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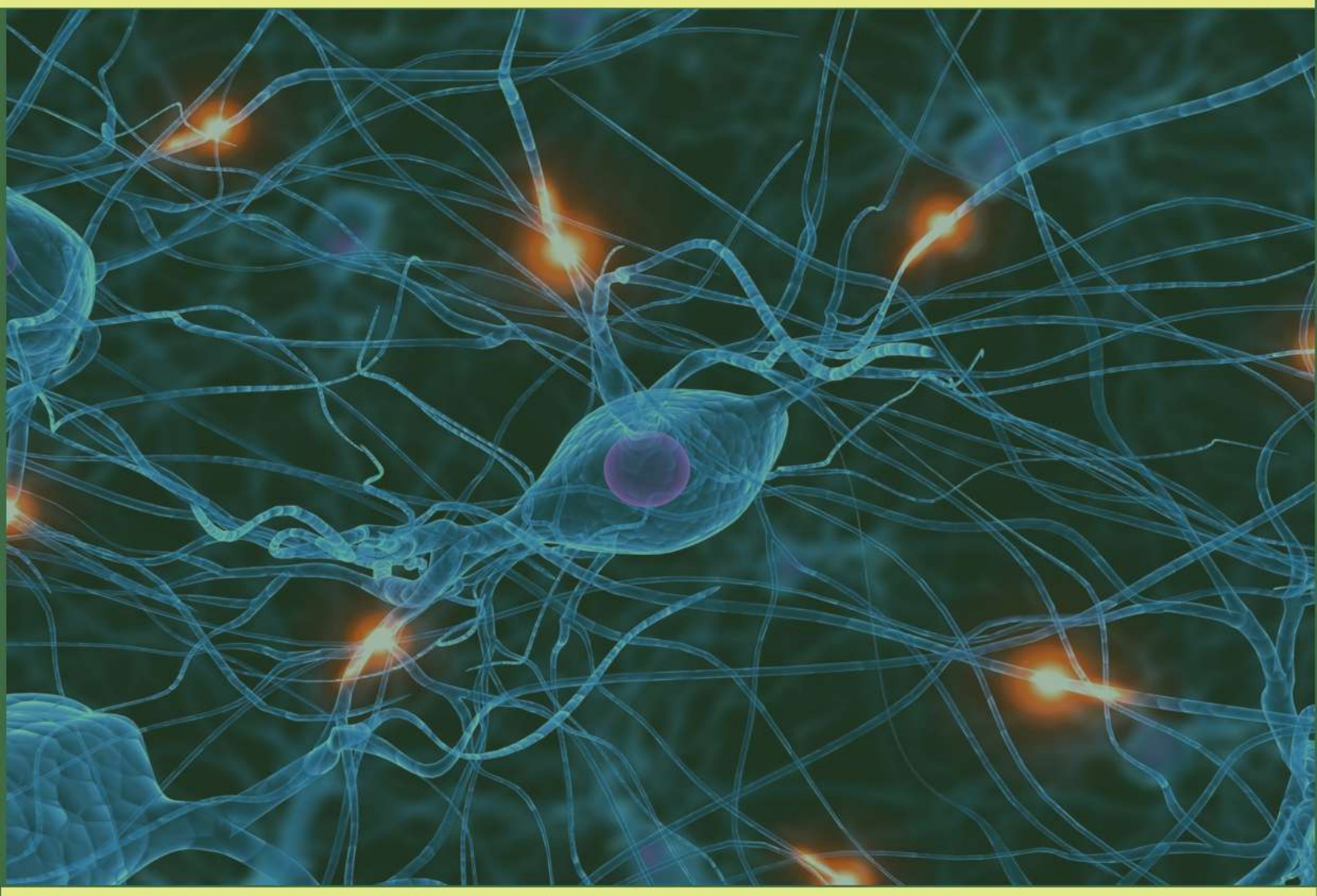

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Editorial

Review on Artificial Intelligence and Applications in Healthcare

Ravish Huchegowda, MBBS, MD[1*]; Srinivas Huchegowda, MBBS, MD, DNB, PhD[2]; Jyothi R. Jain, Mphil, PhD[3]; Manoj Parthasarathy, MBBS Student[4]; Tharika Shraddha, MBBS[5]; Nagalakshmi C. Sathyanarayanshetty, MBBS, MD[6]; Bharat V. Poojary, BE[7]; Farhan Zameer, MSc, PhD[8]; Chetan H Gowda, BE, MTech, PhD[9]; Naveen H. Gowda, BE, MTech[10]; Huskur N. Venkatesh, MSc, PhD[11]

[1]*Department of Neurochemistry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore 560029, Karnataka, India*
[2]*Department of Biochemistry, Maulana Azad Medical College, Delhi 110002, New Delhi, India*
[3]*Department of Biotechnology, Jain (Deemed-To-Be-University), Jayanagar, 3rd Block, Bangalore 560041, Karnataka, India*
[4]*MBBS Student, Mandya Institute of Medical Sciences, Mandya 571401, Karnataka, India*
[5]*General Practitioner, Bangalore 560029, Karnataka, India*
[6]*Department of Biochemistry, Akash Medical College, Bangalore 560029, Karnataka, India*
[7]*Software Engineer, Surya Software Systems Private Limited, Bangalore 560029, Karnataka, India*
[8]*Department of Biochemistry, School of Basic and Applied Sciences, Dayananda Sagar University, Bangalore 560029, Karnataka, India*
[9]*Department of Electronic and Communication, CMRIT College, Bangalore 560029, Karnataka, India*
[10]*Department of Electronic and Communication, New Horizon Engineering College, Bangalore 560029, Karnataka, India*
[11]*Department of Human Genetics, NIMHANS, Bangalore 560029, Karnataka, India*

Corresponding author
Ravish Huchegowda, MBBS, MD
Assistant Professor, Department of Neurochemistry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore 560029, Karnataka, India; Tel. 08026995908, 9741990094; E-mail: docravish@nimhans.ac.in; neuroravish@gmail.com

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ABSTRACT

Artificial intelligence (AI) is going to make huge difference in our day to day lives. AI is influencing the way we live and how we interact with the world, and there is much more to come in the years to follow with more advancement. As AI becomes more deeply integrated into our lives, it will become the new infrastructure powering a second industrial revolution. Bridging the link between current nano-sciences and AI, it can boost research in various disciplines and provide a new generation of information and communication technologies that shows a large impact in our society, probably providing the means so that technology and biology merge. Major changes in the education curriculum of medical professionals need to take place. But the rising cost of healthcare may prove to be an independent driving force to develop these technologies; meanwhile health information technology not only improves the quality of care, but also reduces its cost significantly. AI has the potentiality to reduce the cost of healthcare markedly and in future, this may translate into creation of promotional policies to accelerate investment in AI by rewarding the hospitals and the physicians who incorporates it into their workflow. While a terminator-like scenario is unlikely any time soon, the progression of artificial intelligence techniques and its applications will certainly be very exciting.

Keywords
Artificial intelligence; Deep learning; Healthcare; Diagnostics; Imaging.

Medical knowledge has undoubtedly expanded in the epoch of information technology making it impossible for a single human to keep track of all the knowledge. This has led to heavy application of computer and information technology in medicine, which resulted in evolution of artificial intelligence (AI).[1]

The intelligence can be described as the ability to perceive information and retain it as knowledge to be applied towards adaptive behaviors within an environment or context.[2] These computer systems use a number of different algorithms and decision-making capabilities as well as a vast amount of data, to provide a solution or response to a request. AI is the potentiality of a machine to synthetically imitate intelligence and thought patterns.[3] It is connected with the simulation of human intelligence processes by machines, especially computer systems. AI involves learning, reasoning and auto-correction.[4]

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Alan Turing made a turning point in the history of 1950's in which he speculated about the credibility of creating machines with true intelligence. He noted that "intelligence" is onerous to define and formulated famous Turing test. Turning test soon became the first serious approach towards artificial intelligence, test was a method of finding out whether or not a computer is able to think like a real person.[5]

In 1956 John McCarthy was considered as the father of AI, assembled a Dartmouth conference to pull the talent and expertise of others interested in machine intelligence. From that point on, the Dartmouth conference put forth together the founders in AI and served to lay the preliminary work for the upcoming AI researchers.[6] Diverse areas of AI include: neural networks, game theory, programming languages, expert systems, genetic algorithms, speech/handwriting recognition, vision, robotics, search algorithms, learning systems, natural language processing, common knowledge databases, logic, agents, planning, prediction and automation software.

COMPONENTS OF ARTIFICIAL INTELLIGENCE INCLUDE

- Perception
- Learning
- Reasoning
- Problem-solving
- Language-understanding

AI has multitudinous targets as mentioned with different techniques used for each. The foremost and much significant are artificial neural networks (ANNs) and an advanced version known as deep learning.

Artificial neural networks are algorithms which were inspired by the biological process of the brain. An ANN is set up for a specific application, such as pattern recognition or data classification. Deep learning, while sounding flashy is a term to describe certain types of neural networks and related algorithms that consume often raw input data.

Artificial neural networks and complex deep learning techniques are some of the most capable AI tools to resolve very complex problems and will continue to spread and leverage in the future.[7] A person can train their AI with their proclivity for levels of interaction and frequency. Unlikely, AI is not magic, it's applied science. But most importantly, AI deals with probabilities, not absolutes. The field of artificial intelligence has significantly unfolded many things with introduction of a number of sophisticated algorithms, some of which are capable of self-learning. Today Microsoft, Google, Apple, IBM and Amazon have adopted AI and have already succeeded in providing service to consumers.[8]

The Watson platform has been used in a number of disciplines within healthcare which comprises payers, oncology and patient risk assessment.[9]

APPLICATIONS OF ARTIFICIAL INTELLIGENCE

1. Personal health virtual assistant—Virtual patient assistant in monitoring and helping patients and health care providers.[10]

2. Advanced analytics and research—For example, in oncology cases, AI helps to detect abnormalities in X-rays and MRIs, in genomics to perform complex processing and in precision medicine to provide assistance in creating highly customized treatments for individual patients.[11]

In the example of IBM Watson, the AI has successfully applied its abilities to process structured and unstructured patient data. In the field of oncology, IBM Watson can provide evidence-based treatment recommendations for cancer patients.[12]

3. Personal life coach—Several hospitals have already initiated life coaching services as part of their overall care, however, with today's robust AI capabilities and mobile apps, patients can receive feedback on a number of data elements captured on their phone or wearable devices. As a result, AI provides personal life coach and creates a customized experience for each individual patient and offers proactive alerts as a feedback to physicians.[13]

4. Healthcare bots—Customer service and health care bots are the evolving areas in AI which is going to gain adoption soon as part of what healthcare providers offer. A Bot is an AI application patients can interact through a chat window on a website or via telephone to receive help with their requests. Bots helping 24/7 is near future emerging concept.[14]

Applications and Expert Systems of Artificial Intelligence Getting in Biomedical Field

a) Fuzzy expert systems in medicine: Fuzzy logic is a technique which uses data-handling purpose that allows ambiguity particularly used in medical field. This technique is used in various medical fields such as multiple logistic regression analysis and also used for the diagnosis of many diseases like lung cancer, acute leukemia, breast and pancreatic cancer. It can also predict the survival of patients suffering from breast cancer.[15]

b) Artificial intelligence to improve hospital inpatient care: The most welcome method of AI is a clinical decision support system. This expert system initially focuses on diagnosing the condition of the patient by giving demographic information and his symptoms. It recommends antibiotics for the treatment of infected patients.[16] This method uses Bayesian network which helps in diagnosis of varying form of cancer and for unexpected heart diseases.[17]

c) Artificial intelligence approaches for medical image classification: Some applications of AI are used for diagnostic sciences in categorization of different type of biomedical image such as identifying tumors in brain. Decision-support tools and model-based intelligent system are the most useful methods for the medical image classification for analysis and evaluation purpose.[18] described disorder would have been categorized as Chronic

progressive external ophthalmoplegia (CPEO) plus.

Application of ANN in Health Care Domain

a) MRI brain tumor analysis: To classify images in diagnostic science, ANN techniques are used. Least squares support vector machines (LSSVM) is another mechanism used for the diagnosis of normal and abnormal areas of brain from data of magnetic resonance imaging (MRI). Because of autonomous way to classify MRI image, it shows result with greater accuracy than other classifiers.[19]

b) Gastroenterology: This technique works by merging the methods of fuzzy systems and radial based function.[20]

c) Heart disease classification: Artificial neural network has substantiated its ability by working on the classification of heart disease.[21] In this technique for the classification of stroke, the input of sensor is given to the system that uses forward feed network with the rule of back propagation way.

d) Decision support system to diagnose nodules: Through the concept of ANN, the new proposed system is decision support system (DSS). A decision support system diagnoses nodules into benign and malignant or identifies its severity by analyzing the collected data.[6]

Regardless of its ability to see and listen, AI also smells. Humans aren't particularly aware of the richness of information that can be transmitted through the air and can be perceived by a highly sensitive olfactory system.[22] AI brought change into that by introducing machines in the laboratory which detects very small amounts of substances in the air. Those machines are called gas-chromatography mass-spectrometers or gas chromatography–mass spectrometry (GC-MS), which analyses the air to discover thousands of different molecules known as volatile organic compounds. AI system helps to reveal the illness by smelling human breathe substances.[23]

CONCLUSION

Artificial intelligence is going to make huge difference in our day to day lives. AI is influencing the way we live and how we interact with the world, and there is much more to come in the years to follow with more advancement.

Bridging the link between current nano-sciences and AI, it can boost research in various disciplines and provide a new generation of information and communication technologies that shows a huge scope. Major changes in the education curriculum of medical professionals need to take place. But the rising cost of healthcare may prove to be an independent driving force to develop these technologies; meanwhile, health information technology not only improves the quality of care but also reduces its cost significantly. AI has the potentiality to reduce the cost of healthcare markedly and in future, this may translate into creation of promotional policies to accelerate investment in AI by rewarding healthcare setup and healthcare provider incentives for using AI applications.

While a terminator-like scenario is unlikely any time soon, the progression of artificial intelligence techniques and its applications will certainly be very exciting.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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Original Research

Reirradiation of Recurrent Tumors in Central Nervous System in Children and Adolescents

Jose Alert, MD[1*]; Ivon Chon, MD[1]; Ramon Ropero, MS[2]

[1]*Department of Radiotherapy, Instituto Nacional de Oncologia y Radiobiologia, Havana, Cuba*
[2]*Department of Clinical Research, Instituto Nacional de Oncologia, Havana, Cuba*

[*]***Corresponding author***
Jose Alert, MD
Department of Radiotherapy, Instituto Nacional de Oncologia y Radiobiologia, Havana, Cuba; E-mail: jalert@infomed.sld.cu

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ABSTRACT

Objective
To report the epidemiology and associated health factors of children and adolescents who were subject to several rounds of irradiation at the National Institute of Oncology and Radiobiology in Havana, Cuba

Introduction
Irradiation is often an integral part of the treatment for central nervous system tumors. However, it is particularly challenging to use for the treatment of pediatric and adolescents, as it has been predicted to have drastic effects on the developing brain. Recurrence is frequent and treatment is limited with a few management options. These patients often underwent several parallel treatments including surgery and chemotherapy.

Material and Methods
A retrospective, observational study was conducted for 17 children and adolescents aged 3 to 18-years, who had central nervous system tumor recurrences and were reirradiated with a linear accelerator, three dimensional (3D) planning with a dose range of 36-56 Gy. Survival functions were estimated by Kaplan-Meier method.

Results
The study included eight medulloblastomas, (47.1%); two germinomas, (11.8%); three astrocytomas grade III, (17.6%); two brainstem tumors, (11.8%); one ependymoma, (5.9%) and one oligodendroglioma, (5.9%). All the patients responded to the treatment, with survival rates of 62.5% and 25 % at 1 and 2-years, respectively. The median survival time after reirradiation was 1.13-years. The median interval between radiation courses was 4.7-years. Median age at the first course of radiotherapy was 9-years, and at the second irradiation 14-years. Median total dose for the 2 irradiation courses were 100 Gy. Five patients are still alive with a survival time range of 7.5 and 0.9-years. The cognitive function in surviving patients was preserved, especially for over 12-years of age. Three had a Karnofsky-Lansky (K-L) scale of 100%, and two patients had a K-L of 90% and 70%, respectively.

Conclusions
Reirradiation is an option to be considered in patients with relapsed tumors in order to extend survival time, with a good cognitive functions.

Keywords
Central nervous system tumors; Recurrent central nervous system tumors; Reirradiation.

INTRODUCTION

In Cuba, tumors of the Central Nervous System (CNS) for children and adolescents account between 18 and 20% of all tumors in this group of age.[1-3] The main methods of treatment are surgery, radiotherapy, and chemotherapy.[4] Radiation therapy is a major treatment avenue in medulloblastomas, primitive neuroectodermal tumor (PNET) in some cases of germinomas consist of craneospinal irradiation (CS), and a supplementary boost to the post-operative tumor bed, followed by chemotherapy. In

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diffuse infiltrative brainstem gliomas (DIPG) local radiotherapy is applied, although in our institute it is combined with a monoclonal antibody (Nimotuzumab), which allows up to a 33 % expected survival for as long as 10-years.[5] Ependymomas receive only local irradiation plus chemotherapy, except in cases of extension to the spinal canal, where they received CS. Astrocytomas and glioblastomas only receive local irradiation and in some cases chemotherapy.

The irradiation in CNS tumors in the pediatric ages is associated with damage to uninvolved tissues, which may negatively effects cerebrovascular functions, neurotoxic, neurocognitive, endocrine, psychosocial and the quality of life.[6,7] In patients with recurrent tumors[8] reirradiation has been proposed as a modality of treatment. This reirradiation could be associated with the risk of injury[9] in varying degrees. Thus it is necessary to weigh benefits *versus* toxicity. In order to offer benefits, newer approaches in radiation therapy are employed, as intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery and radiation therapy with particles and so on.[10] The present study is a report for a series of 17 children and adolescents who received reirradiation for relapse of the primary tumor.

MATERIALS AND METHODS

This is a retrospective, observational, non-randomized study of a series of 17 children and adolescents, irradiated at the Instituto Nacional de Oncologia y Radiobiologia, in Havana, Cuba. The patients were treated for the first time between the period of January 1999 and August 2016, with a periodical evaluation until November 2018, or to the time of death. The intention of reirradiation was chosen according to symptoms, prior treatment history and especially in the interest of patients, family and the referring physician. In all cases, a consent form was obtained. The dates for analysis were obtained from the medical records and included data of primary irradiation, data of relapse and reirradiation, as well as information regarding the irradiation doses, data of last follow-up, disease status, and date of death. Overall survival function was estimated by the Kaplan-Meier method.

Initial treatment consisted of surgery, when possible (biopsy or partial or gross resection), and then the first course of radiotherapy, and chemotherapy, if indicated. In all patients, reirradiation was accomplished with a linear accelerator (LINAC) machine, planed in three dimensional (3D) in 2 cases IMRT and with image-guided radiation therapy (IGRT) in 3 cases, with a daily dose of 1.8 Gy, 5 sessions per week of treatment. For two patients with diffuse intrinsic pontine gliomas (DIPG), the irradiation was combined with the monoclonal antibody, Nimotuzumab. The 8 patients with the diagnosis of medulloblastoma received a CS dose of 23.4 Gy in the first irradiation, two of them were reirradiated in CS with 20 Gy, and all with a dose of 46 Gy in tumoral volume. Germinomas received 23 Gy in CS in one patient and 30 in tumor, and in reirradiation 46 Gy in the tumor. Astrocytomas grade III received between 56 and 59.4 Gy, and 54 to 56 Gy in reirradiation. One patient with the diagnosis of ependymoma received the first dose of 54.4 Gy in the tumor and CS dose of 19.6 Gy and 44 Gy in the tumor during the second course of irradiation. Finally, one patient with the diagnosis of oligodendroglioma received 54 Gy in the first irradiation and 54 Gy in the second.

Twelve patients were treated with surgery at the time of recurrence, which ranged from the only biopsy to partial resection. Twelve received also chemotherapy and 3 monoclonal antibodies, according to the treatment plan in our department.[11]

Table 1. *Characteristics of the Reirradiated.Patients*

Id	Sex	Diagnosis	Time-1 (Months)	Dose Reirradiation (Gy)	Cumulative Dose (Gy)	Current Status	Tos (Months)
1	M	Brainste m	44	54	90,0	Alive	90
2	F	Brainste m	21	34	88,2	Dead	14,4
3	M	Medulloblastoma	18	46	80,0 21,0 CS	Dead	10,8
4	M	Medulloblastoma	89	46,0	100,0 23,0 CS	Dead	18,0
5	M	Medulloblastoma	104	50,0	104,0 23,0 CS	Dead	18,0
6	F	Medulloblastoma	131,0	50,0	104,0 23,0 CS	Dead	12,0
7	F	Medulloblastoma	56,0	45,0 23,0 CS	99,0 43,0 CS	Dead	20,4
8	M	Medulloblastoma	15,0	52,2	106,0 23,0 CS	Alive	48,0
9	M	Medulloblastoma	83,0	54,0 20,0 CS	108,0 43,0 CS	Alive	26,4
10	M	Medulloblastoma	34,0	54,0	108,0 23,0 CS	Alive	42,0
11	F	Germi1oma	83,0	44,0 23, o CS	76,0 23,0 CS	Dead	14,4
12	F	Germi1oma	32,0	30,0	76,0	Dead	9,6
13	M	Anaplastic Astrocytoma	27,0	54,0	111,4	Dead	8,4
14	F	Astrocytoma GIII	119,0	57,0	114,6	Dead	9,6
15	M	Astrocytoma GIII	22,0	56,6	112,6	Dead	1,3
16	M	Ependymoma	12,0	42,0	96,0	Alive	8,4
17	M	Oligodendroma	109,0	54,0	108,0	Dead	14,4

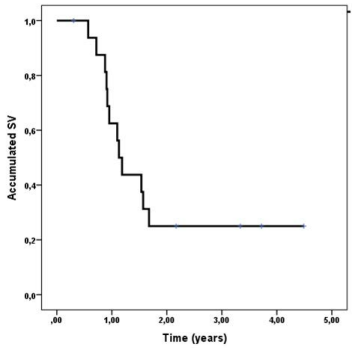
Time-1:Time between first and second irradiation; CS: Craneospinal irradiation;TOS: Tine of survivalafter reirradiation

RESULTS

Seventeen patients were included in this series: 11 male and 6 female, with a median age at the time of the reirradiation of 14.0-years CI 95%.[12-17]

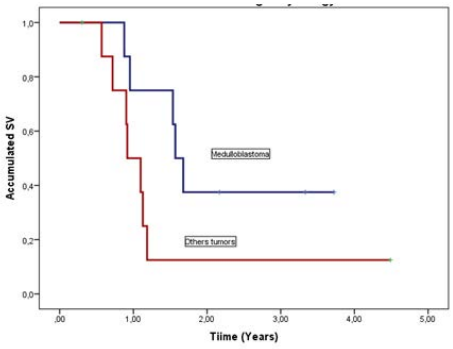
Among those reirradiated the median of time of disease relapse was 8 to 9-years from the first to the second irradiation. Four patients received CS plus tumor volume reirradiation, while the rest only to the primary site of recurrence. Five patients are alive with a follow-up year range between 8 and 1-year. Median total dose received with both irradiations was of 100 Gy IC 95% (94.2- 108 Gy). The estimated survival rate was 62.5% at 1-year and 25% at 2-years (Figure 1), with a median survival time of 1.13-years CI 95% (0.96-1.30)

Figure 1. *Overall Survival Since Time of Reirradiation*



Eight patients with medulloblastoma, constituting the 47.1% of cases, with a survival rate of 37.5% at 2-years compared with 12.5% for other tumors and a median survival time 1.57-years CI 95%(1.38-1.76) compared with 0.92-years CI 95%(0.65-1.19) for other tumors. There was not a statistically significant difference between the two groups (p=0.072) (Figure 2).

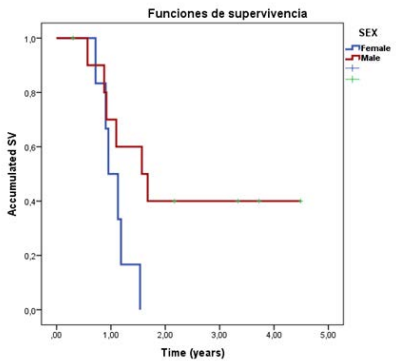
Figure 2. *Survival Functions from Re-Irradiation According to Histology of Tumors*



All the relapse cases who not received reirradiation died between 3-months to one year.

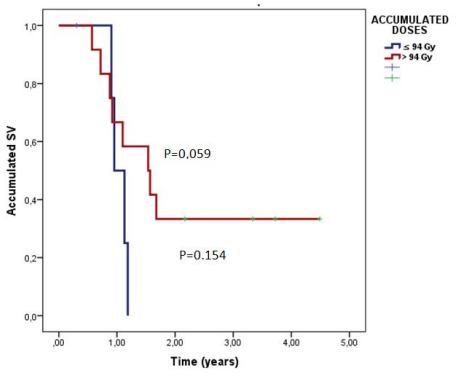
All surviving patients were male (2-year survival, 5 in total, 40%), with a median estimation of 1.57-years CI 95% (0.67-2.46)]; Female patients median survival time estimation was 0.953-years [CI 95% (0.6-1.22)]. Median survival time according to gender is significant in the clinical response, although there was no statistically significant difference between the groups (p=0.059) (Figure 3).

Figure 3. *Survival Functions from Reirradiation According to Sex.*



The survival for 2-years percentage for the patients who received >94 Gy was 33% and their median survival time was 1.09-years [CI 95% (0.57-1.63)]. This was higher than the survival for 2-years percentage for the patients who received ≤94 Gy (14.3%). The latter group had a median survival time of 1.19 [CI 95% (1.04-1.33)]. However, the difference between the two groups was not statistically significant (p=0.154) (Figure 4).

Figure 4. *Survival Functions from Reirradiation According to Total Accumulated Dose*



We found preserved cognitive function in surviving patients, especially over 12-years of age; 3 had a Karnofsky-Lansky (K-L) scale of 100%, 1 had a K-L of 90% and 1 had a K-L of 70%.

DISCUSSION

The management of CNS tumors in children and adolescents include the use of surgery, and/or irradiation, chemotherapy, and monoclonal antibody.[5-29] A response is frequent, nevertheless long-term survival is observed between 20% to 80% of those patients.[11,17,19] During their evolution, there are relapses, that could

occur a few months to years after the first irradiation.[9,13-15]

Rao et al[8] reported reirradiation in 67 children with recurrent CNS malignancies and found that the median overall survival after the completion of repeated radiation therapy (RT) was 12.8-months for the entire cohort and concluded that CNS reirradiation could be a reasonable treatment option. In our study, a similar range of median overall survival was obtained (12.2-months).

Several studied reported positive outcomes for reirradiation. Wetmore et al[21] reported 14 patients with recurrent medulloblastoma, with 6 still alive with a median follow-up of 12.1-years (range 7.2 -14.6-years) and concluded that the use of reirradiation may prolong survival, but that the expected 2-year overall survival after disease progression is less than 25%. In our study, we had 8 patients with recidivant medulloblastomas, with 3 still alive (37.5%). In an overview of treatment options for recurrent ependymoma and medulloblastoma, Nieder et al[24] concluded that reirradiation was associated with a better outcome. In reirradiation of recurrent CNS tumors in children, Chang A et al[26] reported a median follow-up time for survivors of 97.4-months, with 5 of 11 being alive. Lobon-Iglesias MJ et al[27] found an improved survival of 7.5 *versus* 4-months with a second course of radiotherapy in diffuse intrinsic pontine glioma (DIPG). In addition, Waxweiler T et al[29] reported the use of hypofractionated irradiation in 23 patients, with 3 or 5 fractions, with a median tumor stabilization of 10.5-months.

With the reirradiation, we evaluate the possibilities of improving survival. The dose of reirradiation in our study was not always the same for all cases and was based on clinical factors and previous dose received. The eight patients reirradiated for medulloblastoma receive 37.5% of survival, better survival compared with the rest of patients. There has been reported complications in the post radiation and reirradiation evolution[4,7,8,23] nevertheless we did not found significant complications in our patients, as all deaths were due to a progression of the primary tumor.

There has been a debate about the use of reirradiation at the time of relapse because of possible improvement of survival, however, this can be associated with higher toxicity.[9,23] Perhaps the side effects that are associated with reirradiation should be overlooked since the risk of death by the progression of the tumor is high for recurrences. Reirradiation could increase the time of survival, and amelioration of quality of life, which are very important factors for patients and parents. Even a third course of radiation therapy had been reported Tsang D et al[25] and may be helpful in selected cases of ependymomas, for local control and palliation.

CONCLUSION

In this series, reirradiation is an option for the treatment of recurrence of CNS tumors, in order to increase the time of survival, even palliation, with good cognitive functions.

IRB APPROVAL

This study has been approved by the Ethical Committee of Institute of Oncology.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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Mini Review

Vision in the Hearing-Impaired: Enhanced or Deprived?

Jaikishan Jayakumar, PhD

Senior Project Advisor, Center for Computational Brain Research, Indian Institute of Technology, Madras Guindy, Chennai 600036, India

Corresponding author
Jaikishan Jayakumar, PhD
Senior Project Advisor, Center for Computational Brain Research, Indian Institute of Technology, Madras Guindy, Chennai 600036, India; Tel. +91 44 2257 8921; E-mail: jaikishan.jayakumar@gmail.com

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ABSTRACT

By definition, the hearing-impaired lack one functioning sensory channel that transmits information to the brain. What effect does this have on the perceptual systems of the brain is the subject of the review. There are currently two hypotheses on this matter: The perceptual deficit hypothesis that states that lack of a functioning sensory input affects the development and maturation of other sensory channels and results in the impaired functioning of our senses. The second is the perceptual compensation hypothesis which states that when one sensory system is affected, the processing resources within the brain are reallocated to the other sensory system resulting in an enhancement of the other systems. This review is about both these hypotheses and attempts to answer the question if the hearing-impaired can really "see "better. We highlight the important findings from both these hypotheses and provide growing evidence for the perceptual compensation hypothesis.

Keywords
Hearing-impaired; Vision; Perceptual deficit; Perceptual compensation; Audition.

INTRODUCTION

We perceive our environment using a wide variety of senses including vision and audition and rely upon them individually or in combination to make sense of our world. Conventional neuroscience dictates that the neuroplastic processes within the brain allow for the efficient use of its available resources. This results in the phenomenon that is not necessarily beneficial, for example the expansion of somatosensory maps following limb amputation results in spurious perceptual events known as "phantom limb pain"[1] or untreated amblyopia results in the profound loss of visual acuity.[2] How this process works during the complete loss of sensory information from one modality is still a topic of debate. One theory suggests that developmentally the loss of one sense, say hearing, will adversely affect other senses as well, this is known as the perceptual deficit hypothesis. On the other hand, there is mounting evidence that when one sensory system affected, there is the reallocation of resources to another system resulting in an enhancement of other sensory systems. This is termed as the perceptual compensatory hypothesis and is believed to be the direct result of the cross-modal plasticity properties of the brain. In this mini-review, we aim to explore both these hypotheses.

The Perceptual Deficit Hypothesis

The first hypothesis states that a significant deficit in one sensory modality affects the development and organization of the other sensory systems. This is termed as the perceptual deficit hypothesis. In the case of hearing-impaired, the perceptual deficit hypothesis predicts hearing-impaired individuals will exhibit poorer visual and tactile perceptual performance.[3] The secondary assumption is that the lack of one sensory input adversely affects the complex tasks such as language which needs significant interaction between the different senses.[4]

The hypothesis mainly came about because of the increased prevalence of vision-related abnormalities in the congenitally hearing-impaired that has been reported in the literature.[5,6] The seminal studies by Pollard and Neumaier[5] and by Mohindra[6] where visual problems were found to be much more in hearing-impaired school going children as compared to normal school going children. There is some evidence supporting this hypothesis as the hearing-impaired perform significantly worse

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than hearing children in basic threshold perceptual tasks.[7]

The Perceptual Compensatory Hypothesis

The perceptual compensatory hypothesis originated as a direct result of Neville et al,[8] who used visually evoked potentials in hearing-impaired individuals and showed an enhanced recorded signal which implies that the lack of auditory experience somehow reorganized to enhance the visual processing abilities. This work has since been repeated using a wide variety of techniques including electroencephalogram (EEG);[9] magnetoencephalography;[10] functional magnetic resonance imaging[11,12] with similar findings. But the perceptual implications of this enhanced signal are still unclear.

DISCUSSION

Basic Visual Thresholds in the Hearing-Impaired

One of the first studies in determining the differences in brightness sensitivity between the hearing-impaired and the hearing individuals was performed by Bross et al.[13] They revealed no significant differences between the hearing-impaired and hearing individuals. Similar results were obtained by Bross and Saurwein[14] for visual flicker thresholds. This is an indirect contradiction to the compensatory hypothesis.

Other parameters including contrast sensitivity[10] or both center and periphery (2 deg around fixation)[15] (see also, Bavelier et al[11,12] for further evidence of comparable luminance change detection in hearing-impaired and hearing individuals). Interestingly, Stevens and Neville[15] showed that the hearing-impaired exhibited an enlarged field of view (about 196 cm^2) with respect to hearing controls (180 cm^2), in a kinetic perimetry task.

Performance of the hearing-impaired in motion discrimination task shows that there are no significant differences in the performance of hearing-impaired and hearing individuals other than a small shift in the preferred hemifield, where the hearing-impaired preferred the right field compared with the left field.[16-18] Temporal perceptual thresholds for any eccentricities and stimuli time or order showed any differences in the performances of the hearing-impaired when compared with hearing individuals.[14,19,20,21]

Visual Performance in the Hearing-Impaired? Sensitivity *vs* Reactivity

If the hearing-impaired do not show any differences in the various visual discrimination tasks with no evidence of either worse performance (discrediting the perceptual deficit hypothesis) or enhanced (against the perceptual compensation hypothesis), is there any evidence of cross-modal plasticity within the brains of the hearing-impaired and if so what is the behavioral implications of it?

The seminal study by Loke and Song,[22] was among the first to answer this question. They compared 20 congenital or early-hearing-impaired high school students with 19 hearing controls, and by measuring the reaction times for a simple detection task at either fixation (0.5˚), or in the visual periphery (25˚), they were able to show that the hearing-impaired responded faster than hearing controls (85 ms on average), but selectively for targets appearing at peripheral locations. The differences in the central fixation did not reach statistical significance (38 ms). This result was later confirmed by[23] who not only showed that the simple detection of one shape from the other was faster for the hearing-impaired than hearing participants (70 ms on average); but also, the simple detection and subsequent discrimination of the peripheral shapes to be faster in the hearing-impaired than hearing participants (56 ms).

Manipulation of attentional mechanisms by the classical cue-target paradigm[24] has shown that the visual attentional process can be redirected in the hearing-impaired individual.[25] This interpretation is further supported by Colmenero et al[26] who used a task of pressing key "O" appeared on the computer screen. The target appeared for 150 ms, at 20˚ of eccentricity to the left or the right of central fixation and was preceded by a vertical mark delivered at the exact target location (valid condition, 53% of the trials), on the opposite side with respect to the target (invalid condition, 13% of the trials) or on both sides (neutral condition, 33% of the trials). Stimulus onset asynchrony (SOA) between the cue and the target varied between 125-250 ms. Hearing-impaired participants were faster than hearing control at detecting the target (43 ms on average) in this task which involves evoking the exogenous and endogenous attentional mechanism and the interpretation was that the attentional mechanisms including inhibition of return (IOR),[27] which happens as a result of prior location already attended to in the task are somewhat less enduring in the hearing-impaired than in the hearing controls.

Flanker interference tasks, which measure the allocation of attentional resources in the visual scene, have shown that there is a larger interference of distractors in the periphery in the hearing-impaired than the hearing individuals.[28-31] These differences only serve to indicate that the allocation of visual attention resources is quite different in the periphery of hearing-impaired individuals as compared with hearing controls, most likely as a result of cross-modal plasticity in the brain.

The above-mentioned findings indicate that the visual abilities demonstrated in the hearing-impaired do not show any trends towards either an enhancement or suppression. This may be because of a few reasons namely, 1) hearing impairment, by definition, consists of a multitude of factors which cannot be classified as one condition.[32] 2) the definition of the periphery, where the hearing-impaired show enhancement in their reactivity is often muddled. The range of periphery defined in various papers ranges from 1 degree from fixation onwards (for e.g. 8 degrees from fixation in).[9]

CONCLUSION

The past 50 odd years of research on visual cognition of hearing-impaired individuals have not given a clear answer as to whether

the hearing-impaired see better. However, there is certainly a better reactivity rather than threshold enhancement in the hearing-impaired particularly in complex visual tasks such as visual attention. This fact and the related findings provide circumstantial evidence at the least towards the compensatory hypothesis. The role that this peripheral attentional resource enhancement can further be considered as a compensatory mechanism for the allocation of attentional resources which are much more efficient in audiovisual integrative conditions.

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Brief Report

The Praxitype: An Improved Interpretation of Genotype-Phenotype Variation

Vincent M. Riccardi, MD, MBA

Department of Neurology, The Neurofibromatosis Institute, NTAP F.S. Collins Scholar Mentor, 5415 Briggs Avenue, La Crescenta, CA 91214, USA

**Corresponding author*
Vincent M. Riccardi, MD, MBA
Department of Neurology, The Neurofibromatosis Institute, NTAP F.S. Collins Scholar Mentor, 5415 Briggs Avenue, La Crescenta, CA 91214, USA;
Tel. 818-957-3508, 818-957-4926; E-mail: riccardi@medconsumer.com

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ABSTRACT

There is a need for an understanding of the genomic reality that realizes a connector between the genotype and the phenotype by addressing HOW the genotype actually manifests as the phenotype, as a function of the locus or the allele, mutated, variant or wildtype. That understanding is encompassed by the notion of the PRAXITYPE, which assembles and presents the available answers to the HOW!

Keywords
Praxitype; Genotype-Phenotype variation; Genome variation; Neurological disorders; Neurofibromatosis type 1 (NF1).

INTRODUCTION

It is hard to imagine anything more complicated than the organization and function of the mammalian-especially human-nervous system. For a while it seemed simplified by single gene mutations being the basis for complex neurological disorders: specify the mutated gene and "everything was accounted for." A bit more thought and experience made it clear that this was an over-simplification: HOW the mutant gene was expressed was at least as much of a factor as WHICH gene was mutated. Obviously, there were myriad superimposed factors, especially genetic ones. In short, the HOW of gene expression is largely explained by epigenetic factors, such as microRNA, the "availability" of the gene (mutant or otherwise), regulatory biochemical networks (e.g., Ras), etc.

That is, we no longer can rely on the genotype, the "what" of pathogenesis: we also need insight into the "How." I have specified the latter as the Praxitype! Thus, when we look to assess, to evaluate neurological disorders from a genetic vantage point-that is, in terms of "genome variation"- there is more to it than the Genotype, the allele at a specific genetic locus. What follows is an introduction to what is beyond the genotype that addresses genome variation and how genes are fully manifest, critical for understanding genetic neurological disorders!

DISCUSSION

The phrase, "Genome Variation," implies, if not declares, that the relationship of the details regarding an individual's genome (i.e., genotype) to the details of that individual's combination of traits (i.e., phenotype) is variable, sometimes to the point of being confusing or even incomprehensible. Said more succinctly, genotype-phenotype correlations are not as fixed or predetermined as they are usually presumed to be. That is, knowing the genotype, whether in terms of a single locus or a combination of loci, is unlikely on its own specify the derivative phenotype. At the least, one would wonder whether another factor or set of factors was at play. I say there is another factor, and that it is the matter of how the genotype is manifest, how the gene (locus or allele) is put into practice. How the gene is literally put into practice can be referred to as the praxitype, respecting the same etymology of the terms, genotype and phenotype, as I have proposed and employed several times before.[1-5]

In an earlier era, we naively presumed that knowledge of the genotype (γ) readily revealed the phenotype (φ), and vice versa. It was that simple–there was no interloper: γ and φ supposedly just revealed each other. For example, homozygotic loss of the phenylalanine hydroxylase gene translated to phenylketonuria; and heterozygosity for a Huntingtin gene mutation translated to

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Huntington's disease. Conversely, the clinical presence of Sickle Cell Anemia or of Neurofibromatosis type 1 (NF1) translated to homozygosity for certain β-hemoglobin gene mutations and heterozygosity for an NF1 gene mutation, respectively. Such translations were both expected and sufficient.

However, on multiple levels it has gotten much, much more sophisticated and complicated. Details of the genotype just aren't enough to reveal or account for the phenotype. We need to know additional details–the obvious and still undiscovered details of how the genotype actually translates to the phenotype. What does that segment of deoxyribonucleic acid (DNA) actually do and what is done to it and its products? How do the elements of the phenotype initiate and progress in terms of the DNA, its transcribed messenger ribonucleic acid (mRNA), and the latter's protein translation? How are other gene loci involved? How does the genotype become the phenotype ($\gamma \rightarrow \varphi$)? The realistic answers utilizes an intermediary, the praxitype (π). The answer(s) to "How?" is a matter of $\gamma \rightarrow \pi \rightarrow \varphi$.

A.R. Gehrke and his co-workers, in a March 2019 publication in Science,[6] directed themselves at the genetic "regulatory landscape of whole body regeneration" of acoels, which "regulatory landscape" the authors consistently and satisfyingly referred to as the "gene regulatory network" (GRN). I presume that the GRN, so considered, is overlapping with the notion of the Interactome, as used by other authors,[7-10] and contributes to the notion of the praxitype, as I have used and promulgated it (vide supra). Their efforts and mine, individual or combined, promote the same notion–it is not merely the genotype, but how a gene (locus, allele, mutant, etc.) is put into practice; how it is manifest as a phenotype. Or, more precisely, how the genotype is put into practice as a function of the multiple regulatory elements impinging on or blatantly determining the gene's/allele's expression.

In order to understand, to comprehend, to expand genetic regulation, that is, genetic finesse, there must be an interloper between the genotype and its variable phenotypes. That interloper is the praxitype! In order to discuss meaningfully the relationships of γ and φ, there must be categorical appreciation and articulation of the π. Resorting to the praxitype will (respecting it's same logic and same etymology as the phrases/concepts, genotype and phenotype) become increasingly suitable and necessary for understanding and broadcasting the relations between a locus or allele and its consequences. In my own work on the disorder, Neurofibromatosis 1 (NF1), over some 47-years,[11,12] my regular, intense utilization of the praxitype paradigm has magnified for me the veracity and practicality of this logic. The NF1 gene's myriad varieties of causative germinal intragenic mutations or whole-gene-deletions have made it imperative that we uniformly and systematically acknowledge and exploit the interloper that we had otherwise been pursuing piecemeal and inconsistently as the interactome or "gene regulatory network." Allelic interactions, pseudogenes, the timing and intensity of chromatin methylation, micro-RNAs, protein and mRNA degradation, and other aspects of how the genetic code is translated are the substance of the praxitype and our understanding and implementing genetic knowledge. I encourage–downright urge, even coerce–our genetic colleagues and acolytes strongly to consider this approach. Just do it–incorporate this jargon and concept into your writing and watch the salutary impact.

In my introduction to the substance of neurologic diseases, I emphasized their complexity and How this complexity unfolds. Likewise, in my acknowledgment of my involvement with NF1, I emphasized NF1's complexity and how it unfolds. There can be no greater consideration of the complexity and challenge relevant to the details of neurological disease and the Praxitype than the unfolding of NF1's phenotype.[10,13-15] Von Recklinghausen disease, or NF1, is likely the key to elucidation of the Praxitype. Thus, increasingly there is resort to concerns about How the NF1 phenotype becomes manifest. How does one disorder account for cognitive compromise, skeletal deformities (e.g., sphenoid wing dysplasia), three types of neurofibromas and multiple cancers, most commonly neurofibrosarcomas, and on and on and on? Plain and simply, NF1 is likely the disorder to explicate the praxitype and teach us about HOW a phenotype eventuates.

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Review

Stroke Prevention: Extra-Cranial Carotid Artery Therapy

Christopher J. White, MD*; Jose David Tafur Soto, MD

Department of Cardiology, John Ochsner Heart & Vascular Institute, Ochsner Medical Center, 1514 Jefferson Highway, New Orleans, LA 70121, USA

Corresponding author
Christopher J. White, MD
Professor and Chair Medicine and Cardiology, Department of Cardiology, John Ochsner Heart & Vascular Institute, Ochsner Medical Center, 1514 Jefferson Highway, New Orleans, LA 70121, USA; Tel. 504-842-3717; Fax. 504-842-4790; E-mail: cwhite@ochsner.org

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ABSTRACT

A patient-centered approach is reasonable in candidates for carotid revascularization. The patient and their physician should discuss the available treatment options, including revascularization (either carotid artery stenting (CAS) or carotid endarterectomy (CEA)) with their physician. There remains uncertainty regarding the value proposition for revascularization (either CEA or CAS) in asymptomatic patients as a strategy to prevent stroke. Investigation continues into characterizing high-risk carotid plaque subsets, but until that data is available, physicians and patients should continue to strive to achieve the best outcomes with the information that is currently available. The other consideration in asymptomatic patients is that there is a cumulative benefit to revascularization that is dependent on life expectancy. However, the magnitude of the benefit of revascularization, over the longer term in the setting of multifactorial medical therapy, including statins, is not known.

Keywords
Carotid endarterectomy; Carotid stent; Angioplasty; Embolic protection devices.

INTRODUCTION

Nearly 800,000 strokes occur each year in the United States, and over 120,000 Americans die annually from stroke.[1] Atherosclerotic carotid artery disease is the leading cause of non-cardioembolic ischemic strokes.[2] Carotid plaque most often causes cerebrovascular events due to plaque rupture with atheroembolization, rather than carotid artery occlusion (<20% of ischemic strokes) with thrombosis.[3]

The risk of stroke related to carotid artery stenosis is strongly related to the presence or absence of preceding symptoms (transient ischemic attack (TIA), or stroke). Symptomatic patients have a much greater (5 to 10-fold) risk of stroke when compared to asymptomatic patients, but the ratio asymptomatic to symptomatic patients undergoing carotid revascularization is 2.5:1.[4] A TIA is an important warning sign associated with a 30% risk of stroke within 6-months.

ANATOMIC IMAGING

Digital subtraction angiography (DSA) is the gold standard for defining carotid anatomy with the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method of stenosis measurement the most widely accepted methodology. However, invasive cerebral catheter-based angiography carries a risk of cerebral infarction of 0.5% to 1.2%; therefore, non-invasive imaging should be the initial strategy for evaluation. Carotid doppler ultrasound (duplex) imaging, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) are the non-invasive methods of stenosis assessment. Duplex imaging is the best initial choice given its safety profile, low-cost, and wide availability.

Carotid ultrasound has a high accuracy for carotid restenosis after endarterectomy. Criteria have been proposed to diagnose severe carotid stenosis. In most cases, >80% stenosis correlates with systolic velocity >300 to 400 cm/s, diastolic velocity >100 to 135 cm/s and ratio of internal carotid artery/common carotid artery (ICA/CCA) systolic velocity of >3.5. Other factors such as contralateral occlusion diminished cardiac output from severe left ventricular dysfunction, aortic stenosis, and common carotid artery stenosis may make these measurements less reliable.

MEDICAL THERAPY

Current anti-atherosclerotic medical therapy has advanced significantly since the 1990's early trials with the development of angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), direct renin blockers, statin drugs and

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newer antiplatelet agents. Medical therapy for carotid atherosclerosis should focus on preventing stroke and stabilizing atherosclerotic lesions to prevent plaque rupture and atheroembolization. Blood pressure control is of paramount importance since it is a primary risk factor for stroke; it is also a risk factor for atrial fibrillation and myocardial infarction which both increase the likelihood of stroke.[5] Smoking cessation and control of diabetes mellitus are also important factors in reducing cardiovascular events.

Cholesterol lowering with statin drugs in patients treated for cardiovascular disease prevention demonstrated a lower the risk of stroke.[6,7] It is possible that statins prevent strokes through pleiotropic effects on endothelial function and plaque stabilization in addition to their lipid-lowering properties. Current American Heart Association/American Stroke Association (AHA/ASA) stroke guidelines endorse the American College of Cardiology (ACC)/AHA recommendations for the use of statins which recommend that high-intensity statin therapy be initiated or continued as first-line therapy in patients ≤75-years of age that have clinical atherosclerotic cardiovascular disease unless contraindicated and it should be considered in those >75-years of age if the benefit outweighs the risk.[8]

The stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial demonstrated that high-dose atorvastatin is effective for secondary stroke prevention in patients with an ischemic stroke or TIA but no coronary heart disease.[6] The justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) study showed that rosuvastatin treatment in patients with normal cholesterol levels but elevated levels of C-reactive protein is effective in reducing the rate of stroke.[7]

The antithrombotic trialists' collaboration meta-analysis of high-risk patients, found that antiplatelet therapy reduced the occurrence of any vascular event by 25%, non-fatal stroke by about 25%, and death due to vascular cause by about 15%.[9] Aspirin was the most widely used drug with doses of 75-150 mg as beneficial as higher doses. Among patients with symptomatic vascular disease, including stroke, the clopidogrel *versus* aspirin in patients at risk of ischemic events (CAPRIE) trial demonstrated that clopidogrel 75 mg daily was associated with an 8.7% relative risk reduction in ischemic stroke, MI, or vascular death *versus* aspirin 325 mg daily (5.32% *vs.* 5.83% p=0.043).[10] For the patients who presented with stroke, however, the benefit was not significant.

In the management of atherothrombosis with clopidogrel in high-risk patients (MATCH) trial, clopidogrel 75 mg daily plus aspirin 75 mg daily was compared to clopidogrel 75 mg daily alone.[11] Among stroke patients, the combination regimen did not improve vascular outcomes but significantly increased the number of major and life-threatening bleeding complications.

The clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial included over 4,300 patients with a prior TIA or stroke and found that aspirin 75-162 mg daily was as effective as aspirin plus clopidogrel in preventing future MI, stroke, or cardiovascular death in patients with multiple risk factors or with clinically evident cardiovascular disease.[12] This study also found that 81 mg of aspirin is the optimal dose for safety and efficacy for prevention.

The AHA/ASA guidelines recommend that all patients with carotid atherosclerosis be placed on anti-platelet medications. Aspirin 81 or 100 mg daily or clopidogrel 75 mg daily alone in patients who cannot tolerate aspirin should be administered for secondary prevention of stroke.[8]

SURGICAL THERAPY TO PREVENT STROKE

Asymptomatic Patients

There have been three historical randomized studies comparing carotid endarterectomy (CEA) to antiplatelet (aspirin) therapy in the treatment of moderate (≥50%-60%) carotid stenosis in patients without focal neurologic symptoms, that are all made less relevant by the effectiveness of modern anti-atherosclerotic therapy..

The veterans affairs cooperative study (VACS) randomized 444 men with asymptomatic carotid stenosis of ≥ 50% by angiography to medical therapy plus CEA or medical therapy alone.[13] All patients were assigned aspirin 650 mg twice daily though many did not tolerate that dose. The periprocedural 30-day risk of stroke or death in the CEA group was 4.7%. At nearly 4-years of follow-up, the ipsilateral neurologic event rate (including TIA, transient monocular blindness, and fatal and nonfatal stroke), was 8% in the surgical arm and 20.6% in the medical arm (p<0.001). The risk of ipsilateral stroke alone was reduced from 9.4% with medical treatment to 4.7% (p<0.06) with CEA. Notably, there was no difference between surgery and medical therapy for combined stroke or death.

The asymptomatic carotid atherosclerosis study (ACAS) randomized 1,662 asymptomatic patients with carotid stenosis ≥60% to medical therapy or medical therapy with CEA.[14] All patients received aspirin 325 mg daily. Angiography was performed only in the CEA group and was associated with a 1.2% periprocedural risk of stroke. The 30-day risk of stroke or death in the surgical group, including the risk associated with angiography, was 2.7%. The projected 5-year risk of ipsilateral stroke and any peri-operative stroke or death was reduced from 11% in the medical arm to 5.1% with CEA. The number of patients needed to treat (NNT) with surgery to prevent 1 ipsilateral stroke at 5-years was 19. The benefit for women (17% reduction in events) was less than for men (66% reduction).

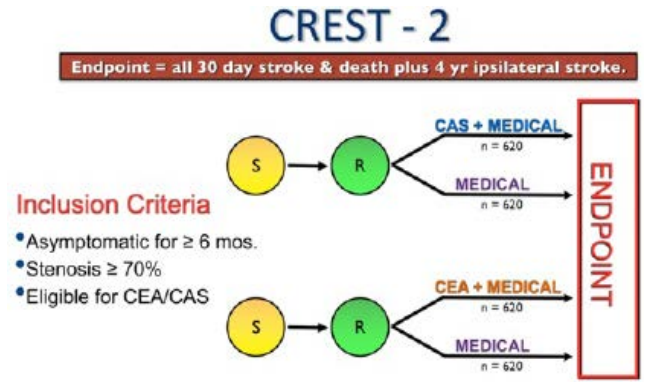
The asymptomatic carotid surgery trial (ACST) evaluated 3,120 asymptomatic patients with ≥60% carotid stenosis by ultrasound. Patients were randomized to CEA with medical management or medical management alone. Drug treatment was left to the discretion of the patients' primary physicians—this usually included antiplatelet medications, antihypertensive therapy, and, in the later years of the study, lipid-lowering agents. The 30-day peri-operative risk of stroke or death was 3.1%. The 5-year risk of peri-operative death or total stroke was reduced from 11.8% to 6.4% with CEA and approximately half the strokes were disabling.

The benefit of surgery was significant across all degrees of moderate to severe stenosis (60-90% stenosis) however, CEA did not reduce overall stroke and death, and did not show any benefit in women or in patients older than 75-years of age.[15]

Current data estimates the risk of progression of an asymptomatic carotid artery stenosis to occlusion with modern medical therapy to be 1% per year. In a cohort of 3,681 patients with yearly duplex follow-up, 316 (8.6%) asymptomatic patients had occlusion that occurred during serial ultrasound observation. Of these, 80% (254) of the occlusions occurred before the initiation of modern intensive medical therapy.[16]

In asymptomatic patients, the AHA/ASA guidelines recommend it is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of peri-operative stroke, MI, and death is low (<3%) and life expectancy is at least 5-years.[8] The CREST-2 trial is currently enrolling asymptomatic patients and features 2 parallel arms (Figure 1) with one arm comparing CEA with best medical management *versus* best medical management alone.

Figure 1. *CREST-2 Trial Design Compares Two Parallel Arms*



CEA with best medical therapy to medical therapy alone and CAS with best medical therapy to best medical therapy alone. The trial does not compare CEA to CAS as they were deemed equal alternatives during trial design.

Symptomatic Patients

Symptomatic carotid disease is defined as focal neurologic symptoms of sudden onset within 6-months and in the appropriate carotid artery. Prior to the development of modern anti-atherosclerotic therapy with antiplatelet, antihypertensive, and lipid-lowering therapy and diabetes control, the natural history of symptomatic carotid artery stenosis in the 1990's was reflected in the medical arm (aspirin, discussion of hypertension and diabetes control, and advice to stop smoking) of North American symptomatic carotid endarterectomy trial (NASCET). Overall, the 5-year risk of ipsilateral stroke in those medically managed was 22% depending on the severity of the stenosis. The NNT for symptomatic patients undergoing CEA to prevent 1 ipsilateral stroke at 5-years was 12. Females derived no significant benefit from CEA. In the medical treatment arm, the risk of any stroke at 5-years was 15% for women and 25% for men.[17] The incidence of stroke increased with the severity of stenosis, and the 3-year risk of ipsilateral stroke in symptomatic patients with stenosis greater than 80% was 26.5%, however, as the stenosis approaches near occlusion (95% to 99%), the risk of ipsilateral stroke dropped down to 17.2%.[18] Results were similar in the European carotid surgery trial (ECST).[19]

Current guidelines recommend CEA in symptomatic average surgical risk (ASR) patients if the stenosis is >70% as documented by non-invasive imaging or >50% as documented by catheter angiography and the anticipated rate of peri-operative stroke or mortality is less than 6%.[20]

CAROTID ARTERY STENTING

High Surgical Risk (HSR) Patients

When interpreting data on carotid stenting, it is important to realize that a patient who is at high-risk for surgery (HSR) is not necessarily at increased risk for stenting (and *vice versa*). The stenting and angioplasty with protection in patients at high-risk for endarterectomy (SAPPHIRE) trial is the only randomized trial comparing HSR patients treated with CEA or carotid artery stenting (CAS).[21] Features that place a patient at increased risk for complications from CEA and CAS are summarized in Table 1. SAPPHIRE randomized 334 patients with a symptomatic stenosis of ≥50% or an asymptomatic stenosis ≥80% (~30% were symptomatic) to either CEA or CAS. The primary endpoint of death, stroke, or MI at 30-days plus ipsilateral stroke or death from neurological cause between day 31 and 1-year occurred in 12.0% of patients in CAS *versus* 19.2% for CEA (p=0.004 for non-inferiority) (Figure 2). The 30-day stroke and death rate among asymptomatic patients was 4.6% for the CAS group and 5.4% for the CEA group. At 3-years, there were no differences between CEA or CAS.

Table 1. *High Risk Features for Carotid Artery Stenting (CAS) and Carotid Endarterectomy (CEA)*

High Risk Features for CAS		High Risk Features for CEA	
Clinical Features	**Angiographic Features**	**Comorbidities**	**Anatomic Features**
Age≥75/80	Severe Tandem Lesions	Age≥80	Lesion C2 or higher
Renal failure	≥2 acute (90° bends)	Class III/IV CHF or angina	Lesion below clavicle
Multiple lacunar Strokes	Circumferential calcification	LM/≥2 Vessel CAD	Prior neck surgery (including ipsilateral CEA)
Dementia	Evidence of thrombus	LVEF≤30%	Contralateral carotid occlusion
Bleeding disorder	Poor vascular access	Recent MI (>1 but <30 days)	Contralateral laryngeal nerve palsy
		Severe chronic lung disease	Neck Radiation
		Renal failure	Tracheostomy

The vast majority of contemporary CAS registry data focuses on HSR patients, and data from over 10,000 HSR patients have been published. These registries generally include symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥70-80% stenosis. Data from many of these studies are summarized in Figure 3. In HSR patients who require revascularization for stroke

prevention, CAS is the preferred strategy in patients who 1) can be treated by an experienced operator and 2) have suitable anatomy for CAS.

Figure 2. *Sapphire Trial Results*

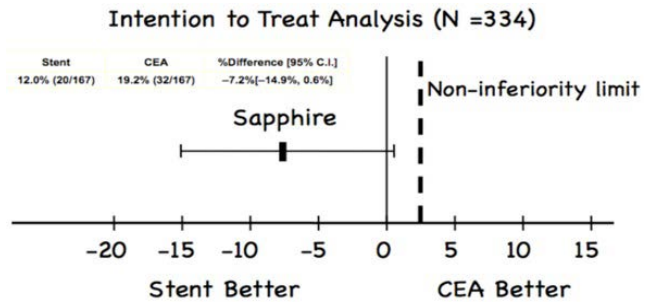
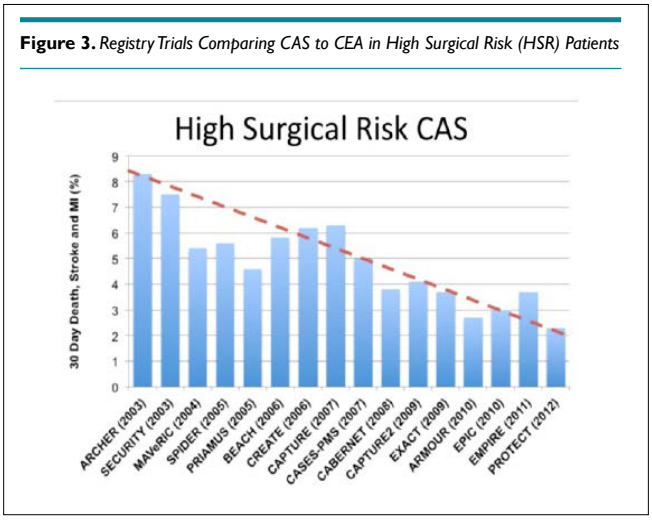


Figure 3. *Registry Trials Comparing CAS to CEA in High Surgical Risk (HSR) Patients*



CAS in Symptomatic Patients

Four large randomized studies in ASR patients have compared CAS to CEA.[22-25] Three of these trials were conducted in Europe and their results were compromised by allowing inexperienced CAS operators to participate in the trials and not requiring the use of embolic protection devices (EPD's).

The endarterectomy *versus* angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial randomized only symptomatic ASR patients with carotid stenosis of ≥60% to either CEA or CAS.[23] All patients had to be "suitable candidates" for both procedures and had ipsilateral neurological symptoms within 120-days of enrollment. The use of EPDs was "optional" and many of the investigators were "tutored" while treating patients. The 30-day incidence of stroke or death was 9.6% in the CAS group and 3.9% (p= 0.004) in the CEA group.

The stent-supported percutaneous angioplasty of the carotid artery *versus* endarterectomy (SPACE) trial randomized 1,214 symptomatic, ASR patients to either CEA or CAS.[22] The use of EPDs was optional and inexperienced operators were tutored during patient enrollment. The 30-day rate of ipsilateral stroke or death was not different between the two groups (6.8% in the CAS group and 6.3% in the CEA group, p=0.09 for non-inferiority). However, the two-year outcomes for this trial demonstrated a statistically significant benefit for CAS over CEA in patients <68-years of age.

International carotid stenting study (ICSS) enrolled over 1,700 symptomatic ASR patients and randomized them to either CAS or CEA.[24] Use of EPDs was optional. To qualify as an experienced center, a center had to have a surgeon who had performed 50 CEA procedures and an intervention a list who had performed 10 CAS procedures. If the center was less experienced, they were "tutored" while enrolling patients into the study. The number of fatal or disabling strokes and cumulative 5-year risk did not differ between the CAS and CEA groups (6.4% *vs* 6.5%; hazard ratio [HR] 1.06, 95% CI 0.72-1.57, p=0.77). The distribution of modified Rankin scale scores at 1-year, 5-years, or final follow-up did not differ between treatment groups.[26]

Carotid revascularization endarterectomy *versus* stenting trial (CREST) is the largest (n=2,502) randomized trial published comparing CAS with EPD's to CEA in ASR patients and included both symptomatic (n=1,321) and asymptomatic (n=1,181) patients.[25] The primary outcome of peri-procedural stroke, death, or MI and follow-up ipsilateral stroke at 4-years in symptomatic patients was not significantly different between the two groups (8.0% for CAS and 6.4% for CEA, p=0.14). During the periprocedural period, rates of the primary end point did not differ significantly between the CAS group and the CEA group among 1,321 symptomatic patients (6.7% *vs.* 5.4%; hazard ratio for stenting, 1.26; 95% CI, 0.81 to 1.96). The primary outcome of periprocedural stroke, death, or MI and follow-up ipsilateral stroke at 4-years in symptomatic patients was not significantly different between the two groups (8.0% for CAS and 6.4% for CEA, p=0.14).

In the overall trial, the 30-day risk of all stroke was higher for CAS (4.1% *vs.* 2.3%, p=0.01), whereas CEA was associated with a higher 30-day risk of MI (2.3% *vs.* 1.1%, p=0.03). The rate of ipsilateral stroke over a mean follow-up of 4-years was similar between groups. CAS appeared safer than CEA for patients ≤69-years of age while CEA yielded better outcomes in those >70-years of age (Figure 3).

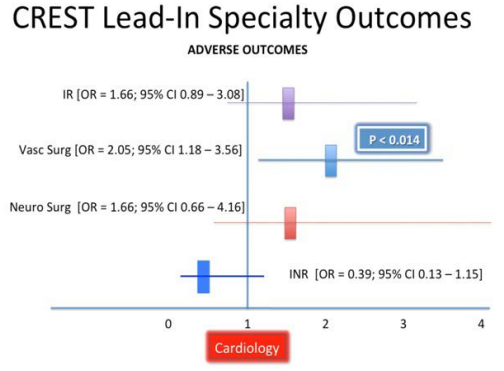
The CREST 10-year follow-up demonstrated that patients with periprocedural stroke were at increased risk of death compared with those without stroke (adjusted hazard ratio [HR]=1.74; 95% CI, 1.21-2.50; p<0.003).[27,28] This increased risk was driven by increased early (≤90-days) mortality (adjusted HR=14.41; 95% CI, 5.33-38.94; p<0.0001), with no significant increase in late (>90-days and 10-years) mortality (adjusted HR=1.40; 95% CI, 0.93-2.10; p=0.11). Patients with a periprocedural MI were at 3.61 times the risk of death compared with those without MI (adjusted HR=3.61; 95% CI, 2.28-5.73; p<0.0001), with an increased hazard both early (adjusted HR=8.20; 95% CI, 1.86-36.2; p=0.006) and late (adjusted HR=3.40; 95% CI, 2.09-5.53; p<0.0001). This

points out the importance or including periprocedural MI in the combined outcome endpoint for carotid revascularization trials.

CREST differed from the previous trials in three significant ways. Most importantly, the European randomized controlled trials (RCT) allowed inexperienced CAS operators to enroll patients. All allowed CAS operators, but not CEA operators, to be "tutored" while enrolling patients. CAS operators in the European trials were not very experienced (EVA-3S required that operators perform at least 5 CAS procedures, ICSS required 10 CAS procedures, and SPACE had no minimum number of carotid stents required). CREST requirements were more stringent. CREST required low volume CAS operators to "qualify" to enroll patients in the trial with "lead-in" patients. This step was unique and critically important when attempting to reasonably compare the newer and evolving CAS procedure with a mature, stable operation like CEA. There were 1,565 lead-in patients in CREST which is more CAS patients than were enrolled in any of the European trials.

The results obtained by relatively in experienced CAS operators participating in the lead-in phase of CREST emphasizes the importance of experience and further confirms the flaws in the European trials. Vascular surgeons, the most inexperienced specialty, had a significantly worse outcomes than did Cardiologists or Radiologists (Figure 4).[29] However, that difference went away after the surgeons qualified for the trial with lead-in patients. The fact that so many (15% to 20%) peri-procedural neurologic events involve the non-culprit carotid circulation is evidence of the importance of catheter skills in navigating the aortic arch to reach the carotid arteries. The importance of an experienced procedure team and CAS operators cannot be overstated. Second, CREST mandated the use of EPDs whereas the other trials did not. Lastly, just over 50% of the patients in CREST were symptomatic whereas the European trials enrolled only symptomatic patients.

Figure 4. *CREST Specialty Lead-In Results*



IR = interventional radiology, INR = interventional neuroradiology

CAS is indicated as an alternative to CEA for symptomatic ASR patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%.[20] It is also reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.

CAS in Asymptomatic Patients

In CREST, for the 1,181 asymptomatic patients, the periprocedural period rates of the primary end point did not differ significantly between the CAS group and the CEA group (3.5% *vs.* 3.6%; hazard ratio, 1.02; 95% CI, 0.55 to 1.86, p=0.96) and at 4-year follow-up there was no difference between the CAS and CEA groups (5.6% to 4.9%; hazard ratio, 1.17; 95% CI, 0.69 to 1.98, p=0.56).[25]

The asymptomatic carotid trial (ACT-1) randomized 1,453 asymptomatic ASR carotid stenosis patients to CEA or CAS.[30] CAS was non-inferior to CEA with regard to death, stroke, or MI within 30-days after the procedure or ipsilateral stroke within 1-year (3.8% *vs.* 3.4%, p=0.01 for non-inferiority). There was no difference for CAS *vs* CEA for rates of stroke or death within 30-days (2.9% and 1.7%, p=0.33). Freedom from ipsilateral stroke from 30-days to 5-years was 97.8% in the CAS group and 97.3% in the CEA group (p=0.51).

CAS in asymptomatic patients may be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.

SUMMARY

In 2019, CAS has become one of the most studied medical procedures of all time. In HSR patients there is randomized trial data[31-47] favoring CAS over CEA in patients suitable for stenting.

In ASR patients, the largest randomized clinical trial (CREST)[25] confirms the equipoise for CAS and CEA, when these procedures are performed by experienced operators with experienced teams supporting them. In recognition of this extensive evidence-base, there is a multi-societal expert consensus document[48] and guidelines[20,49] that recommend that CAS be considered a reasonable alternative to CEA.

A patient-centered approach is reasonable in candidates for carotid revascularization. The patient and their physician should discuss the available treatment options, including revascularization (either CAS or CEA) with their physician. There remains uncertainty regarding the value proposition for revascularization (either CEA or CAS) in asymptomatic patients as a strategy to prevent stroke.[50] Investigation continues into characterizing high risk carotid plaque subsets, but until that data is available, physicians and patients should continue to strive to achieve the best outcomes with the information that is currently available. The other consideration in asymptomatic patients is that there is a cumulative benefit to revascularization that is dependent on life expectancy. However,

the magnitude of the benefit of revascularization, over the longer term in the setting of multifactorial medical therapy, including statins, is not known.

No one can know exactly what the future holds for carotid stenting, but there are several reasonably safe bets. The first is that less invasive CAS will eventually replace the more invasive CEA. This change will be largely driven by the acceptance of CAS by younger, endovascularly trained vascular surgeons, who will replace the senior surgeons, who have effectively protected their surgical turf. The second is that far fewer asymptomatic patients will undergo any form of revascularization as multimodality medical therapy continues to improve. Clinical expansion of the volume of CAS cases will drive further technical enhancements and procedural evolution that will make CAS safer than CEA for stroke, death and MI and make cranial nerve injuries, a vestige of the past.

The uncertainty regarding the current best strategy for managing patients with asymptomatic carotid artery disease will be answered in the he CREST-2 trial that is currently enrolling patients and features 2 parallel arms (Figure 1): one arm compares CEA with best medical management *versus* best medical management alone and the other arm compares CAS and best medical management *versus* best medical management alone. CREST-2 does not compare CEA to CAS, but recognizes the equipoise for these two revascularization strategies in asymptomatic patients.

The stroke lowering benefit of modern pharmacotherapy has been firmly established. It has been estimated that the combined effects of antiplatelet therapy, lipid lowering, and blood pressure control could reduce the risk of recurrent stroke by as much as 80%.[51] Secondary analyses from trials of lipid lowering therapy in patients with stroke suggest that control of blood pressure (<120/80 mm Hg), low-density lipoproteins (LDL) level (<70 mg/dL), triglycerides level (<150 mg/dL), and high-density lipoproteins (HDL) level (>50 mg/dL) can lead to a significant reduction in the risk of recurrent stroke can reduce the hazard ratio (HR) to 0.35.

Reimbursement constraints continue to be a serious barrier to the clinical dissemination of CAS.[52] food and drug administration (FDA) has approved multiple CAS as "safe and effective" but centers for medicare and medicaid services (CMS) has decided that CAS is not "reasonable or necessary". CMS however reimburses for CEA without restraint or conditions.

CONCLUSION

Carotid artery stenting is a well studied therapeutic strategy for carotid revascularization, it must be performed by experienced operators using embolic protetction in orther to provide results similar to those reported in the clinical trials. The clinical benefit is clear in symptomatic patients. On the other hand, the current CREST-2 trial is evaluating its performance compared with current maximal medical therapy for patients with asymptomatic disease.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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