHI system, defining quality standards for health care services), Institute for Quality and Efficiency in Health Care, and Federal Office for Quality Assurance (BQS) (Busse *et al.*, 2009).

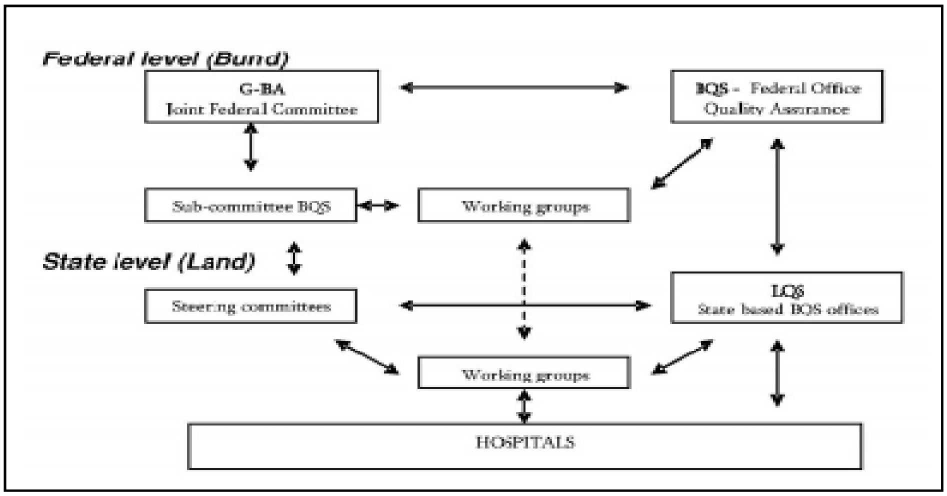
In the early 1970s, the process of quality assurance was first introduced in the form of disease or procedure specific registers in all federal states. The internal quality assurance of each hospital has been shifted from voluntary to obligatory in the 1990s. That involves the documentation of quality indicators, the majority of these indicators are based on procedures and very few are based on diagnoses from readily available administrative data (that shifted from the separately collected data), and nursing perspective indicators are directly relevant to patients such as falls and pain management. The indicators are gathered every two years by the individual hospitals then handed over to each of the sixteen federal states (quality office) for quality assurance. The Federal Office for Quality Assurance (BQS) is responsible for measuring quality in hospitals that will define procedures or diseases subjected to quality measures. BQS get the data through each state office. The hospital will be subject to financial penalties by law if it fails to collect data, and when the data cover fewer than 80 percent of cases (checked by the number of respective reimbursement cases), it will be charged 150 euro per missing case. The collected data are compiled and analyzed at the national level, the report and recommendations will be sent to each hospital, and also publicly published. The quality assurance is not intended to compare the hospitals, but rather to serve as an intra-professional tool for physicians to require them to implement standard treatment processes and identify important complications (Busse *et al.*, 2009; Breckenkamp *et al.*, 2007). Additionally, in 2002 German legislation decided to use annual minimum volumes standard as a quality assurance measure in the hospital sector. In case a hospital will not comply with this standard, the relevant procedure will be no longer conducted. There were five complex surgical procedures subjected to a minimum volume standard in 2004 which consist of liver (≥10), kidney (≥20), stem cell transplantations (≥10-14), complex oesophageal (≥5) and pancreatic intervention (≥5). The result in 2004 showed that 28% (485 out of 1710 hospitals) were affected by at least one minimum volume standard (de Cruppé *et al.*, 2007).

Minimum volume	**MVS* per hospital, suggested by health insurance funds**	**MVS since 2004**	**MVS since 2006**
Liver transplantation	25	10	20
Kidney transplantation	40	20	25
Stem cell transplantation	20	12±2	25
Complex pancreatic intervention	10	5	10
Complex oesophageal intervention	10	5	10
Complex interventions of the mamma	150		
Heart transplantation	9		
Coronary surgery	100		
Carotis-TEA	20		
PCI	150		
Total knee replacement	-		50**

**Mimimum volume standard per year, **Interim arrange: hospitals with 40-49 total knee replacements and good quality can participate in 2006. Source: (de Cruppé et al., 2007)*

Table 28. Annual minimum volume standards and their time of coming into effect

The typical characteristic of the German health care system of two separated sectors of administrative divisions of the inpatient care and ambulatory care that revealed the problems of high fragmentation in quality assurance and a lack of coordination at the interface between the two sectors, affecting the quality of care and health outcomes for the population (Breckenkamp *et al.*, 2007) (Figure 20). To overcome the problem, the Federal Joint Committee passed a crosssectoral quality assurance act in 2008. This task was assigned for the AQUA Institute in 2009, including the external quality assurance in the hospital sector, which was previously made responsible by the BQS-federal office for quality assurance (since 2001). The AQUA Institute has to develop a document to describe the approach to implement the new cross-sectoral quality assessment. This will make it possible to trace the way of the patient through the different sectors of health care, i.e. ambulatory, inpatient and rehabilitation. However, this reform may result in higher administrative burdens and hospital employees fear that they must adjust to new method of collecting data (Wörz M, 2009).



(source: Breckenkamp et al., 2007)

Figure 20. The structure of external quality management in hospitals

Some challenges of the quality management system were to transfer the obtained data and results into practical quality improvements; the bureaucracy of data generation and communication of the hospitals should be reduced to ensure reliable data gathering; insufficient outcome quality, as hospital self-reporting is limited to the timeframe of hospital observation, although the results of hospital treatment often can be only measured in the post-hospital treatment; the coordination of the various decision making bodies and expert committees; and the coordination between the state and federal levels (Breckenkamp *et al.*, 2007; Peters-Klimm *et al.*, 2009).

Besides the above mentioned quality management system, there are some different approaches that have been introduced and applied in the hospital system of Germany, and it is the choice of each hospital to choose the appropriate one. For instance, during 1998 – 2001, one project was initiated by Federal Ministry of Health to develop measured indicators in the aspect of outcome quality comparison between hospitals, following the European Foundation for Quality Management. Fourty four hospitals voluntarily participated in the pilot project that was funded by the Ministry of Health. The results of the pilot project were recognized as a valuable contribution to the development of internal quality management and considerable for the external quality comparisons among hospitals.

Ambulatory sector quality assurance

Typically, the ambulatory sectors in Germany are mostly office-based physicians. One of the cornerstones of the 2003 reform act is to introduce the obligation of internal quality management in the office-based physicians, transformed from initially voluntary tasks as partly prompted by the recognition of inappropriate provision of chronic disease care services from the Advisory Council in 2000. The initiative entered into force in January 2004. Quality assurance in the ambulatory sector is also characterized by a range of actors at various political levels. Basing on the respective guidance developed by G-BA, office-based physicians will choose the quality management system which is appropriate to the scope of quality management with respect to the individual local situation. Additionally, they participate in the external quality assurance measurement, this task is conducted by GKV (accredited physicians), to monitor and control following the basic guidelines provided by G-BA. To the year 2007, 4700 quality circles for office-based physicians have been offered by the Federal Association of SHI Physicians, serving as forums in which accredited physicians can exchange experiences and engage in reciprocal evaluation. To ensure quality assurance, physicians are obliged to follow structured continuing education (Breckenkamp *et al.*, 2007).

Aiming at improving the routine quality management system in ambulatory practice, since March 2004 a pilot testing phase has been conducted in 60 practices, called Quality and Development for Practice (QEP). Then the specialist quality management system for GKV (or SHI checking again) accredited physicians/psychotherapists in ambulatory care was developed. The indicator-based method was used to address the issues of patient safety, patient care, information, documentation, collaborators, continuing education, office organization and basic conditions (Kassenärztlicher Bundesverband, 2005; Breckenkamp *et al.*, 2007).

Conclusion

The health care system of Germany is structured into three levels: the national, state and corporatist levels. It has been seen as of important priority to the German Federal Government, with a high proportion of GDP spent on health care (10.5% of GDP in 2008).

The health care services are mostly paid by public funding made up of over 80% of total health care expenditures. The own autonomous and elected representatives, governments are given to all political units from all above mentioned three levels.

Over the last decades, the health care system of Germany has implemented a strong and comprehensive reform in many different aspects: organizational structure, personnel resources, human resource development, health care financing, quality management, and health care service provision in primary, secondary and tertiary health cares. The overall health care performance was ranked 25th worldwide in the year 2000 by WHO and number 4th among seven industrialized countries (Netherlands, United Kingdom, Australia, Germany, Canada, and United States) on health system performance based on measures of quality, efficiency, access, equity and healthy lives in 2010 by Commonwealth Funds of US (The Commonwealth Fund, 2010). The health care reform is ongoing in attempting to create “the prerequisites for our citizens to continue to have access to our solidarity and high-quality health system in the future", to ensuring the “health for all”.

The health of women: The physical, psychological and social aspects of women at all stages of life and all age groups are importantly considered. The main focuses are on diseases which more frequently occur in women or those have a more serious clinical outcome; and the influence which social factors exert on women’s health and on health risks and diseases which affect women exclusively.

The health of men: The challenges which men face in society are different from those which women face, for example, men experience greater prevalence of cardiovascular diseases, suicide, injury and accidents (by car). To address these challenges, more attention will be given to important aspects of workplace health promotion; and for the reasons mentioned, prevention, prevention measures and health promotion need to be gender-specific.

The health of children: To equally distribute the chances to live a healthy life without disease and impairments, especially for the children who live in the socially disadvantaged families.

The highlighted questions of how to stay healthy; what the potential health risks are; and what this knowledge means for the prevention, diagnosis, therapy and rehabilitation of diseases are the main focus of the health care system of Germany now and then (Federal MOH, 2011c).

PART IV. COST-EFFECTIVENESS OF A NEW HOSPITAL-BASED HEALTH TECHNOLOGY IN A LOW-MIDDLE-INCOME COUNTRY AND A HIGH-INCOME COUNTRY

Chapter 7. The cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of brain metastasis in Vietnam from the perspective of patients and families

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Abstract

Objectives: This study aims to evaluate the cost-effectiveness of the treatment of brain metastasis with surgical resection (SR) and stereotactic radiosurgery (SRS) in the lower-middle-income country of Vietnam from the perspective of patients and families.

Methods: The treatment of 111 patients with brain metastases who underwent SR (n=64) and SRS (n=47) was retrospectively reviewed. Propensity score matching was used to adjust for selection bias (n=30 each); mean and curves of survival time were defined by the Kaplan-Meier estimator; the cost analysis focused on the time period of relevant treatment.

Results: The mean survival times of SRS and SR were 11.9 and 10.5 months; and the 18 month survival rates were 32% and 14%, respectively (p=.346). The mean of hospital bed days was significantly higher for SR than SRS (16.5 versus 7.6 days, p<.05), but direct costs of SR were significantly lower (14.5 as opposed to 35.3 million VND per patient, p<.001). However, indirect costs of SR were 10 times higher (26.0 versus 2.5 million VND per patient, p<.001). The cost per life year gained is higher for SR than SRS (46.4 and 38.1 million VND, respectively).

Conclusion: SRS is similarly effective as SR. However, in the broader context of the cost-effectiveness from the perspective of patients and their families, SRS is more cost-effective. The lower costs directly charged by the hospital for SR may prevent poorer and older patients from choosing SRS. Thus, the overall cost-effectiveness of each treatment option should be taken into consideration in deciding upon the treatment.

Keywords: brain tumors, economics, stereotactic radiosurgery, surgical resection

Introduction

Within a given budget, a CEA is one of the most common measures supporting the decision-making process among various options of treatments or health programs, especially in developed countries. CEA is one form of full economic evaluation, concerned with the assessment of the effect and cost of treatments, resulting in a cost per unit of effect which enables a comparison of different treatments within a given field (van Hout *et al.*, 1994; Neymark *et al.*, 2002; Drummond *et al.*, 2005-chapter 5). Brain metastasis, which is the most common CNS neoplasm, occurs in 20% to 40% of cancer patients during the course of their disease, possibly even up to 85% based on radiologic, autopsy, surgical, and medical records data (Nussbaum *et al.*, 1996; Walker AE, 1985; Wen PY, 2001), and is often considered a terminal stage of the disease (Boogerd W, 1993; Kim *et al.*, 2009). Recently, there appears to be a trend towards an increase in the incidence of brain metastasis due to the earlier diagnosis and/or more effective treatment regimes of systemic disease. Stereotactic radiosurgery (SRS) and surgical resection (SR) are among those treatment regimens. Of these, SRS has recently become well known in high-income countries as more cost-effective than SR (Rutigliano *et al.*, 1995; Mehta *et al.*, 1997; Wellis *et al.*, 2003). However, less attention has been paid to the cost-effectiveness of the treatment of brain metastasis, especially of SRS versus SR, in lower-middle-income countries such as Vietnam, where there is a higher rate of out-of-pocket payment for health services. The aim of this study is to identify the cost-effectiveness of SRS versus SR in the treatment of brain metastasis with a main focus on the patient's and family's point of view during the time period of the relevant treatment.

Material and methods

Patient profile

We retrospectively reviewed the records of all 141 patients who were consecutively treated with SR (mostly by the conventional operation) at Choray Hospital and Vietnam-Germany Friendship Hospital; and with SRS (by Leksell Gamma Knife) at Choray Hospital and Hue Medical University Hospital, between 2006 and 2008. This group of patients included 87 SR patients within the age range of 17 – 76 years and 54 SRS patients within the age range of 18 – 87 years. Follow-up data were collected by contacting the patient's family or the communal health care station in the area where the patient lived. Twenty three of the 87 SR patients and 7 of the 54 SRS patients, who were lost to follow-up less than 3 months after the intervention was performed, were excluded from the analysis. A total of 111 patients remained and were included in the analysis. The male to female ratio was 2.6 : 1. Patients were characterized by sex, age (less than 60 of age versus 60 years and older), number of brain metastasis (up to 2 versus 3 or more), primary tumor sites (due to the small sample size, PTS were stratified into 2 groups of lung cancer or others), volume of brain metastases (smaller than 115 versus at least 115 ccm; this was measured by the result given in MRI compared to the pathology result to make sure that all tumors were removed), and performance status (absence versus presence of hemiparesis). Regarding the performance status, unfortunately medical doctors in Vietnam use only the Glasgow Scale (whereby all samples have the same score of 15). Taking the additional information of neurological impairment related to movement disorders due to paresis, we had to use two sub-groups, namely patients with and patients without metastasis-related paresis of the arm or leg in our PSM, instead of using the Karnofsky Performance Score or Recursive Partitioning Analysis.

Treatment cost calculations

The treatment costs consist of two parts: direct costs (health care costs, food and accommodation costs) and indirect costs (lost working days of patients and their relatives) (Drummond FM, 2005a; Rutigliano *et al.*, 1995). These costs were limited to the time period that the patient stayed in the hospital to have the treatment and home care according to the relevant treatment. The hospital cost data was based on the hospital charge bill, which involved diagnostic procedures (medical imaging and laboratory services), consumables (medications and disposables), inpatient stay (both at the ward and the intensive care unit), drugs and operation procedures (1.8-2.5 million VND for SR and 30-35 million VND for SRS). Those direct costs were paid directly ("out of pocket") by the patients who have no health insurance. Such a situation applied to 51% of the population (in 2007) (Ekman *et al.*, 2008). Beside the main cost of the discharge bill, SR patients generally pay the charge of self-purchased drugs which are not available in the hospital inventory and a gift to health care staff which was roughly estimated to be 10% of the hospital charge (Lieu HD, 2005). The overhead costs of general expenses, administration and operation, maintenance, insurance and other personnel costs of non-patient services, and the depreciation costs of capital investment on equipment and buildings were not included in the cost calculation, as these costs were mostly paid by the government. Accommodation costs for relatives in the hospital were assumed to be equal for all three cities, at approximately 100,000 VND (US$6.1) per night, and such an amount of money was also estimated for higher expenses for food in the hospital compared to home. Indirect costs were mainly considered the loss of working time of patients (those under 60 years for males, 55 years for females) and their relatives who had to take care of the patient in the hospital and at home while the patient recovered. We estimated that patients treated with SRS needed one relative to accompany and attend to the patient while SR patients needed one relative before the operative procedure and two relatives during the post-operative inpatient time, due to the more intensive care required, so the family had to take turns to look after the patient, to provide additional care besides the services of health staff. For the lost workdays, as this information was not recorded, we used the results of Cho *et al*. as patients treated with SR needed 160 days off work to recover plus 30 days of support from relatives at home (the number of relatives' attendance days was roughly estimated by communicating with relatives by phone). Patients who received SRS needed 8 days to recover and no further support from their relatives at home (Cho *et al*., 2006). The overall average net value added per employee was used to calculate the cost of lost working days (Drummond FM, 2005b), as follows: the monthly average income per employee in all kinds of economic activity within the 3 years 2006-2008 (GSO, 2010-In: social - economic statistical data), adjusted to the year 2008 by using the Consumer Price Index of Vietnam for the year 2007 (8.3%), and 2008 (19.89%) (GSO, 2010-In: social - economic statistical data) (exchange rate 1 USD = 16,506 VND on 30th June 2008) plus the employment benefit at the rate of 50%; resulting in an average cost of one working day of around 128,000 VND (7.8 USD) (Drummond FM, 2005b; Runckel C, 2010).

$$C_i^{tr} = \sum C_i^d + \sum C_i^{id}$$

Where: $$\sum C_i^d = C_i^{hs} + C_i^e + C_i^{af}$$

$$\sum C_i^{id} = C_i^{w-p} + C_i^{w-r}$$

C_i^{tr}: cost of treatment of patient i; C_i^d: direct cost; C_i^{hs}: charge from the hospital; C_i^e: cost for the extra drug and gift to the health staff; C_i^{af}: cost of accommodation and food during hospital stay; C_i^{id}: indirect cost; C_i^{w-p}: cost of working time lost; C_i^{w-r}: cost of working time lost of relatives

Statistical analysis

For the CEA of health care interventions, survival time is considered as the principal outcome of the effect, which was expressed by the mean and median survival time of patients. Of these, the mean survival time provides a better estimate of survival time, because its value is equal to all the area under the curve of survival time, while the median is a sole point on the survival curve (Neymark *et al.*, 2002). The survival time was measured from the time of the intervention (SRS or SR). Uncensored cases were those which reached the endpoint of interest (i.e. death) and censored cases were those which were lost to follow-up. Overall survival time was calculated from the date of receiving the intervention (SRS or SR) to the date of last follow-up (Mayo *et al.*, 2010). Survival time mean and survival curves were defined by the Kaplan-Meier estimator (Kaplan EL, 1958). The differences between the Kaplan-Meier curves of the two treatment groups were determined with the Log-rank test (univariate analysis) and univariate Cox proportional hazard models were used to assess the effect of each predictor on the shape of the survival curve, then the prognostic factors were found to be significant with $P<0.05$, which were included in a multivariate Cox proportional hazard model (Cox DR, 1972). Death within 30 days was also reported and attributable to complications of the operation (Vecil *et al.*, 2005).

Propensity score matching

For the comparison of the cost-effectiveness of the two modalities of SRS and SR, potential confounding and selection biases may exist as the treatments were not randomly assigned in this patient population. This problem was minimized by the propensity score matching approach (D'Agostino, 1998; Rubin D, 1973), for those prognostic factors found to be significant in the Cox proportional hazard model (unadjusted sample) and those previously identified from the literature as predictive factors of survival. Finally, matched factors consisted of number of brain metastases, primary tumor sites, volume of brain tumors, as well as demographic factors (age and sex) (Eichler and Loeffler, 2007; Kim *et al.*, 2000; Lagerwaard *et al.*, 1999; Rades *et al.*, 2007). To estimate the propensity score, a logistic regression model was fitted to assign to each individual a probability (from 0-1) based on the prognostic factors. We used a 1:1 optimal matching without replacement, meaning that for each SRS patient one SR patient was identified. The match was conducted by randomly ordering all patients from the treatment groups and choosing the most similar propensity score to the initial patient, these 2 patients formed a matched pair.

This matching process was conducted separately for each treatment group. The balance of the baseline characteristics of both unadjusted and adjusted samples is measured by using the standardized difference (D'Agostino, 1998):

$$Standardized\ difference = \frac{100(X_{srs} - X_{sr})}{2\sqrt{S_{srs}^2 + S_{sr}^2}}$$

where X_{srs} and X_{sr} are the sample means in the SRS and SR groups of the i^{th} covariate, respectively, and S_{srs}^2 and S_{sr}^2 are the corresponding sample variance. Small absolute value of standardized difference (<10%) support the assumption of balance between treatment groups (Cohen J, 1997).

Then medians of follow-up time were estimated; mean survival times were calculated again for matched pair groups and adjusted survival curves were plotted for the comparison of the SRS and SR groups by the Kaplan–Meier estimator; a univariate Cox proportional hazard regression was performed to determine if survival was improved in the SRS group compared to the control group of SR by the effect of treatments. Multivariate proportional hazard regression of prognostic factors (including the propensity score as a covariate in the model for adjusting the selection bias) was used to test the association between those factors and the principal outcomes of the SRS and SR treatments. To evaluate the capacity of the final model of the multivariate analysis to predict the treatment effect on the patient, we calculated the Harrell's C statistic, which is the area under the receiver operating characteristic (ROC) curve and which provides a measure of predictive power. A value of .50 indicates no discrimination and a value of 1.0 indicates perfect discrimination (Ash and Shwartz, 1999; Hanley JA, 1982).

All reported P values are two-sided and exhibited a significant difference with a level of 0.05 or less. Statistical analyses were performed with SAS version 9.3.1 and STATA 10 software.

Sensitivity activity

Although PSM was well balanced between the two groups, a potential selection bias due to imbalances in unmeasured covariates might still be possible. We conducted a formal sensitivity analysis to test the robustness of the results by using the Bootstrap method which used a resample from the original data to build an empirical estimate of the sampling distribution of the ICER (Hlatky, 2002a). The uncertainty in cost-effectiveness measures was tested by the CEAC. The CEACs were derived from the joint uncertainty in different costs and effects on the cost-effectiveness plane, to determine the probability of whether SRS was more cost-effective given that the decision maker may have a willingness-to-pay threshold (van Hout *et al.*, 1994).

Results

For the entire cohort, the most common types of primary tumor were lung (38.3% in SRS; 34.4% in SR). The majority of patients had 1-2 tumors which accounted for 82.9% and 62.5% in SRS and SR, respectively (Table 29). The mean survival times were 9.8 months in the SR group and 11.3 months in the SRS group, but the survival distribution curves of the two groups were determined by a Log-rank test with no significant difference (Figure 21, p=.23). Improved survival probability was significantly associated with the absence of hemiparesis versus presence of hemiparesis (p < .05); and the brain metastatic numbers of <3 metastases versus ≥3 metastases (p=.01). In the multivariate analysis of survival, both prognostic factors, hemiparesis (HR, 1.71; 95% - CI, 1.12-2.61; p=.01) and the number of brain metastasis (HR, 2.11; 95% - CI 1.23- 3.63; p<.01) remained significant (Table 30).

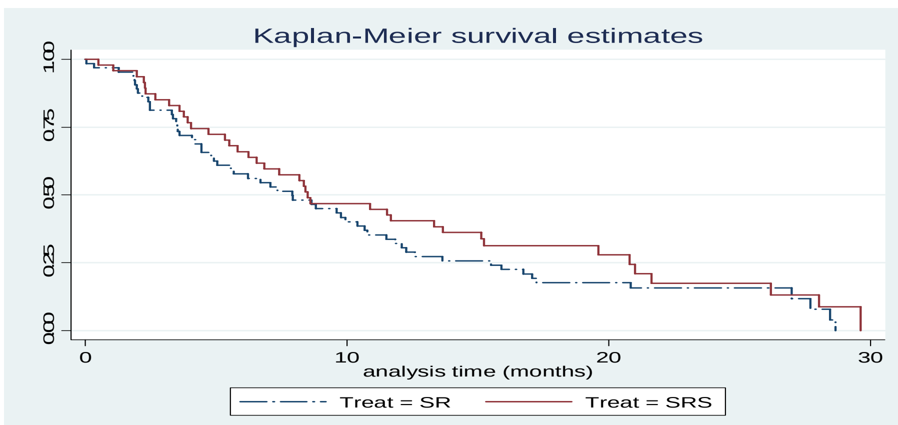

Figure 21. Unadjusted survival curves of two treatment groups– Months post interventions

Patient characteristics	Before matching (unadjusted samples)			After matching (adjusted samples)		
	SRS group	SR group	SD	SRS	SR	SD
(1)	(2)	(3)	(4)	(5)	(6)	(7)
Number of patient	47	64		30	30	
Gender (female vs male)						
- Female (%)	42.6	32.8	14.88	33.3	40.0	-10.12
Age (<60 vs ≥60 years)						
- < 60 years (%)	82.9	62.5	30.11	83.3	86.6	-5.07
Number of BM (<3 vs ≥3)						
- ≥ 3 (%)	29.8	6.3	54.05	13.3	13.3	0.00
Volume of BM (<115 vs ≥115 ccm)						
- <115ccm (%)	46.8	40.6	9.41	50.0	50.0	0.00

(1)	(2)	(3)	(4)	(5)	(6)	(7)
Primary tumor sites (lung vs others)						
- **Lung (%)**	38.3	34.4	5.97	40.0	36.7	5.06
- **Others (%)**	61.7	65.6				
o **Breast (n)**	6	4				
o **Unknown (n)**	14	23				
Neurological impairment (absence vs present of hemiparesis)						
- **Absence of hemiparesis**	76.6	50.0	38.03	73.3	70.0	5.06

(SD stands for Standardized Difference)

Table 29. Patient characteristics of the treatment groups (preoperation).

Patient characteristics		Survival at 12 months (%)	Mean survival time (months)	Univariate analysis		Multivariate analysis (Cox) HR/P value/ CI
				Log-Rank test	Cox PHM HR /P value	
Treatment				.23	0.78 / .23	
	SR	32.1	9.8			
	SRS	40.0	11.3			
Gender				.27	1.26 / .27	
	Female	41.4	11.8			
	Male	32.2	9.6			
Age				.53	1.14 / .54	
	< 60 years	40.0	10.7			
	≥ 60 years	25.0	9.8			
Primary tumor site				.06	0.67 / .07	
	Lung	26.1	8.7			
	Others	40.8	11.4			
Number of Brain metastasis				.00	1.99 / .01	2.11 /.006
	< 3	39.3	11.2			(1.23-3.63)
	≥ 3	16.7	6.6			
Volume of brain metastases				.07	1.45 / .07	
	< 115 c.cm	47.9	12.9			
	≥ 115 c.cm	26.2	8.6			
Neurological impairment				.01	1.64 / .02	1.71 /.01
	No hemiparesis	45.6	11.4			(1.12-2.61)
	Hemiparesis	19.3	8.2			

Table 30. Survival function and mean survival time - Univariate and multivariate analysis (unadjusted samples).

Adjusted sample: Matches by propensity score with respect to prognostic factors of number of BMs, primary tumor sites, volume of brain tumors, presence of hemiparesis and demographic factors of age groups and sex were found for 63.8% of the patients in the SRS group and 46.8% in the SR group, resulting in a matched sample of 60 patients (30 in each group).

The median follow-up times were 10.3 months for SR and 10.1 months for SRS. One SR case died within 30 days while the shortest survival time for SRS was 1.1 month. The means of survival time were 11.9 months for SRS and 10.5 months for SR; the 18-month survival rate was 32% for SRS and 14% for SR, but the difference was not significant (p=.34; Table 31, Figure 22). The model was tested by the c-statistic, which indicated a moderate capability (c=.63) to predict higher probabilities for patients who had a shorter survival time than a longer survival time. The highest predictive capacity belonged to the factor of age (less than 60 versus ≥60 years) (Table 32).

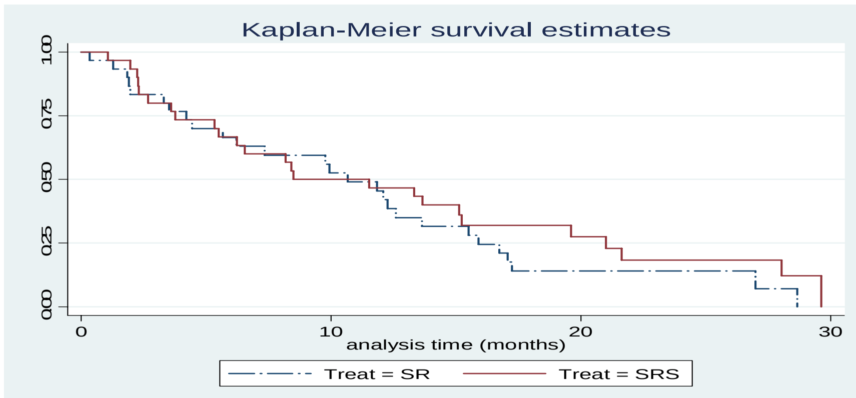

Figure 22. Survival curves of two treatment groups after PSM – Months post interventions

		Mean survival time	Survival function (%)		Cox PHM		
		(month)	12months	18months	HR	95% CI	P value
Treatment	SR	10.5	45.5	14.0	0.76	0.43-1.33	.34
	SRS	11.9	46.0	32.0			

Table 31. Univariate analysis of treatment effect (adjusted samples)

Patient characteristics	Multivariate PHM (95% CI)		
	HR	**SE**	**P value**
Treatment (SRS vs SR)	.67	.20	.19
Propensity score	5.42	49.07	.85
Gender (female vs male)	1.05	.57	.92
Age (<60 vs ≥60 years)	1.63	2.60	.75
Number of BM (<3 vs ≥3)	5.03	17.70	.64
Volume (<115 vs ≥115 c.cm)	.92	.85	.93
Primary tumor sites (lung vs others)	.48	.39	.38
Neurological impairment (absence vs presence of hemiparesis)	.73	1.53	.88

Note. ROC curve (c-statistic) = .63. (SE stands for Standard Error).

Table 32. Details of overall logistic and proportional hazards model evaluating the association of treatments and survival (adjusted samples)

The mean number of days patients had to stay in hospital was about 2.2 times higher for patients treated with SR than for those treated with SRS (16.5 days versus 7.6 days, p=.01), especially for the number of days after the intervention procedure (9.4 days versus 3.0

days, p=.01; 15 out of 30 SRS-treated patients were discharged within 1 day after treatment). However, the direct costs, which represent the majority of the hospital care costs, were lower in the SR group, with an average of 14.5 million VND, compared to the 35.3 million VND in the SRS group (p<.001). On the other hand, indirect costs in the SR group were 10 times higher than in the SRS group (26.0 versus 2.5 million VND, p<.001). The average total cost per patient was 40.6 million VND in the SR group and 37.8 million VND in the SRS group, which, adjusted to the cost per life year gained, was equal to 46.4 million VND (US$2,811) for SR compared to 38.1 million VND (US$2,309) for SRS (Table 33).

	Mean	SD	P value
Hospital bed days (days)			.01
SR group	16.8	21.6	
SRS group	7.6	6.1	
Hospital bed days after operation (days)			.01
SR group	9.4	14.9	
SRS group	3.0	4.2	
Direct cost (million VND)			<.001
SR group	14.5	7.7	
SRS group	35.3	1.8	
Indirect cost (million VND)			<.001
SR group	26.0	9.5	
SRS group	2.5	1.4	
Total of treatment cost (million VND)			.15
SR group	40.6	14.5	
SRS group	37.8	2.8	
Cost per one life year gained (million VND)			
SR group	46.4		
SRS group	38.1		

Table 33. Resource utilization per patient

Results of sensitivity analysis

The scatter of points on the plane is based on the results of a non-parametric Bootstrap analysis, the cost difference of SRS versus SR ranged from -50.7 to 38.6 million VND; the survival time difference were between -27.6 to 29.3 months for SRS compared to SR. The plot data of ICER demonstrated a 62.5% probability that SRS would have a lower cost than the cost of SR, and 55.5% probability that SRS would have a relatively greater effect than SR. In the quadrant IV, 34.2% of the plots of ICER were concentrated, to indicate that SRS has a lower cost and greater effect in contrast to 16.1% of the plots in quadrant II where SRS has a higher cost and smaller effect (Figure 23), this means that the CEAC never exceeded 95% and the 95% certainty was not estimated. However, Figure 24 shows that although CEAC associated with SRS being more cost-effective tended downward, at any willingness to pay threshold it was always more likely to be the more cost-effective treatment compared to SR and above .50.

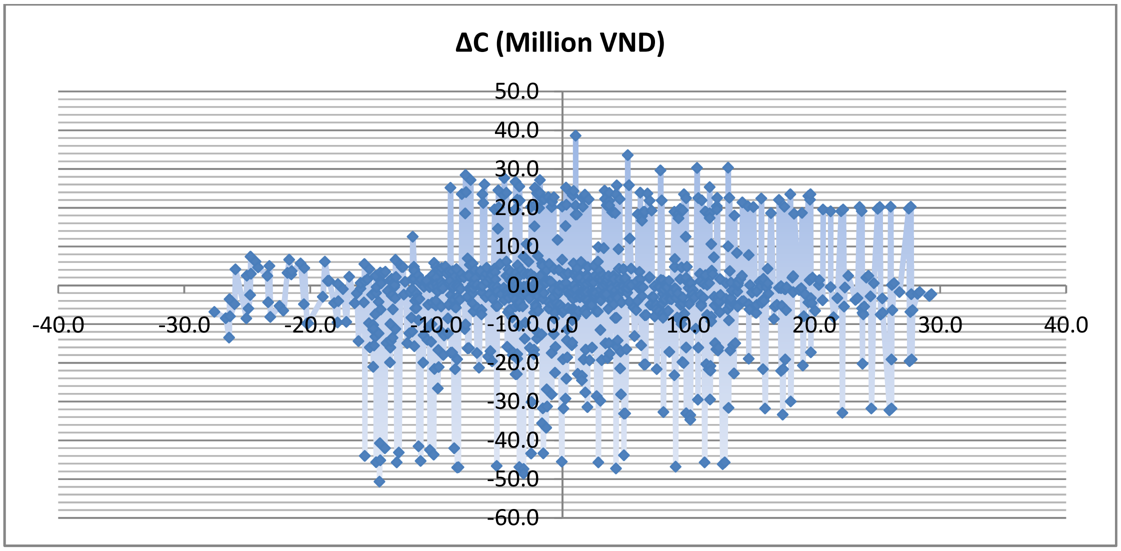

Figure 23. ICER results of bootstrap replication of SRS vs SR in the cost-effectiveness plane (adjusted samples)

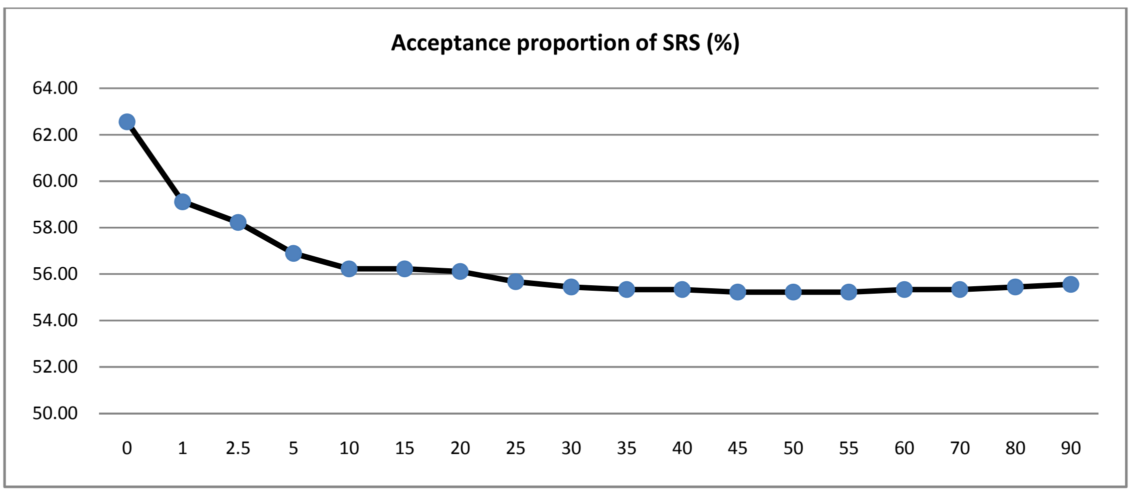

Figure 24. Cost-effectiveness acceptability curve of SRS

Discussion

The present study compared the cost-effectiveness of SR and SRS in the treatment of brain metastasis by evaluating the mean costs of SR and SRS from the perspective of patients and families during the period of the hospital stay for intervention. These mean costs were compared to the outcome in each of the two groups. The outcome was considered as the survival time following treatment. According to the current study results, SRS is more cost-effective than SR (cost per life year gained was 38.1 million VND and 46.4 million VND, respectively). Contributing to this difference was the fact that the direct costs of SR were just one third of the direct costs of SRS (14.5+/-7.7 million VND and 35.3+/-1.8 million VND, respectively) but its indirect costs were up to 10 times higher than the indirect costs of SRS (26.0+/-9.5 million VND for SR versus 2.5+/-1.4 million VND for SRS).

The lower direct cost of SR versus SRS found in Vietnam are very different to the previous studies in high-income countries conducted by Mehta and colleagues (in the US), Rutigliano and colleagues (a meta-analysis of studies in the US, UK, and Netherlands), and Wellis and colleagues (in Germany), where the net costs of SR were 1.8, 1.3, 1.9 times higher than those of SRS, respectively (Mehta *et al.*, 1997; Rutigliano *et al.*, 1995; Wellis *et al.*, 2003). However, when the direct and indirect costs are combined, i.e. taking the perspective of the patient and the family who has to pay for the health services into account, the cost-effectiveness of SRS in the treatment of brain metastases is also greater than that of SR. This is consistent with earlier studies in high-income countries, such as that of Rutigliano and colleagues which found that SRS had a better incremental cost-effectiveness than SR ($40,648 versus $52,384 per life year, respectively) (Rutigliano *et al.*, 1995); and Mehta and colleagues which concluded that SRS appears to be more cost-effective, with an average cost per week of survival of $524 for SR plus radiation, and $270 for SRS plus radiation (Mehta *et al.*, 1997).

In addition to the drugs officially dispensed in the hospital, which comprised the biggest proportion of hospital costs (31.4 to 68.2%) (Lieu HD, 2005), the patient also had to pay for additional drugs and consumables that were not available in the hospital and they self-purchased on the prescription of their physicians. These costs were not recorded in the hospital receipt which the current study used to calculate the direct costs of the treatments. The study of MOH 2003 reported that the proportion of these costs, as well as a gift to hospital staff, lodging, meals, and transportation was about 40% of the total cost, and was even higher in higher levels of treatment facilities (MOH, 2003). Based on the costs of lodging, meals, and transportation, we roughly estimated the expenditure on additional drugs, consumables, and gifts to be around 10% of total hospital costs. The gift is actually not given in all cases, but is quite common in Vietnam to express the deep gratitude of the family for the kindness of health care staff, and also in some cases in the hope of encouraging doctors to give them special attention. The LOS of SRS group was found to be rather high, because Gamma Knife is one department inside the general hospitals and almost all SRS patients were first admitted as inpatients. The LOS was calculated for the whole time in the hospital (not only in the Gamma Knife department) for diagnostic procedure, SRS intervention, and recovery care. In some cases of serious illness, patients were kept longer to relieve symptoms such as pain, seizures, and paresis. For these reasons, the reimbursement through fee-for-service could lead to the longer duration of stays (Lin *et al.*, 2008; Nelson EC, 1998).

The lower direct costs of SR may be the reason that older and poorer patients use this treatment. In the current study, from the unadjusted samples there were more older patients using SR compared to SRS (37.5% versus 17.1%) which also accorded with the higher number of patients in the SR group who were lost to follow-up (26.4% versus 12.9%) because more of them lived in rural and remote areas where the administration was not thorough enough in regard to the registration of houses' numbers, and because they also more commonly used temporary prepaid SIM cards to be contactable only during hospital stays. Even for those who were back in hospital for ongoing treatment (other than SRS or SR) we were also not able to get such information, due to the lack of connections in the patient databases between different hospitals in Vietnam. With this restriction in available information, the additional treatment of the whole brain radiation therapy was not considered in our data analysis, because we could not precisely obtain this information by phone when contacting the patient or their relatives. However, all these constraints mentioned did not act as a bias, because the adjusted samples were matched by PSM and those lost to follow-up (before 3 months from the date of intervention) were excluded in the final model for CEA.

In addition, the current study has some limitations as the sample size is rather small: it consisted of 60 cases, 30 in each group. However, it met the minimum sample size to arrive at reliable estimates of the three major functions (survival, probability density, and hazard) and their standard errors at each time interval (Gonzalez RH, 2010). Patients were not randomly assigned to the treatment. They were assigned by the recommendation of medical doctors plus the patient's ability to pay for the service, regardless of whether the patient was insured or not insured because the insured still had to pay almost 40% of the cost of SRS, as it exceeded the ceiling cost health insurance would cover. Additionally the study is limited by the nature of the observational data, which we had to overcome by PSM, but matching was done following exposure, so the treatment subjects and standard subjects in the matched sample do not form two independent samples. However, the propensity score approach has several theoretical and practical advantages compared to other methods such as adjustments based on case mix or severity of illness alone. It has been successfully used in other medical settings in which data from controlled trials were lacking, and is increasingly used to evaluate the effectiveness of medical treatments using data obtained from non-experimental studies in adjusting for selection bias; and the matched nature of the sample was accounted for in the statistical analysis in this study to estimate the precision or significance of the estimated treatment effect (Austin, 2008; D'Agostino, 1998; Radford and Foody, 2001).

Conclusion

In the context of the lower-middle-income country of Vietnam, the innovative technology of SRS in the treatment of brain metastases is similarly effective as SR, as it is in high-income countries. However, in the broader context of the cost-effectiveness from the perspective of patients and their families, SRS remained a more cost-effective treatment than SR. The lower costs directly charged by the hospital for SR may prevent poorer and older patients from choosing SRS. Thus, the overall cost-effectiveness of each treatment option should be taken into consideration in deciding upon the treatment.

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Appendix: Cost-effectiveness of SRS versus SR in the treatment of brain metastasis in Vietnam adjusted to the Health Insurance perspective

To make the results available for international comparison, we adjusted our current study results to the perspective of Health Insurance by calculating the cost that health insurance paid to the hospital basing on the charge of the hospital for each patient. Of which, the SRS service, health insurance paid for 60% only – the left paid by the patient (this part is excluded in the cost calculation of SRS service in our current study).

(C_i^{hs} : *charge from the hospital to the patient i*)

	Mean (Million VND)	Mean (Ajusted to PPP.US$)	SD	P value
Treament cost by				<.001
SRS	19.756	2,570	1.310	
SR	7.952	1,034	2.444	
Cost per one year gained				
SRS	19.922	2,591		
SR	9.088	1,182		

(PPP stands for purchasing power parity, in 2008, 1 US$ equal to 7.688 VND at the source: UN data. A World of information)

Table 34. Total cost of one treatment by SRS or SR (Adjusted to health insurance perspective)

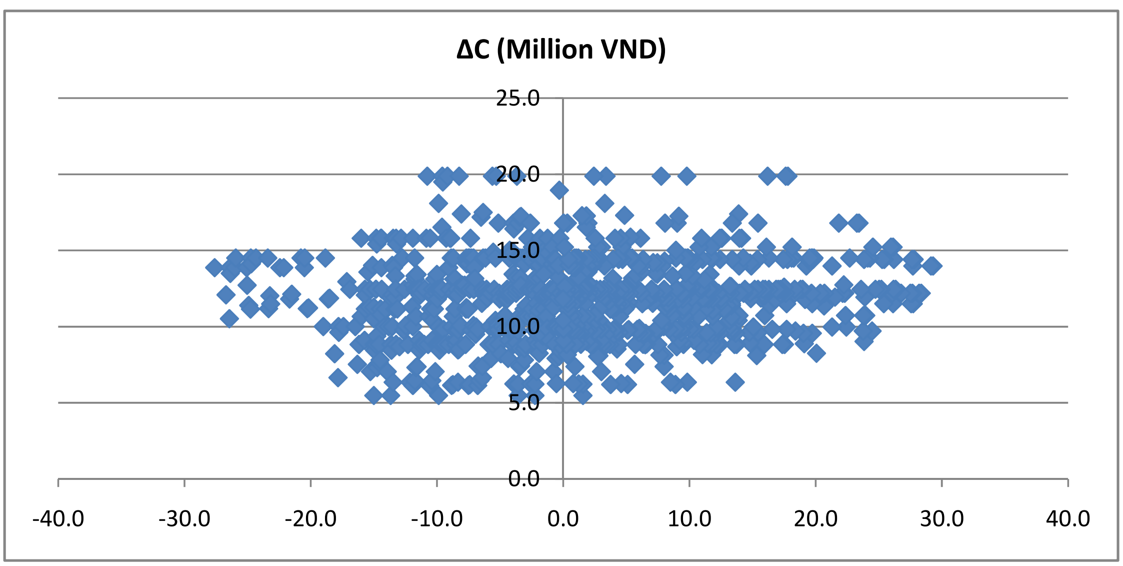

Figure 25. ICER results of bootstrap replication of SRS vs SR in the cost-effectiveness plane, adjusted to health insurance perspective

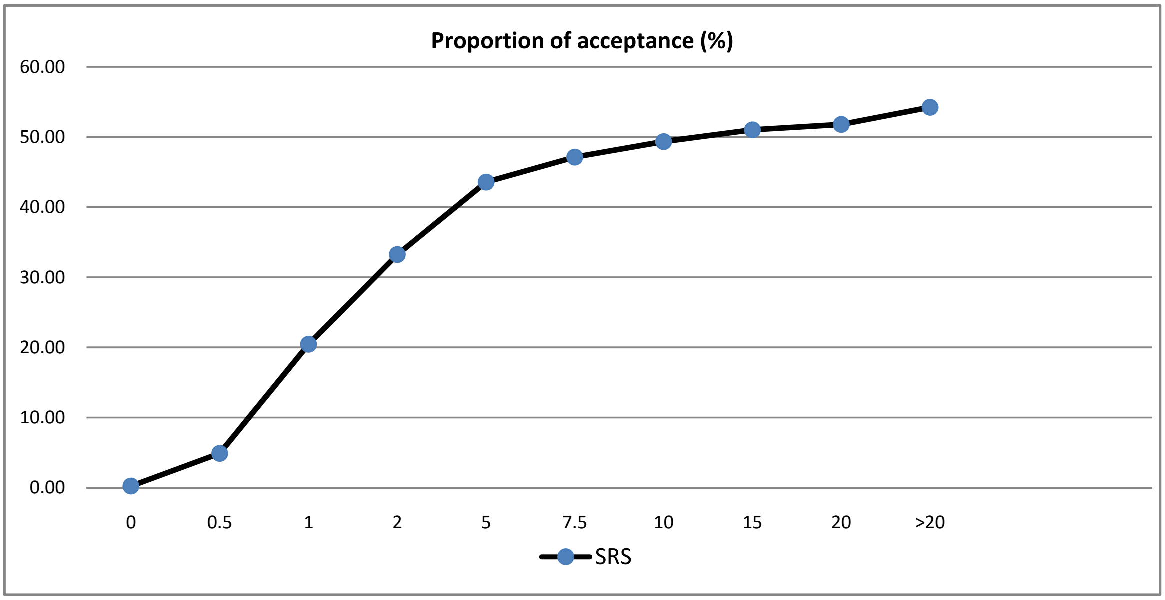

Figure 26. Cost-effectiveness acceptability curve, adjusted to health insurance perspective

Results:

The mean of survival times of SRS was 11.9 months higher than that of SR (10.5 months), but no significant difference was found (p=.346); Cost per life year gained was much higher for SRS than SR (19.922 and 9.088 million VND, respectively). The uncertainty of ICER of SRS versus SR was estimated by non-parametric bootstrap replication to show that all the point estimates fall in the upper left and right quadrants of the cost-effectiveness plane, meaning that cost of SRS was greater than cost of SR or SRS was more costly than SR. Probability of the point was more relatively distributed in the right-upper quadrant compared to the left one, suggesting that SRS was more likely to be effective than SR, but only achieve to be acceptable at highly incremental cost, meaning that SRS would have a 50% probability of being cost-effective if an incremental cost ceiling of 12.4 million VND between SRS and SR set.

Chapter 8. Cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of brain metastasis with German statutory health insurance perspective

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(Submitted)

Abstract

Objectives: This study aims to identify the cost-effectiveness of two brain metastatic treatment modalities, stereotactic radiosurgery (SRS) versus surgical resection (SR), from the perspective of Germany's SHI System.

Methods: Retrospectively reviewing 373 patients with brain metastases who underwent SR (n=113) and SRS (n=260). Propensity score matching (PSM) was used to adjust for selection bias (n=98 each); means of survival time and survival curves were defined by the Kaplan-Meier estimator; and medical costs of follow-up treatment were calculated by the Direct (Lin) method. The bootstrap resampling technique was used to assess the impact of uncertainty.

Results: Survival time means of SR and SRS were 13.0, 18.4 months, respectively (P<0.001). Medians of free brain tumor time were 10.4 months for SR compared to 13.8 months for SRS (P=0.003). Number of repeated SRS treatments significantly influenced the survival time of SRS patients (R^2 =.249; p=.006). SRS had a lower average cost per patient (€7212 - SD: 1047; Skewness: 7273) than those of SR (€10964 - SD: 1594; Skewness: 0.465), leading to an ICER of €-8338 per life year saved (LYS), meaning that using SRS costs €3752 less than SR per targeted patient, but increases LYS by 0.45 years.

Conclusion: SRS is definitely a more cost-effective treatment than SR in the treatment of brain metastasis from the SHI perspective. When the clinical conditions allow it, early intervention with SRS in new brain metastatic cases and frequent SRS repetition in new brain metastatic recurrent cases should be advised.

Keywords: brain tumors, economics, stereotactic radiosurgery, surgical resection

Introduction

There are approximately 427 000 new cancer cases occurring annually in Germany. Men are affected 1.16 times more frequently than women. Compared to 1980, this number has increased by 35% for women and 80% for men. Age-standardized incidence rates have gone up by 15% and 23% respectively. The relative five year cancer survival rates have improved considerably from approximately 50% to 60% for women and from 40% to 55% for men (RKI, 2008). With early diagnosis and more effective treatment prolonging survival, an increase in the occurrence of brain metastasis has been observed. 10-15% of patients suffer from brain metastases at first diagnosis of cancer (Petrovich *et al.*, 2002) and during the course of the disease brain metastases appear in 20-40% of the patients (Arnold and Patchell, 2001; O'Neill *et al.*, 2003; Kondziolka *et al.*, 2005; Eichler and Loeffler, 2007). In Germany, this means 43,000-64,000 new patients developing brain metastases per year and a total of 300,000-550,000 patients with brain metastases. Besides the impact on the individual cases these figures show that brain metastasis is a serious and growing clinical and socioeconomic problem.

The health care system of Germany is characterized by a predominance of SHI. Around 85% of the population is covered by SHI that pays for the vast majority of cancer therapeutic costs (Busse R, 2004; Drummond and Mason, 2007). As in most European countries, in Germany cost efficiency and reimbursement are more and more formalized in HTA and are of great importance in the decision making process about which costly therapies are worth paying for (Drummond and Mason, 2007). Recent studies on CEA and the treatment of brain metastasis show higher cost-effectiveness for SRS than for SR (Mehta *et al.*, 1997; Cho *et al.*, 2006; Rutigliano *et al.*, 1995; Wellis *et al.*, 2003). Despite of this outcome most HTA recommend more overall studies on CEA concerning therapies and combinations of therapies especially for the German health care system (Riemenschneuder *et al*., 2009). The scope of this study is the CEA of two treatment modalities which are SR and SRS from the perspective of Germany's SHI system.

Material and methods

Patient profile

All patients with single or multiple brain metastases who received an initial SR or patients who had an initial SRS with the diameter of the largest tumor smaller than 3 cm, the number of tumors less than 10 on a MRI scan, but the total volume of the brain which was exposed to more than 10 Gy less than 100 ccm, were considered for this study. In the SR group, we excluded previous SRS, and leptomeningeal metastasis; prior SR and leptomeningeal metastasis were excluded in SRS group. Follow-up had to be limited to 5.5 years for both groups due to limitations in the SR database. Patients in both of the two arms with less than 6 months of follow-up were also excluded unless a specific event like death occurred.

All patient data were retrieved from retrospective and prospective patient databases created between 1999 and 2009. For SRS we used data from the Gamma Knife Centre Krefeld metastatic database. This centre is located in Nordrhein-Westfalen state and is specialized in gamma knife radiosurgery. It provides services for local and regional patients as well as patients from the rest of Germany. Data for the SR group were from the Radiation Oncology Department of a hospital located in Schleswig-Holstein state. Eventually 373 patients met all of the above-mentioned criteria and remained for propensity score matching, 260 patients in the SRS arm and 113 in the SR group. All patients were followed at regular intervals which involved contrast enhanced magnetic resonance imaging and neurological examination data on additional treatment associated with local or distant recurrence within the brain was available and is shown in Figure 27 (Mindermann, 2005).

SR was performed in general anaesthesia. Patients were treated with 24 mg dexamethasone at least 10 days postoperatively. The use of anticonvulsive medication depended on clinical circumstances. A state-of-the-art tumor resection was performed with microsurgical techniques, and neuro-navigation was only used if indicated. Postoperative WBRT was applied as soon as possible after healing of the skin incision. There were three possible fractionation schemes applied: 5x4 Gy, 10x3 Gy or 20x2 Gy. Radiation was applied using a two field technique or 3D computer plan.

SRS was performed as an outpatient procedure. The Leksell stereotactic frame was applied with local anaesthesia. MRI scans were performed in a dedicated MRI scanner which was submitted to a rigid quality assurance regime to guarantee a spatial accuracy within a margin of 0.4 and 0.6 mm for the entire diagnostic, planning and treatment chain. Dose plans were calculated on the Leksell gamma plan. The radiosurgical procedure was performed with a C type Gamma knife with APS which was later upgraded to a 4C type. Conformal dose plans were created using 4, 8, 14 and 18 mm collimators. The mean marginal dose was 21.4 Gy (Standev. 2.38). The mean isodose was 50.3% (Standev. 4.62). Dexamethasone and anticonvulsive medication was applied in an identical fashion as for the SR group.

Statistical analysis

Treatment cost calculations

From the SHI perspective, the costs were calculated for the utilization of direct health sector costs only (Chernyak *et al.*, 2009), which were measured in the current study for medical costs of initial intervention (SRS or SR) and retreatment cost of more potentially life-saving procedures such as SRS, SR, LINEAR (STX), WBRT until death or during 5.5 years of follow-up. We excluded the cost of follow-up visits and the adjunct treatment of the chemotherapy, rehabilitation and other pain relief therapies as we considered those to be equal between the two treatment arms (Eichler and Loeffler, 2007). There was no co-payment by the patients. The treatment costs were calculated based on the year 2009 rates of the DRG system, the weighting of each single case in SR arm was based on our available information of ICD, Standard of Operation and Procedure (OPS - Operationen und Prozedurenschlüssel), sex, age, LOS (UKM). It was previously determined for an average of 15.4 days (Wellis *et al.*, 2003). The DRG rate in Germany does not include equipment and infrastructure investments, which are generally paid for by local authorities. However, it is considered a standard price or fee, as it represents the actual cost of care for a large proportion of the population (Scheller-Kreinsen *et al.*, 2009). The price of other procedures such as STX, WBRT, SRS was based on the outpatient tariff provided by the actual figures of the two centers where our patient samples treated. Finally, the price of each procedure included in our current study is 4700 EUR for SRS; 9419 EUR for SR; WBRT: 718 EUR for 5x4 Gy, 927 EUR for 10x3 Gy, 1344 EUR for 20x2 Gy; and 552 EUR for any single fraction STX.

No discounted rate was implemented due to the fact that the life expectancy of brain metastasis is usually short, around 12 months, and due to the cost of resource utilization based on the same year tariff (2009) (Johannesen *et al.*, 2002). Censored cases were those in which the retreatment cost was not fully observed before event (i.e. death) occurred. Because the censored cost is a common issue in estimating the average lifetime cost, in our sample population, patient was obviously by chance lost follow-up, it is reasonable to assume that censored cases are independent of all other random variables (Willan AR, 2006; Heitjan *et al.*, 2004).

We applied the Direct (Lin) method with the non-history cost using approach, rather only using the observed total cost at the last follow-up date to estimate the medical cost of our incomplete follow-up sample population (Lin *et al.*, 1997). Following this method, the mean total cost (E_T or E_S) of the whole sample size in each arm (T stands for SRS and S stands for SR) was estimated by the sum of the deduction of the Kaplan-Meier estimator for the probability of being alive at the start of each interval S_k and S_{k+1}, which was partitioned by the entire time period of interest into small intervals (k), multiplied by the average total cost A_k of those who died at the start of such relevant interval, which is described below in greater detail:

$$\hat{E}_T = \sum_{K=1}^{K+1} \hat{A}_K (\hat{S}_k - \hat{S}_{k+1})$$

$$\hat{A}_k = \frac{\sum_{i=1}^{n} Y_{ki} . C_i}{\sum_{i=1}^{n} Y_{ki}}$$

Where,

Y_{ki} = 1 for patient i being observed to die and Y_{ki} =0 for patient i being censored in the k interval

C_i is the total cost of each patient, since our main concern is to compare the effect of two treatments on the patient-related variables of total medical cost. For simplicity we did not include the coefficients of monthly dummy variables, so it was calculated by the sum of the price of each resource used multiplied with the quantity of resource used for patient i (Hlatky, 2002a). S_k is S step function that decreases at those times of death occurred that was estimated using the product-limit method of the Kaplan-Meier estimator:

$$\hat{S}_k = \prod_{j:t\ j<ak} \frac{n_j - d_j}{n_j}$$

Where, d_j is the number of deaths occurring at those times; n_j is the number of patients at risk of death at those times.

The estimator of the difference between the two arms in the mean cost is given by

$$\Delta_c = E_T - E_S$$

An algorithm indicating the flows of patients treated with SRS or SR and other retreatment interventions for brain tumor recurrence that were constructed for the estimation of the total medical cost (Figure 27).

Propensity score matching (PSM)

In this current retrospective observational study of two heterogenic populations, maybe there was no random assignment of patients to the treatment arms, and hence the validity of the results compromised by selection bias and confounding factors. To minimize this problem we applied the statistical method of propensity score matching (Rubin D, 1973; Austin, 2008; D'Agostino, 1998).

In order to find the prognostic factors used for PSM, survival time of the entire cohort was measured from the time of the initial intervention, either with SRS or SR. Uncensored cases were those who reached the endpoint of interest (i.e death). Those who had no additional follow-up data available were censored on the last seen date. Survival curves were constructed by the Kaplan-Meier estimator, the mean survival time was estimated as the area under the survival curve (Kaplan & Meier, 1958). The difference between the Kaplan-Meier curves of the two arms were determined with the Log-rank test (univariate analysis) and Cox proportional hazard model (multivariate analysis), the prognostic factors were found to be significant with $P<0.05$ (Cox DR, 1972). Then, the propensity score was calculated by a multivariable logistic regression model with those covariates of treatment methodologies, number of brain tumors, extra-cranial metastases which have been found significant in the multivariate Cox proportional hazard model of unadjusted sample to be the prognostic factors for the survival time of brain metastatic patients (Table 35); and covariates of gender, age groups, primary tumor sites, KPS, RPA were previously defined from the literature and available in our database (Eichler and Loeffler, 2007; Cox DR; Kim *et al.*, 2000; Lagerwaard *et al.*, 1999; Rades *et al.*, 2007). The regression model calculates for each patient a propensity score (0 - 1). A ratio of 1:1 optimal matching without replacement was applied to randomly match each SR patient to SRS patients with the most similar propensity score. The balances of the prognostic factors in the two arms of both unadjusted and adjusted samples are measured by using the standardized difference (Aoyama *et al.*, 2006).

$$Standardized\ difference = \frac{100(X_{srs} - X_{sr})}{2\sqrt{S_{srs}^2 + S_{sr}^2}}$$

where X_{srs} and X_{sr} are the sample means in the SRS and SR groups of the i^{th} covariate, respectively, and S_{srs}^2 and S_{sr}^2 are the corresponding sample variance. Small absolute value of standardized difference (<10%) support the assumption of balance between treatment groups (Cohen J, 1997).

For the matched sample (adjusted sample), the mean survival time was used as the best estimate of the principal outcome (survival time) for CEA (Neymark *et al.*, 2002). The survival time mean and curves were constructed by the Kaplan–Meier estimator, for which it was determined whether survival improvement was attributable to the effect of treatment methodologies of SRS versus SR by the univariate Cox proportional hazard regression model. Multivariate Cox proportional hazard regression of prognostic factors and propensity score was used to test the association between prognostic factors and the survival time of the treatments on patients. The capacity of the final multivariate analysis model to predict the treatment effect on the patient was evaluated by Harrell's C statistic, which is the area under the receiver operating characteristic (ROC) curve, claiming to be a measure of predictive power (Ash and Shwartz, 1999). This model yielded a C-statistic of 0.73 that indicated a rather good ability to predict higher probabilities for patients who lived for a shorter survival period than a longer survival one. The highest predictable capability was given by the factor of the number of brain tumors (1 versus >1 tumors) (Table 36). The linear regression was used to test the survival time of SRS patients (of those who died) on the number of repeated SRS treatments.

All reported P values were 2-sided and detected a significant difference with a level of 0.05 or less.

Statistical analyses were performed with SAS version 9.3.1 and STATA 10 software.

Sensitivity activity

Although PSM was well balanced between the two treatment arms, as both costs and effects were determined from data that sampled from the same patients in the study, a potential selection bias due to imbalances in unmeasured covariates might be possible. In addition, cost-effectiveness of the treatments would be highly sensitive to the number of deaths and the cost of these. It would be important to analyze the sensitivity of results. We applied in the current study a formal sensitivity analysis, by using the bootstrap resampling technique to assess the impact of uncertainty on the estimated ICER. A resample from the observed data of both arms was used to build an empirical estimate of the sampling distribution of ICER (Hlatky *et al.*, 2002b).

Results

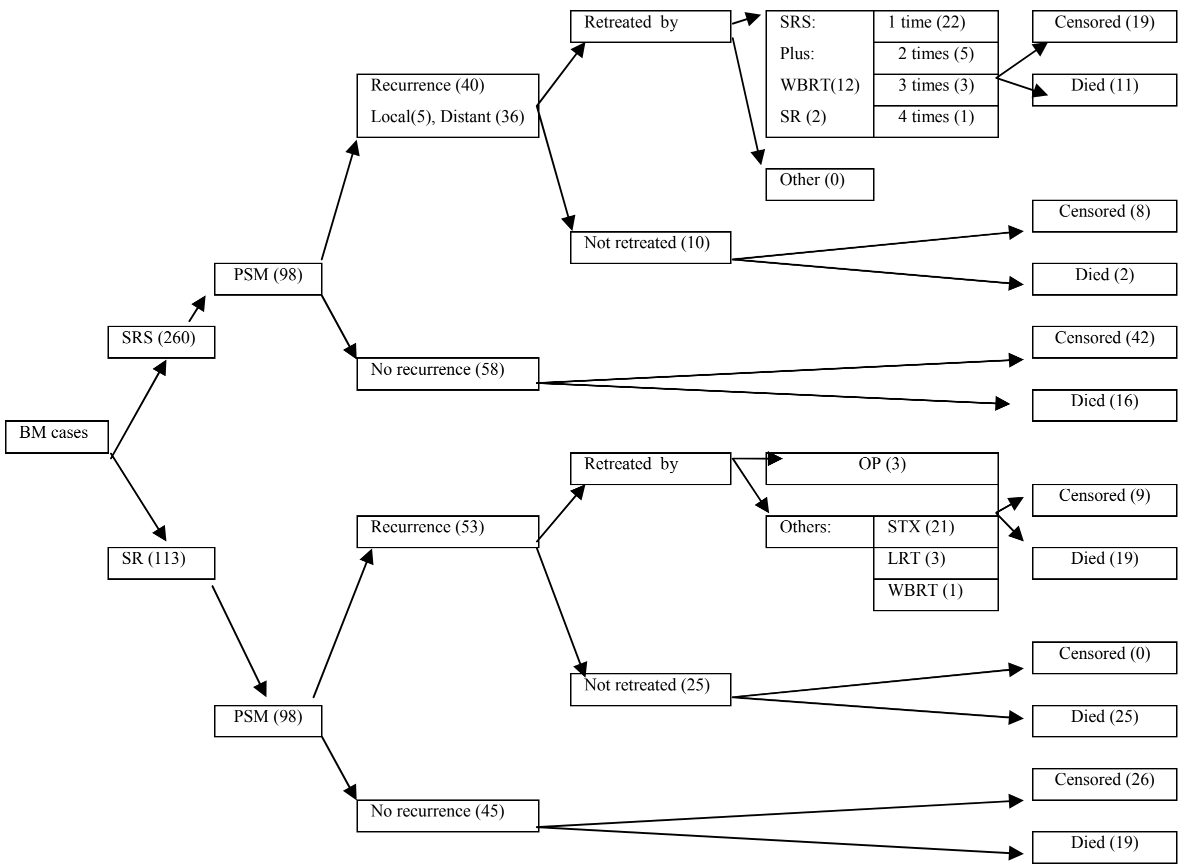
For the entire cohort, the median survival time was 10.2 months in the SR group compared to 14.0 months in the SRS group. The Log-rank test determined statistically significant differences between the two survival distribution curves (p<.001). Improved survival probability of the entire cohort was identified by multivariate analysis of the Cox proportional regression with respect to potential predictors of survival, which found the statistically significant associations with the covariates of the treatment methodologies (SRS vs SR), number of brain metastases (1 vs >1), extra-cranial metastasis (non active vs active) (Table 35).

Patient characteristics		**Survival function at 12 months (%)**	**Median survival time (month)**	**Univariate analysis/Log-Rank test**	**Multivariate analysis/Cox prop. hazard model**	
					HR/ p	CI. 95%
Treat				<.001*	0.25/ <.001*	0.17-0.37
	SRS	81.7	14.0			
	SR	55.1	10.2			
Gender				.05	1.19/.38	0.79-1.79
	Female	77.6	13.7			
	Male	68.2	11.3			
Age groups				.12	1.41/.07	0.96-2.07
	≤60 yrs	79.0	13.9			
	>60 yrs	66.6	11.4			
Primary tumor sites				.53	1.13/.36	0.86-1.49
	Breast	73.0	14.0			
	Lung	76.5	12.9			
	Others	70.1	11.3			
Number of Brain metastasis				.21	1.78/<.001*	1.20-2.63
	1 BM	73.9	12.9			
	≥ 2 BMs	74.1	12.7			
Extra-cranial metastasis (prior)				.38	1.68/.04*	1.01-2.80
	No active	75.8	13.6			
	Active	70.3	12.1			
KPS				.87	0.76/.60	0.28-2.08
	<70	60.3	12.4			
	≥70	74.2	12.6			
RPA				.97	0.88/.67	0.50-1.55
	Class 1	76.7	14.3			
	Class 2	73.1	12.0			
	Class 3	**63.7**	**13.1**			

** Statistically significant*

Table 35. Median survival time, univariate and multivariate analysis (unadjusted samples).

Propensity score matching identified a total of 196 patients (98 patients on each arm). The baseline characteristics of the adjusted samples are summarized in Table 35. The standardized difference of each prognostic factor confirmed no difference between the two arms, except for the primary tumor site of lung cancer (Standardized difference -10.16) (Table 35). The medians of follow-up were 13.8 months in the SRS arm and 13.6 months in the SR arm. The follow-up treatment was SRS in 31 patients, WBRT in 12 patients, SR in 2 patients of the SRS arm; and WBRT, STX, SR, local radiation therapy (LRT), and WBRT in 98, 21, 3, 3, and 1 patients in the SR arm, respectively (Figure 27).



(number in parentheses represent number of patients)

Figure 27. Algorithm indicating the flows of patient under SRS, SR and other retreatment regimens

Patient characteristics	Before PSM (unadjusted sample)			After PSM (adjusted sample)			Multi-analysis Proportional Hazards Model Survival (95%CI – Adjusted sample)		
	SRS	SR	SD	SRS	SR	SD	HR	SE	P value
Treat (n)	260 (100)	113 (100)		98 (100)	98 (100)		0.27	0.06	<.001
Gender (n)							1.18	0.29	.49
- **Female (%)**	153 (58.9)	59 (66.7)	9.54	54 (55.1)	48 (49.0)	8.7			
Age groups (n)							0.67	1.45	.85
- **< 60 years (%)**	156 (60.0)	52 (58.8)	20.24	54 (55.1)	58 (59.2)	-5.9			
Primary tumor sites (n)							1.26	0.33	.38
- **Breast (%)**	68 (26.2)	28 (31.6)	2.56	23 (23.5)	19 (19.4)	8.57			
- **Lung (%)**	108 (41.5)	52 (58.8)	-6.45	47 (48.0)	54 (55.1)	-10.16			
- **Others (%)**	84 (32.3)	33 (37.3)	5.16	28 (28.6)	25 (25.5)	5.49			
Number of Brain tumors (n)							4.61	12.65	.57
- **< 2 tumors**	136 (52.3)	92 (104.0)	-49.89	79 (80.6)	80 (81.6)	-2.36			
Extracranial metastasis (prior) (n)							2.03	0.84	.08
- **No active (%)**	77 (29.6)	69 (78.0)	-49.72	56 (57.1)	57 (58.2)	-1.48			
KPS (n)							2.48	10.03	.82
- **< 70**	16 (6.2)	6 (6.8)	5.49	6 (6.1)	6 (6.1)	0.00			
RPA (n)							2.05	5.84	.79
- **Class 1**	44 (16.9)	48 (54.2)	-45.32	35 (35.7)	31 (31.6)	6.47			
- **Class 2**	162 (62.3)	59 (66.7)	14.73	57 (58.2)	61 (62.2)	-6.03			
- **Class 3**	15 (5.8)	6 (6.8)	3.10	6 (6.1)	6 (6.1)	0.00			
Propensity score							70.71	823.58	.71

(Note. ROC curve c-statistic = .731. SE stands for standard error, HR stands for hazard ratio)

Table 36. Patient characteristics of the two arms before and after PSM; the overall logistic and proportional hazards model evaluating the association of treatments and survival in adjusted samples

At last follow-up, 30% of SRS patients and 64% of SR patients in the adjusted sample had died. The Kaplan-Meier curves demonstrated differences between the two curves (Figure 28). The differences between survival time means of the two treatment arms (18.4 months in the SRS arm compared to 13.0 months in the SR arm) determined by the Cox proportional hazard regression model that were statistically significant (P=.000; Table 37), which indicated the treatment methodologies of SRS versus SR significantly influenced the survival times of brain metastatic patients.

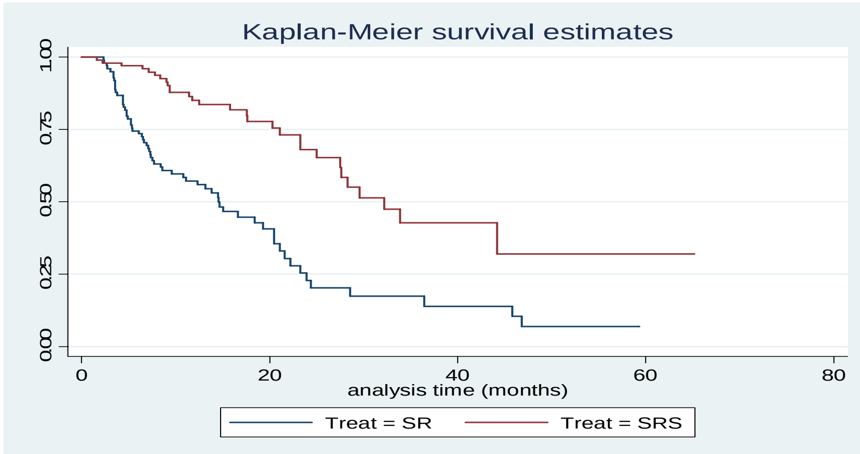


Figure 28. Survival curves of two treatment groups (adjusted samples) – Months post interventions

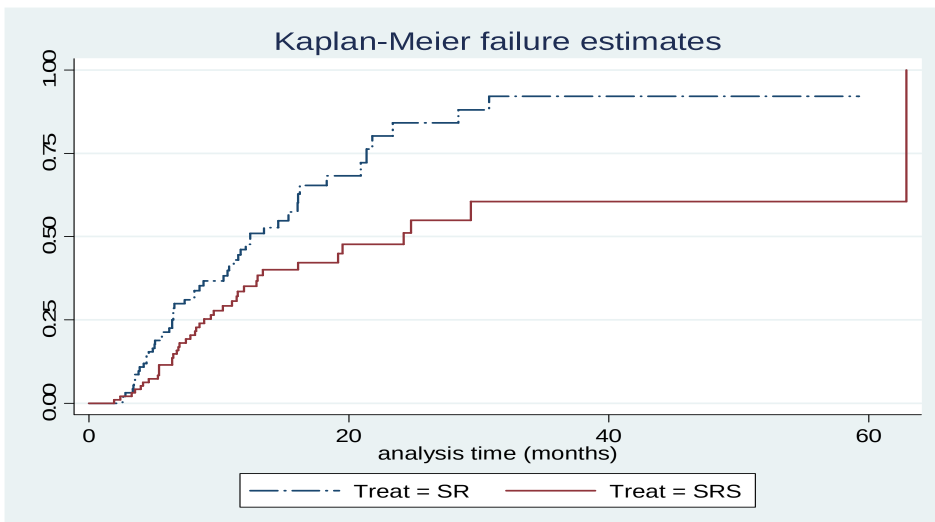


Figure 29. Free BM interval curves of two treatment groups (adjusted samples)

		Survival time (month)	Survival function (%)		Cox Proportional Hazard Model		
		Mean	**12 months**	**18 months**	**HR**	**95% CI**	**P value**
Treatment	SR	13.0	57.1	44.7	0.30	0.19-0.48	<.001
	SRS	18.4	85.0	77.6			

Table 37. Univariate analysis of treatment effect on the survival function (adjusted samples)

The recurrence of brain metastases (combination of local and distant recurrence) in the adjusted samples at last follow-up occurred in 40.8% (5 patients out of 40 with tumor recurrence had local recurrence) of the SRS patients and 54.1% of the SR patients (53 patients). Using Kaplan-Meier failure function analysis for tumor control of brain metastases (Figure 29), the difference of the mean tumor control interval time between the two treatment arms (10.4 months in the SR arm versus 13.8 months in the SRS arm) tested by the Cox proportional hazard regression model, to determine that the treatment of SRS versus SR had a significant influence on the failure function of tumor control for brain metastases (P=.003; Table 38). It was relevant to the interval time of retreatment. Thirty three out of 40 recurrence cases in the SRS arm underwent repeated SRS. The mean interval between the initial and the subsequent treatments of SRS were 13.3; 13.5; 11.2 between the first and second; second and third; third and fourth treatments (Table 39). The number of repeated SRS treatments significantly influenced the survival time of SRS patient (R^2 =.249; p=.006). In the SR arm, 28 out of 53 recurrence patients underwent repeated treatment by different interventions such as SR, STX, and WBRT (Figure 27).

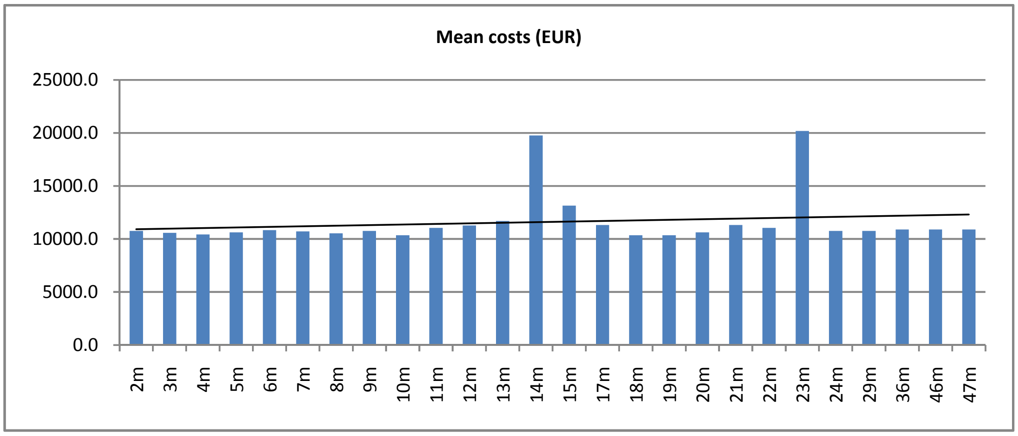
		Free tumor interval time (month)		Cox Proportional Hazard Model		
		Mean	**Median**	**HR**	**95% CI**	**P value**
Treatment	SR	10.4	8.1 (2.3-59.2)	0.53	0.34-0.80	.003
	SRS	13.8	10.8 (1.5-62.9)			

Table 38. Univariate analysis of treatment effect on the failure function of free tumor control (adjusted samples)

Time of SRS patient's retreatment (months)	**N**	**Mean**	**Range**
1st SRS – 2nd SRS	32	13.3	1.9-62.9
2nd SRS – 3rd SRS	8	13.5	4.0-28.4
3rd SRS – 4th SRS	3	11.2	4.1-22.5
4th SRS – 5th SRS	1	3.6	

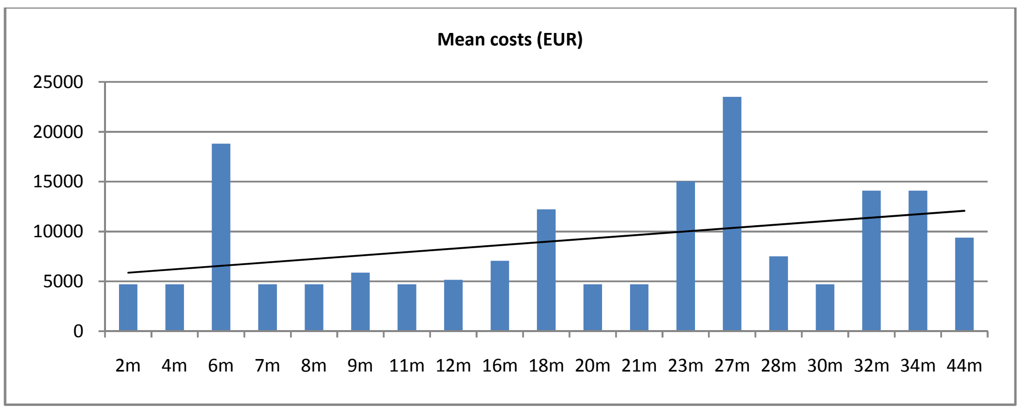
Table 39. Mean interval of SRS patients' retreatment regarding to the brain tumor recurrence (months)

The distribution of patient cost was positively skewed, with some patients having much higher costs than the majority (Figure 30, Figure 31). SRS had a lower average cost per patient (€7212 - SD: 1047; Skewness: 7273) than those of SR (€10964 - SD: 1594; Skewness: 0.465); and was also significantly more effective in terms of LYS than SR (1.53 LYS versus 1.08 LYS). Adjusting to the ICER expressed in Euro per LYS that is minus €8338/LYS. Which is derived from the negative of different cost (Δc) and positive of different effect (Δe), the treatment arm of SRS is dominant to the standard arm of SR (Table 40). In practice, this means that using SRS costs the equivalent of €3752 less than the cost of SR per targeted patient, and could lead to a mean increase in targeted patient life expectancy of 0.45 year.



(In x-axis: m stands for month)

Figure 30. Medical cost associated to relevant interval of survival functions in SR arm according to Kaplan-Meier estimator.



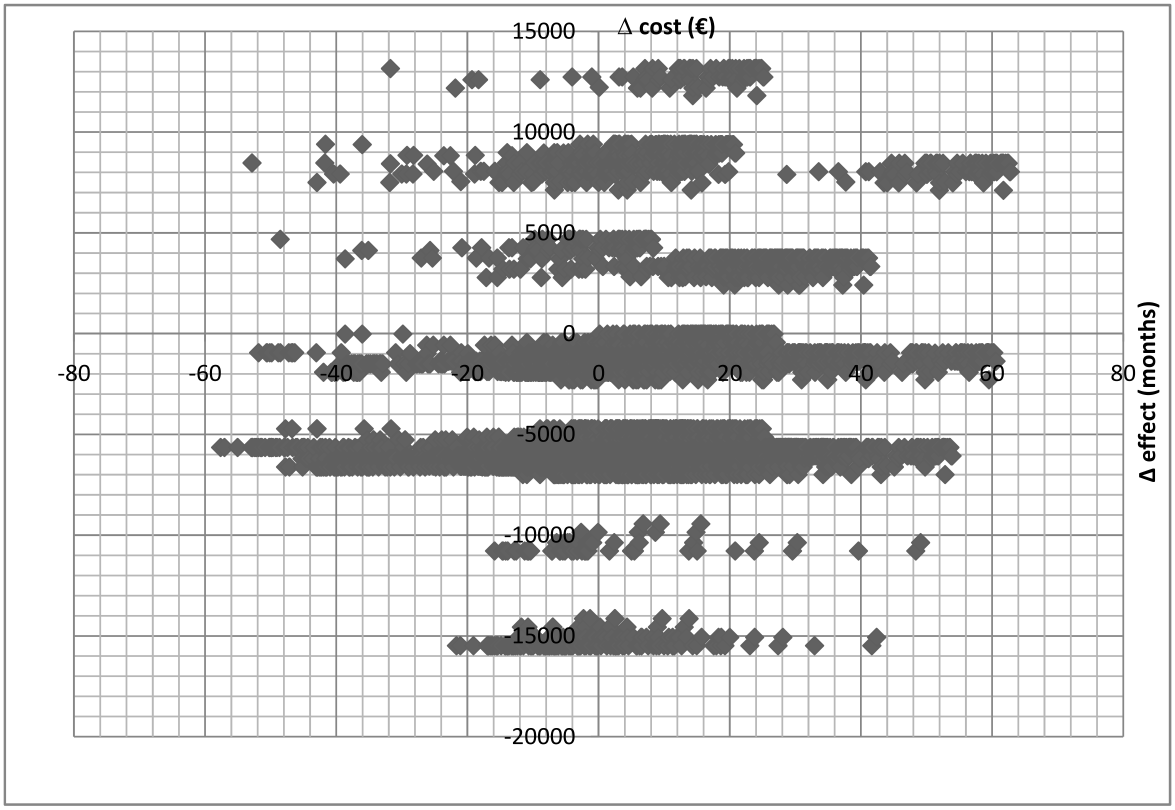
(In x-axis: m stands for month)

Figure 31. Medical cost associated to relevant interval of survival functions in SRS arm according to Kaplan-Meier estimator

Treatment	Mean costs per case (in Euros)	Effect (LYS)	ICER
Treatment arm (SRS)	9,964	1.53	
Standard arm (SR)	11,647	1.08	
Differrence	-1,683	+0.45	-3740

Table 40. Incremental cost-effectiveness ratio (in Euros/LYS) of SRS in relation to SR

Result of sensitivity analysis Figure 32 shows 9000 bootstrap replicates of ICER and the scattering of points on the cost-effectiveness plane is based on the results of a nonparametric bootstrap analysis. Within a 95% CI of the bootstrap replications, the cost difference of SRS compared to SR ranged from €-10365 to €8848; the prolonged life years were between -31,8 months to 41,7 months for SRS compared to SR. In terms of the proportions of the ICER estimates falling in each of the four quadrants, 66% of the points in concentrated in SE+NE quadrants of the plane to indicate that SRS is more effective; the 92% of the points distributed in SE+SW to show the SRS is lower cost. The 59% of the points are in SE quadrant to indicate that SRS has a lower cost and higher effect, compared to 2% of the points distributed in NW which expresses SRS having a higher cost and lower effect. The hypothesis of higher cost-effectiveness of SRS versus SR is definitely confirmed, meaning that the T arm (SRS) dominates the S arm (SR) or that SRS is more effective and less costly than SR.



(NW, NE, SE, SW stand for North West, North East, South East, South West quadrant, respectively)

Figure 32. ICER results of CI95% bootstrap replications of SRS vs SR in the cost-effectiveness plane (adjusted samples)

Discussion

This study uses costs and clinical trial data from Germany to compare the cost-effectiveness of SRS and SR for the treatment of brain metastases, from the perspective of Germany's SHI System. The mean of medical costs from initial intervention to event occurrence (i.e death or censored) was taken into account for the outcome effect determined for each of the two treatment arms. The outcome effect was measured as the LYS after the initial treatment (SRS in the SRS arm and SR in the SR arm) until event occurred (i.e death). The two treatment arms were well-balanced in terms of prognostic factors, with the majority of matched samples cases of single brain metastasis (81%) and KPS of ≥70 (94%) (Table 36). The results have definitely confirmed that the SRS treatment was more cost-effective, associated with less costs and higher effect (LYS) compared to the SR treatment option. These results favorably compared to those previously reported. Rutigliano *et al* (1995) conducted a meta-analysis from some studies in US, UK, Netherlands and found that SRS had better ICER than SR ($40,648 versus $52,384 per life year) (Rutigliano *et al.*, 1995); Mehta *et al* (1997) also confirmed in another meta-analysis that SRS appeared to be the more cost-effective procedure (an average cost per one life week saved of $524 for SR+RT versus $270 for SRS+RT) (Mehta *et al.*, 1997); Sperduto and Hall (1995) found the marginal cost of SR plus WBRT versus SRS plus WBRT ranged from $10,609 to $15,236 and SRS was more cost-effective than SR (Sperduto and Hall, 1996).

What could contribute to this higher cost-effectiveness of SRS versus SR? The effect of SR was found here to be relatively similar to the previous studies. Although SR plus WBRT typically resulted in 6-10 months survival gained (Patchell *et al.*, 1990; Auchter *et al.*, 1996; Wroński and Arbit, 1999; Bindal *et al.*, 1993), there were some reports with longer survival after SR and WBRT. In a retrospective analysis of 231 patients Wronski *et al* (1995) found the overall median survival time for the entire cohort was 11 months from the time of initial craniotomy (a mean of 21 months). However, 47 out of 231 patients had more than one resection (maximum 5 times) (Wroński *et al.*, 1995). Schackert (1996), Penar and Wilson (1994) even found the median survival time average was up to 16 months, or 26 months depending on the different subgroups of the primary tumor site (Schackert G, 1996; Penar and Wilson, 1994). In the SRS arm, LYS was also not discordant to previous findings, which frequently reported 8 to 12 months for the median survival time after the first SRS (Aoyama *et al.*, 2006; Huang *et al.*, 1999; Williams *et al.*, 2009; Kondziolka *et al.*, 1999a; Chen *et al.*, 2000; Flickinger *et al.*, 1996). However, some cohort studies had resulted in longer survival times than our current study. Pan *et al* (2005) studied a cohort of 191 patients who underwent treatment for 424 brain metastases and found that the median survival was 15 months after GKS alone and 14 months after a combination of SRS plus WBRT (Pan *et al.*, 2005); and in a subgroup of patients with no extracranial metastases, no neurologic deficits and a small tumor without necrosis Kim *et al* (1997) found a median survival time of up to 26 months (Kim *et al.*, 1997), and some patients were even found to survive up to 90.8 months after initial SRS (Williams *et al.*, 2009). To our knowledge, the statistical significant difference in the effect of treatments found in this study was not confirmed in previously published studies concerning the comparison between SRS and SR with WBRT (Muacevic *et al.*, 2008; Muacevic *et al.*, 1999).

This significant difference is plausibly attributable to the lower tumor recurrence rate in the SRS arm versus the SR arm (O'Neill *et al.*, 2003; Matsunaga *et al.*, 2010), as our study found that the interval free from intracranial metastatic relapse after SRS as opposed to SR was significantly different (p=0.003). Recurrence rates of brain metastases are associated with survival period, taking advantage of the less potentially radio toxicity of SRS, this regiment can be repeated to treat the intracranial tumor recurrence months to years after the initial treatment (Kondziolka *et al.*, 1999b; Chang and Adler, 2000). In a randomized controlled trial study of Kim *et al* (1997), 48% of the patients had repeated SRS, and one patient had undergone 7 procedures over a survival period of 10 years (Kim *et al.*, 1997). Our study supports the claim that frequent repetition of the SRS treatment when new brain metastases appeared resulted in longer patient survival times compared to SR treatment. That was proved by the positive linear regression between survival time and number of SRS retreatment.

The strength of our study is that the result is derived from a large database which allows us to restrict appropriate criteria such as the minimum follow-up period; and that the SRS or SR procedure was the initial intervention in the SRS or the SR arm, respectively. The database had sufficient information associated to vital prognostic factors for the final outcome of survival time such as KPS, RPA, primary tumor site, extracranial metastases, number of brain metastases, gender, ages, which resulted in a good predictive model (C-statistic 0.73). The application of PSM was well-balanced in the sufficient covariates between the two samples.

The higher censored rate in the SRS arm of 70%, compared to 35% in the SR arm, may influence the prediction capacity of the model (Kretowska, 2010). This can be explained by the patients' location. The SRS patients were not only those living in Nordrhein-Westfalen, they were more scattered throughout all states of Germany and some were even from surrounding countries. SR patients were more concentrated in the area of Schleswig-Holstein. However, the higher censored rate in the current study could not influence the result due to the facts that, first, the follow-up time in the two arms were well-balanced (13.8 months for SRS versus 13.6 months for SR), the total time at risk was even higher for SRS than for SR (1811 months and 1211 months, respectively), and 17 patients were still alive at last contact near the end of the period of study. Second, Kaplan-Meier assumed that all censored survival times occur immediately after their censored times, which perhaps means that the survival times predicted are underestimated compared to the actual times, but only at the component level, not necessarily at the system level (QCP; Reineke *et al.,* 1998*)*. The incremental effectiveness rate between SRS and SR is actually confirmed to be even higher, so it cannot influence the significant difference between the effects on the two treatment groups. One possibility in the Lin (direct) method biases the assumption that was the withdrawn of the patient from the study, which was due to health or cost reasons (Lin *et al.*, 1997). However, this would not be really a problem in Germany with SHI-insured patients who are covered for the payment of health interventions, and patients could receive radiosurgery it was indicated.

In addition, PSM also had certain limitations, as matching was done following exposure, so the two treatment arms the adjusted samples did not form two independent samples. However, it had been recognized as having more advantages in both theory and practice compared to other methods such as adjustments based on case mix or severity of illness alone. It made sure the matched nature of the samples was accounted for in the statistical analysis to estimate the precision or significance of the estimated treatment effect (Austin, 2008; D'Agostino, 1998).

Conclusion:

SRS is definitely a more cost-effective treatment modality than SR in the treatment of brain metastasis from the point of view of health insurance. When the clinical condition allows it, early intervention with SRS treatment in new cases of brain metastasis and frequently repeated SRS treatment in new cases of recurrent brain metastasis should be advised in order to prolong survival time.

PART V. DISCUSSION AND CONCLUSION

General discussion

The life expectancy at birth in Germany was 77.1 years for males and 82.4 years for females in the period 2005-2010 (with an increase of 4.5 and 3.3 years for males and females, respectively, over the last 15 years). These are higher than those for Vietnam, where males are expected to live to 70 years of age and females to 75 years of age (WHO, 2010a). The size of the population in Germany is predicted to decrease, as the birth rate was just 8.3 per 1000 inhabitants (in 2008) which had already decreased by 1 per 1000 inhabitants over the previous 13 years. In Vietnam over the last decades the government has tried to control the birth rate, but the population still grows, with the birth rate at 17 per 1000 inhabitants in 2009, compared to 31 in 1990 (Unicef, 2010). Consequently, a big difference between Vietnam and Germany is the aging population in Germany (where 20.4% of the population is over 65 years of age and 12.62% is under 14 years of age), while in Vietnam 6.6% and 25% of population is over 65 and under 14 years of ages, respectively (GOPFP, 2008; Kowal *et al.*, 2010). The disease pattern of Germany is more related to demographic trends such as cardiovascular diseases, cancer, obstructive lung diseases, and urogenital diseases. Neoplasm diseases accounted for 10.4% of total inpatient visits (in 2008), positioned in second place, just lower than disease of the circulatory system (chapter 6). In Vietnam, the pattern of diseases has shifted from communicable to non-communicable diseases. Non-communicable diseases comprised 66% of all deaths in the year 2002. Cancer has become the second highest cause of mortality after cardiovascular disease, the two accounting for 12% and 32% of all deaths, respectively (WHO, 2008; van Minh *et al.*, 2009).

Cancer has been considered an emerging major public health problem in both countries. The ASR of cancer incidence in Vietnam increased by $8.87/10^5$ for males and $37.13/10^5$ for females from the period 1993-1998 ($151.1/10^5$ and $106.8/10^5$, respectively) to the period 2006-2007 ($160.0/10^5$ and $143.9/10^5$, respectively); by sites, there were increasing trends in 61% of cancer sites in males and 77% of cancer sites in females (chapter 1). In Germany, over the course of a lifetime each second male (45.39%) and each third female (37.85%) is likely to develop a cancer, but a slightly higher probability of developing cancer was observed in females (10.19%) than males (8.63%) before the age of 60 years (L. Breitscheidel & A. Sahakyan, 2006). The crude incidence rate was 568.2 and 469.9 per

100,000 in men and women, respectively. It is estimated that the annual number of new cancer cases is approximately 230,500 among males and 206,000 among females (in 2006). Rising trends for both sexes were observed, but at different levels. The average age of cancer death is approximately 71 for males and 75 for females. Compared to 1980, this number has increased by 35% for women and 80% for men. ASR has gone up by 15% and 23% respectively. The relative five-year cancer survival rates have improved considerably from approximately 50% to 60% for women and from 40% to 55% for men (RKI, 2008, 2010). During the period 1991-2004, cancer in children (under 15 years of ages) increased 0.7% per year in the west and 1.1% in the east (Spix *et al.*, 2008). However, the patterns of cancer between the two countries are totally different. The ASR incidence rate in Germany is 2 times higher than in Vietnam. This may be attributable to underestimation of cancer registration in Vietnam, and may also be partly explained by the aging population as the incidence rate is increased by age: at the age of 60 years it is 7.3 times higher than at the age of 30 years. However, in fact probably neither is the cause because compared to other countries in the region, the statistics are not so different from China and Japan, even though Japan has a higher life expectancy than Germany and aging population is also a big problem in Japan (chapter 1), as over 20% of the population exceed the age of 65 and this number is predicted to increase (Willacy, 2009).

Brain metastasis is when a cancer from another site in the body spreads to the brain, and is far more prevalent than primary brain cancer. Brain metastasis is the most common neurological complication of systemic cancer, and the most common intracranial neoplasm in adults, occurring in 20-40% of all adult patients with cancer, and two–thirds of them become symptomatic during their lifetime. It is observed in males more frequent than in females (56.4%; 43.6% respectively $P<0.001$), and most often from cancer of the lung (51.2%), breast (12.3%), unknown (7.5%) primaries, kidney and renal pelvis (4.0%), and melanoma of the skin (3.9%). The most common primary tumors acting as sources of brain metastases, by sex, were lung cancer and cancer of unknown primary in male patients, and lung cancer and breast cancer in female patients (chapter 3). Therefore, the pattern of PTS in the cohort of brain metastatic patients is completely different than that of the original cohort of cancer patients within the same population community. Based on the more common sources of brain metastasis, there are different cancer patterns in Vietnam and in Germany. For males, German cancer patients suffer more commonly from cancer of the prostate, colon and rectum, lung, bladder, stomach, kidney and efferent urinary tract (chapter 2); but in Vietnam more common is cancer of the lung, stomach, liver, colon, pharynx, esophagus, rectum and anus. For females, the most common types of cancer are breast, colon and rectum, lung, uterus, ovaries, malignant melanoma of the skin in Germany, and breast, cervix uteri, lung, stomach, colon, thyroid, rectum and anus in Vietnam (chapter 1, chapter 2). Therefore, it is expected that cancer in Vietnam will have a higher probability of leading to brain metastasis than cancer in the German population.

The administration in Vietnam is divided into different levels: central, province, district and commune. This is similar to Germany which is administratively categorized into the federal level (Bundes), states (Laender), administrative districts (Kreise), counties (Bezirke), and municipalities (Gemeinden). The health care system is differently organized. In Vietnam it strictly follows the hierarchy of the administrative level and the health care network entirely cover from the central level to the commune level. In Germany, in contrast, the state level hospital facilities are responsible for secondary care, of which general and specialized private clinics are satellites. With the increasing demand for long-term care for patients of general chronic diseases and chronic-degenerative diseases of the aging population, the private clinics and more medical centers are now established for the integration of DMP and ambulance care services (chapter 5, 6).

In regard to management authority, Germany has a century-old tradition of social protection legislation. Almost all autonomous authorities are assigned to self-governing insurers and associations of providers within the health care sector (Tulchinsky and Varavikiva, 2009). In Vietnam, it is governed by the relevant administrative unit such as the Ministry of Health or provincial health bureau or district health division. Since the implementation of Decree No 43 in 2006 more financial autonomy has been devolved to the hospital managers (chapter 5).

A big problem of medical human resources is faced in both countries, even though the number of physicians in Germany is 355.4 per 100000 inhabitants, which is the 11th highest among all EU member states. However, a shortage of physicians is one of the major challenges of the German health care system, not only shortage of GPs working in rural areas but also physicians in hospitals. Physicians working in hospitals have to work as many as 55.3 hours per week (chapter 6). This situation is even more severe in Vietnam, as there are only 67 physicians per 100000 inhabitants (GSO, 2009-In: Education, health, culture and life), at a ratio of only 1:5 compared to Germany. There are shortages of medical human resources in all sectors within the system. In particular, there are significant problems in some specialized areas, for example, mental health, where there are only 0.90 psychiatrists per 100000 inhabitants, none of whom work in outpatient facilities (chapter 4, 6).

In both health care systems, the response by the health care system is not completely matched to the health care demands of population, although of course the levels of unmatched demands are different and problems are of a different nature and magnitude. For instance, there is an extreme situation of overloading of hospital beds, and a low percentage of patients getting treatment or care compared to the current prevalence of diseases in Vietnam (chapter 4, 5). In Germany, the problem of discrepancies in access to health care is the result of differences in the level of incentives of different health insurance schemes in the SHI and PHI (private health insurance) systems. Due to a higher level of PHI outpatient reimbursement for physicians, which is up to 20-35% higher than that of SHI, SHI patients wait 3.08 times longer than PHI patients for an appointment for elective treatments which are not known to be associated with an inferior quality of medical results for patients with later treatment, such as gastroscopy, allergy tests plus pulmonary function tests, pupil dilation, MRT of the knee, and hearing tests (Lungen *et al.*, 2008). The use of waiting lists is now more and more common, for instance in the growing rate of cancer incidence resulting in the shortage of radiotherapy service in relation to demand. This is the case even though there are enough radiotherapy locations, but the number of machines is at the lower limit (Schäfer *et al.*, 2005).

The quality assurance system in Germany is a comprehensive system of comparative hospital quality data, a project undertaken on the same scale by no other country and which has ranked Germany number 3 in European countries in terms of transparent monitoring of health care quality (Bjoernberg *et al.*, 2009). At the moment, Vietnam has not yet got a similar universal approach for quality management. Instead the hospital quality control has been advocated for the last few years, and each hospital is free to decide its own quality management approach, and most use ISO, TQM, etc. In addition, MOH annually initiates a cross-checking process of hospital performance among all hospital networks.

The total health care expenditure share in Germany is 10.5% of GDP (in 2008), which represents almost twice that of Vietnam (where it is 5.9% of GDP), and the health care expenditure per capita is 22.9 times higher in Germany (PPP_US$3,465) than in Vietnam (PPP_US$151) (WHO, 2009). The basic difference in health care services between the two countries is the private-based system in Germany in contrast to the public-based health care system in Vietnam. Funding for health care is in both countries derived from a mix of public and private contributions. However, there is a paradox that in Germany the private-based system receives a major proportion of funding for health care from public sources such as SoHI and taxation, which accounted for over 77.3% of total health expenditure (in

2008), of which SoHI alone accounted for 70% (chapter 6), while the public-based system in Vietnam receives a major portion of its funding from private contributions, that is, OOP. The OOP is a dominant source of funding, accounting for 75% of total health expenditure. The funding derived from health insurance is only 13% of the total health expenditure (MOH, 2008b), 46.7% of in- and outpatient visits to the hospital are paid by OOP (chapter 4, 5).

The payment system for hospital services is completely different between the two countries, a prospective payment system based on a DRG scheme in place in Germany and an FFS scheme in Vietnam. Germany shifted from experiencing the inefficiency of a historically-based hospital budget payment mechanism. The revenue from hospital reimbursement accounted for 80% of total hospital expenditures. The remaining 20% is contributed by the government. In Vietnam, the revenue derived from FFS accounted for 44.6-77.9% of the total full costs of hospital unit costs, and almost half of total hospital expenditure, the rest is directly provided by the government (chapter 5, chapter 6).

Specific discussion

1- Data collection process

Before data collection in each country, the researcher had to undertake certain steps such as getting the letter of introduction from the supervising professor, contacting relevant health facilities, getting initial agreement of patient data utility from the health facility authority, finding out data availability, presenting the study proposal to the scientific committee and the signing of the commitment form, and attaining the final permission for access to the data for research.

The data collection in Vietnam was done by the researcher. To do it, the researcher had to search for the list of relevant patients during the study period in the hospital administrative management software, to find patient records in the archives of the hospitals studied, to study the patient records, and find the information required to fill in the data collection sheet. In Germany, the data was collected from the database of the health units, and cross-checking with the patient records was necessary in cases of uncleally understandble information.

The fundamental differences between the data sources on the cost of each treatment episode between the two countries were that patients at each treatment episode in Vietnam had different cost data which was calculated by every detail of a single item used in the treatment duration in the health units. The document was then stored in the archive of the financial and accounting division of the health units. The researcher had to request the document for each patient treatment episode. In Germany, it was much more simple, because the price was almost always the same for the same outpatient service, and DRG tariff was used for inpatient treatment which was much transparent and could be used to calculate the cost based on the details of the patient and their treatment.

2- Hospital-based data collection

In Vietnam, there were some clinical practice issues, namely that the clinical indicator used was inconsistent with international practice, which is to use Glasgow instead of KPS or RPA (chapter 7, chapter 8); the cause of diseases was not absolutely determined, and a higher rate of unknown PTS was found in the research in Vietnam compared to in Germany. There is no universal standard protocol (clinical pathway) within or among hospitals in the treatment of brain metastasis in Vietnam. Therefore the laboratory test data and clinical symptoms are insufficiently exploited in some patient cases (i.e. data on the extracranial metastasis and magnitude of different brain tumors, for which the researcher had to self-calculate from the images of MRI or CT-Scan with the help of specialized physicians in some cases). Therefore, the number of predictable factors in PSM of Vietnam research is fewer than in the research in Germany. However, by c-statistics both two main pieces (chapter 7, 8) of the research are credible enough to predict the effect of treatments.

In addition, NHT adoption in Vietnam is lagging behind in comparison to Germany. Within the surgical resection groups of samples in both two main pieces of the research into brain metastasis management, the majority of cases in Germany were treated with microsurgery while this group was predominantly treated with open surgery in Vietnam. This is a common situation in developing countries; for example, in the management approach of prostate cancer, nowadays the transurethral resection is widely applied in developed countries while open suprapubic prostatectomy remains the gold standard treatment in the developing world (Abeygunasekera, 2004).

Data is probably deviated in the case of the researcher sefl-studying the patient documents, picking out information to fill in the data collection sheet (which depends on the knowledge and experience of the researcher in this field of study) to compare to the available data in the electronic database which had been directly created by the physicians who treated these patients. Therefore, attention bias of the researcher was assumed more often in the study of Vietnam than that of Germany. Additionally, the hospital-based data in Vietnam is more incomplete than initially planned for the comparative analysis of

Vietnam and Germany. This issue is in accordance to the finding of Flessa, a main problem of data in developing countries is incomplete (Flessa, 2009).

3- The follow-up information collection

The follow-up information regarding patients after their hospital treatment was very different between the two countries. In Vietnam, there was no confirmation if patient got back for follow-up. In case they returned for follow-up visit, the information was also not available in the hospital patient records because at each follow-up visit, the patient got a new patient code and a new record folder, and then the new and the old records were not kept together in one folder. Therefore, the researcher had to collect the information by telephoning the patient, their relatives or a nearby health center. Collected in such a way, more study samples were missed because of invalid telephone numbers, inaccurate information in regard to the continuous treatment during the follow-up duration which was given by people without medical education, or biased information provided by relatives whose recollections were affected by grief or other emotions. Even in Germany, the follow-up information was not sufficient for all patients at the end of the study time period, but the information was recorded in the database of the health units (hospitals or clinics) at each follow-up visit to the health units, or in the exchange of information on the patient among different health units which were involved in the treatment of that patient (the follow-up information of the patient was sent to hospitals which had refered patients to private clinics).

The greater awareness of the German public about the diseases was revealed in their compliance and adherence to the treatment as they were more willing to correctly follow the advice of physicians by periodically returning for check-ups.

The evaluation of the treatment effectiveness in Vietnam was more limited in comparison to that conducted in Germany. Because no information on the continuous treatment during the follow-up time period was available, the research done in Vietnam only mentioned the first treatment, whereas the research in Germany could analyze in more detail the retreatment information which essentially contributed to the final effectiveness of the treatment.

Information on the cause of death due to intracranial tumor or systematic diseases was not credible and scientific enough for the research done in Vietnam.

4- Perspectives on the cost-effectiveness of treatment

There were different perspectives between the two country studies. While the interest in the cost of the treatment in Vietnam lies more with the patient and their relatives who self-paid for the treatment, in Germany health insurance is the main source of payment for the treatment of the patient, hence, the interest of the patient treatment cost was a matter of concern only from the health insurance perspective. Additional care during the hospital stay was given by patient's relatives in Vietnam while this was not the case in Germany. Therefore the cost in regard to patient and their relatives was an important consideration for the research in Vietnam.

5. A comparison of the results of the two cost-effectiveness studies in Vietnam and Germany (chapter 7, 8)

The effect of SRS versus SR was not found to be significantly different in the research in Vietnam, with a mean survival time of 11.9 and 10.5 months for SRS and SR, respectively (p=.346), compared to 18.4 months for SRS and 13.0 months for SR in Germany (p=<.001) (Table 41). The life years gained in Germany was much longer than in Vietnam which was partly explained by the difference in patient characteristics. German patient have better compliance and adherence to the treatment; and there were probably more severe cases in the sample of Vietnam compared to that of Germany (not clearly seen in the sample patient characteristics due to irrelative comparison between the KPS indicator used in the Germany study and the neurological impairment indicator in the Vietnam study).

Simply based on the concerns of those who pay for the services the studies arrived at relatively similar conclusions that SRS is more cost-effective than SR in the treatment of brain metastases: the Vietnam study found that it costs 46.4 and 38.1 million VND per one life year gained for SR and SRS, respectively; and German study resulted in €3,752 less for SRS compared to SR per targeted patient, but an increase of 0.45 life years gained (SRS is dominant to SR). However, it is an irrelevant comparison, because the results come from two completely different perspectives (the perspective of health insurance for the German study and patient and family perspectives for the Vietnam study), with different components of cost containment. Taking the same perspective of health insurance results in a big difference in the two study results, whereby in Germany SRS was much cheaper, while in Vietnam SRS was more costly than the cost of SR. In Vietnam, the cost per LYS was much higher for SRS than SR, equal to 19.922 and 9.088 million VND; ICER gave a high degree of uncertainty, even SRS was more likely to be effective than SR, but only managed to be acceptable at highly incremental costs, meaning that SRS would have a 50% probability of being cost-effective if an incremental cost ceiling of 12.4 million VND between SRS and SR was set. In the German sample group on the other hand, SRS is absolutely dominant to SR: SRS even costs €3752 less than SR per targeted patient, but results in an increase of 0.45 life years gained.

In regard to the value of the unit costs, we found that the price of services in Vietnam was much cheaper than in Germany (19.756 and 7.952 million VND per SRS and SR targeted patient in Vietnam and €7,212 and €10,964 per SRS and SR targeted patient in Germany, respectively, adjusted to USD by PPP which are equal to US$2,570 and US$1,034 for SRS and SR in Vietnam; US$8,299 and US$12,616 for SRS and SR in Germany, respectively) (Table 41). This difference is partly caused by the nature of health insurance in Vietnam, which did not cover the majority of the actual costs of the treatment, for example: the cost of SR comprised only 56.7% of the total hospital actual cost; and only 60% of the price charged by hospital for SRS was paid by health insurance, with the rest paid by the patient.

SRS vs SR in health Insurance perspective	**Vietnam**	**Germany**
Effectiveness (months)	11.9 vs 10.5 (p=.346)	18.4 vs 13.0 (p=<.001)
Cost per targeted patient		
Local currency	19.756 vs 7.952 (MillionVND)	7,212 vs 10,964 (€)
International currency (by PPP)	2,570 vs 1,034 (US$)	8,299 vs 12,616 (US$)

Table 41. Final result of cost-effectiveness of SRS versus SR in health insurance perspective

The differences in the results of the two cost-effectiveness studies on SRS versus SR in the treatment of brain metastasis were mostly affected by the differences in demography between the two countries, patient characteristics; the differences in the health care system, that is, between the DRGs scheme in Germany versus the FFS scheme in Vietnam, the limitations imposed by the copayment ability of patients for the service in Vietnam, and non-constraints in the maximal utilization of NHT in Germany; the differences in clinical practices; and the differences in patient characteristic, which meant that more compliance and adherence to the treatment was found in German sample patients than in those of Vietnam (Figure 33). The factors found here are mostly consistent with those found in previous publications (Drummond *et al.*, 2005-chapter 10; Goeree *et al.*, 2007; Cappellaro *et al.*, 2011).

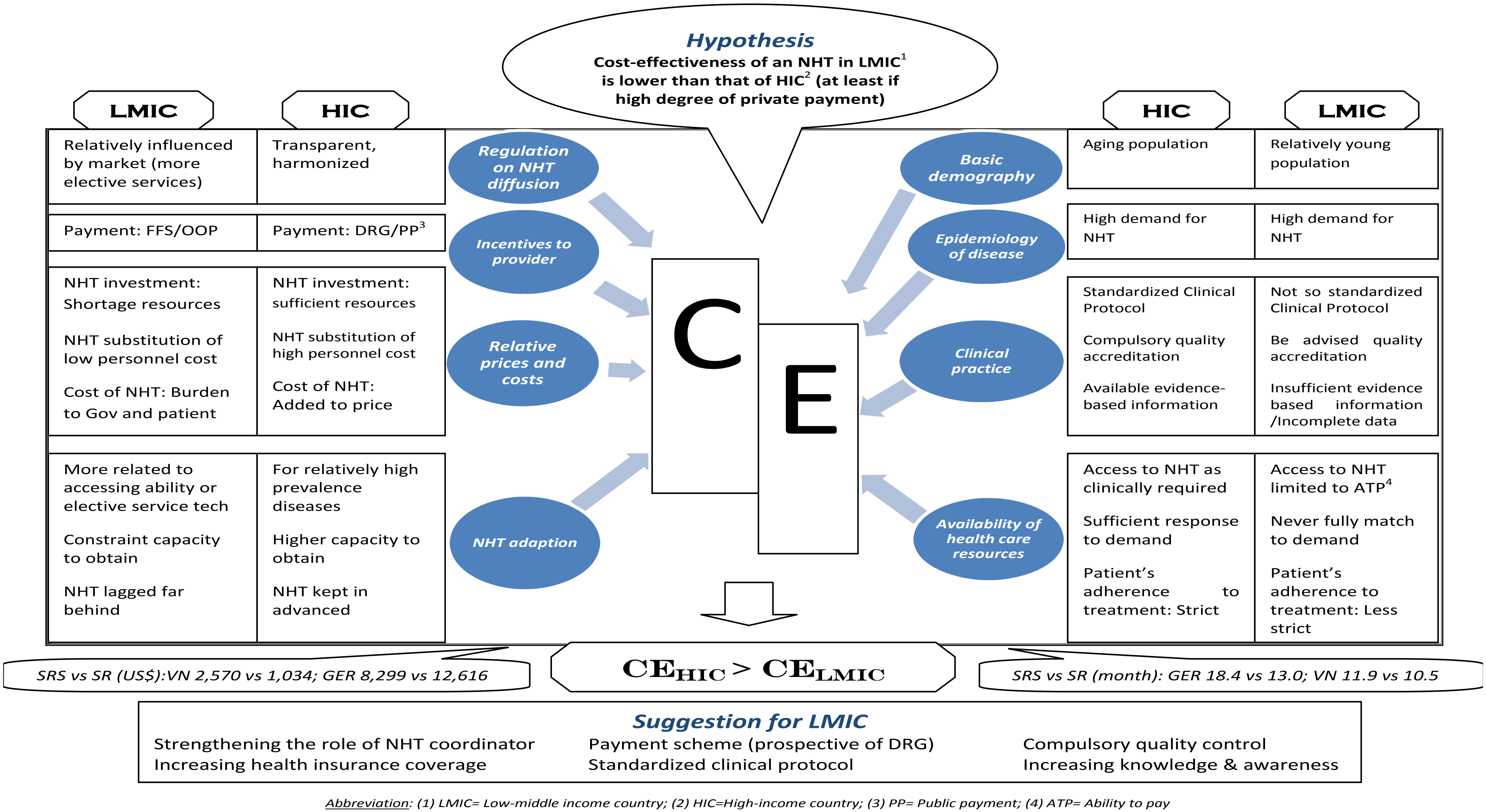


Figure 33. A model of cost-effectiveness analysis of an NHT in a low-middle income country and a high-income country

Conclusion:

By using a combination of primary data methods from population-based registration, administration, hospital-based, patient level data; and secondary data methods from academic and grey literature for the research in multiple fields of demography, epidemiology, clinical practice, patient characteristics, health services and health finance to assess the adoption of NHT of SRS versus the standard treatment technology of SR in the treatment of brain metastasis, in two countries one representative of a low-middle-income country (Vietnam) and the other of a high-income country (Germany). Some conclusions were made:

SRS is clearly dominant to SR in the treatment of brain metastasis in the high-income country of Germany, while there is high uncertainty regarding cost-effectiveness between these two methodologies in the low-middle-income country of Vietnam.

The repeated treatment of the new technology of SRS for the patient with reoccurrence of brain tumors in the allowed clinical conditions significantly influences the higher cost-effectiveness of SRS comparing to surgical resection, which was more feasibly performed in the high-income rather than low-middle-income countries.

The difference between the cost-effectiveness of SRS versus SR in the treatment of brain metastatic in these two countries was affected by different factors which include:

(1) Basic demography whereas it is an aging population in Germany on the contrary to relatively young population in Vietnam.

(2) Epidemiology of brain metastasis is rather different between two countries in the cancer incidence rate (it is lower in Vietnam than in Germany), cancer pattern (more frequent occurrence of primary tumor sites which act as main sources of brain metastasis in Vietnam than in Germany). However, both countries have high demand to the NHT of SRS for the treatment of brain metastasis.

(3) Clinical practice whereas Germany has more standardized clinical protocol/practice; more strict quality accreditation; and more available medical evidence-based information than these in Vietnam.

(4) Health services which are more available in Germany, where the regulation on NHT diffusion is transparent and harmonized in comparison to the market driven decision making of NHT diffusion in Vietnam. In addition, NHT services are relatively sufficient to respond to the demand as clinically required in Germany, while that is rather limited to the ability to pay of patient on the access to health technology services in Vietnam. This difference is mainly determined by the coverage of health insurance and the rate of copayment for the NHT services between two countries.

(5) Patient characteristics which includes the ability to access new technology of each patient, and their adherence to the treatment, regular check-up during the follow-up period which is found more strict for the patient in Germany comparing to the patient in Vietnam.

(6) Health finance, it is totally different between two countries, where German hospital get reimbursement by DRG scheme; the cost of NHT is under certain circumstances added to the price paid by public payment; there are sufficient resources in the investment of NHT which is contrary to Vietnam, where the reimbursement of the health technology service is by fee-for-service scheme, and the NHT investment cost is responsible more by Government and out-of-pocket payment of the patient, giving shortage of resources for investment of new health technology.

To be better advised for the decision making regarding NHT adoption, each country needs to conduct its own study of cost-effectiveness assessment of an NHT, in which an assessment of the cost-effectiveness of an NHT is examined in the broad context of demography, epidemiology, clinical practice, patient characteristics, health services and health finance.

Vietnam is recently making progress into providing better health care services to the population, although it still falls far behind Germany. Vietnam needs to address certain health problems that are now effectively controlled in the health care system of a high-income country such as Germany. At the same time, Vietnam is experiencing similar issues to Germany, such as the consequences of demographic changes, increasing public involvement in and awareness of health care, and the explosive growth of new and innovative health technology and its rapid acceleration of adoption and diffusion in worldwide health care systems, etc. To ensure to get higher cost-effectiveness of an NHT adoption; more eligible people access and benefit from improved medical technology to save, prolong the life and improve the quality of life of the population, the role of government in medical technology adoption should be strengthened by providing more authority to the coordinator (MOH) of health technology adoption, which can strongly facilitate and coordinate among different sectors out- and inside the health care system in respect to adoption of NHT. Specifically, the coverage of health insurance should be rapidly increased to cover the costs of treatment that enable the population to access and benefit from new medical technology; there should be a move towards a prospective payment system based on a DRG scheme; more standard protocol and quality control of clinical practices should be established; and the health care knowledge and awareness of population should be improved.

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