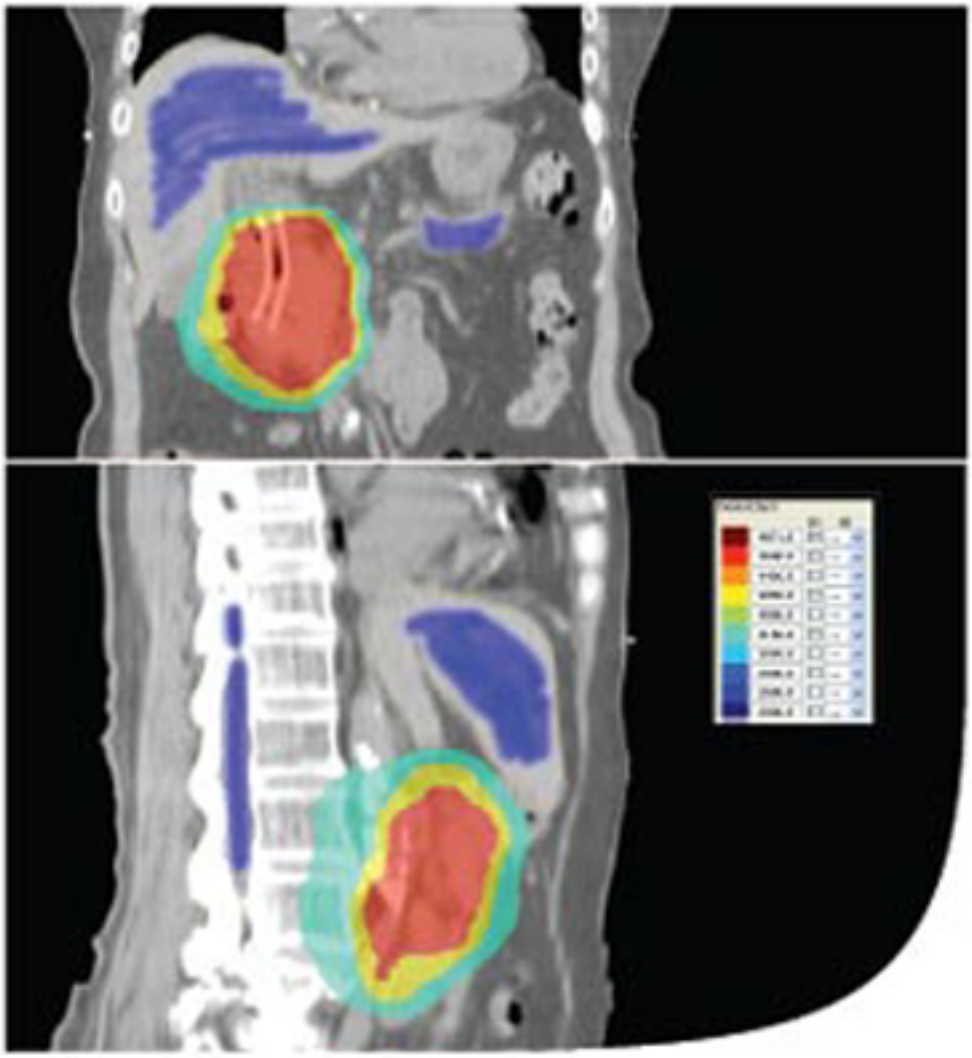
Bangkok Hospital Group

THE BANGKOK MEDICAL JOURNAL

February 2011 Vol. 1

Highlight issues



VMAT for early pancreatic adenocarcinoma in case where surgery is contraindicated

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Preface

"This is the place where advances in medicine are met with compassion".

With regard to the above mentioned philosophy of this hospital, our strength of purpose in bringing this idea to fruition has never faded away. Over the last 40 years, we have never stopped striving to establish ourselves not only as an excellent hospital but as a "Home of Medical Care".

In order to realize this goal of becoming a "Home of Medical Care", compassion must walk hand in hand with medical science. Unquestionably, our physicians, nurses, medical practitioners and personnel should be highly proficient in the practice of medical science, but that they also develop appropriate attitudes is crucial. They need to exhibit compassion and demonstrate caring approaches, in order to give heartfelt empathetic care to patients.

A systematic approach to the delivery of excellent healthcare in the 21st Century differs considerably from approaches used in the past, due to continued advances in technology and the borderless world of today. Taking care of the patients, requires a process-based quality management system, and patient safety quality management tools. Knowledge is considered the most precious asset of organizations, and "*Knowledge Sharing*" is one such tool that will never become obsolete; it remains essential for all organizations, especially the healthcare concerns, where precise and accurate information is vital. Using knowledge management as a tool, sharing knowledge, techniques and methodology, will create more opportunities for the members of our organization as well as assisting them to develop expertise and wisdom.

It is our wish that this edition of ***"The Bangkok Medical Journal"*** will lead to great opportunities for medical professionals and all other parties concerned, in exchanging profound knowledge and experience about technical matters, together with practices for excellent patient care. We believe that this way of knowledge sharing is not only of great relevance to the wider medical community; it will further strengthen our organization to be a real "Home of Medical Care" and will enable us to continue to giving valuable benefits to the patients we serve.

I wish to extend my most sincere thanks and appreciation to the journal team and to everyone who contributed and dedicated themselves to this publication. May you all continue to uphold the philosophy and best practices of our organization.

Pongsak Viddayakorn, MD.
Chairman
Medical Staff Organization Committee
The Bangkok Hospital Group
Bangkok Dusit Medical Services PCL.

Preface

A hospital should not be only a place for providing healthcare but a *"Hospital"* should be "a place of compassionate and admirable medical care hospitality" provided by proficient physicians, medical practitioners and personnel, with advanced medical technology and facilities.

To become a place of compassionate and admirable medical care hospitality, the hospital must have proficiency in delivering the highest quality medical care service, training and developing physicians, nurses, medical practitioners including personnel effectively, and managing an organization professionally. To achieve this, the organization needs constant improvement and development; both in managerial, medical, and technical knowledge. Thus; ***learning organizational culture*** has to be primarily built and developed by applying a so-called tool *"Knowledge Management (KM)"* and the Research and Development (R & D), to indoctrinate habit and culture in searching and sharing knowledge. KM and Research processes will enable us to have fast access to precise information and knowledge, enhance our analytical conceptual thinking skill, enable us to analyze in-depth and solve specific problems, guide us to the right decision-making, particularly on the subjects which directly impact patients' life and safety, which has to be based on accurate evidence.They allow us to learn how to explore the development opportunities available in our organization which we can make use of for long term development.

I am proud to welcome all of you to the first edition of ***"The Bangkok Medical Journal".*** I am confident that you will find this journal to be of great value as this worthwhile journal delivers readers a diverse set of selected, interesting articles, case reports and review that canvass a range of issues which can be applied in enhancing a better quality of patient care.

In this connection, I wish to extend my heartfelt gratitude and appreciation to everyone who dedicated and sacrificed their time to deliver expertise, effort, and contribution to this publication, and I would welcome your participation and contributions in this journal.

Chatree Duangnet, M.D. FAAP, FACMQ
Vice Chairman
Medical Staff Organization Committee
The Bangkok Hospital Group
Bangkok Dusit Medical Services PCL.

Editorial

Bangkok Hospital was the first private medical institute in Thailand. With persistent commitment towards realizing the goal of becoming a leading healthcare provider, Bangkok Hospital continually developed its medical technology together with its medical staff, to become an accredited and an admired medical leader both in Thailand and globally. Today Bangkok Hospital has expanded its hospital network to cover over 19 locations throughout Thailand and overseas; we are now the largest hospital operator in South-East Asia.

For almost 40 years, Bangkok Hospital Group has meticulously dedicated itself to research and development that contributes tremendously towards saving and sustaining our patients' lives. After the successful publishing of the BMC Medical Conference booklets in 2002 and 2007, we now feel it is the right time for Bangkok Hospital Group to continue to introduce some of its research projects and formal studies to interested readers worldwide on a more regular basis. We are therefore very proud to be publishing the first formal edition of, ***"The Bangkok Medical Journal".***

This issue of the Bangkok Medical Journal contains many interesting articles which range across various medical and scientific fields. We have an interesting article about Off pump coronary bypass grafting, to which we give full credit to Dr. Kittipan Visuttarom, Dr. Permyos Ruensakulach and their colleagues, who pioneered using these techniques in Thailand, without stopping the patient's heartbeat. Another interesting article introduces VMAT, which is a powerful technology used at Wattanosoth Hospital, to treat the early stage of pancreatic cancer for whom surgery is contraindicated. It is an innovative technology that delivers a high dose of radiation to the tumor whilst reducing exposure to the normal organs. The next remarkable article discusses treatment options for lumbar spinal stenosis in the elderly. Dr. Phudhiphorn Thienprasit provides interesting details to readers about an evidence based approach to surgical treatment in the spine field. Dr. Montri Saengparrtachai, who is a writer involved with CME has contributed an interesting paper about autism and epilepsy.

These studies not only illustrate the high competence of medical staff in, and the international standards at Bangkok Hospital; they also show how well placed Bangkok Hospital is to be a destination of choice for international medical care.

Finally, it gives us great pleasure to express our cordial appreciation to
Dr. Prasert Prasarthong-Osoth (The President of Bangkok Dusit Medical Service, Plc.),
Dr. Pongsak Viddayakorn (The Chairman of Medical Staff Organization Committee, Bangkok Hospital Group, Bangkok Dusit Medical Service, Plc.),
Dr. Chatree Duangnet (The Vice Chairman of Medical Staff Organization Committee, Bangkok Hospital Group, Bangkok Dusit Medical Service, Plc.), the Editorial Board Committee, physicians, technicians, Ms. Pasuta Sangprasert and everyone else who has dedicated their spirit and valuable time contributing to this publication.

Chirotchana Suchato, MD.
Editor in Chief

Rergchai Varatorn, MD.
Co-Editor

Accuracy of the 256 Multi-detector Computerized Tomography in Detecting Coronary Artery Stenosis

Experience from Bangkok Heart Hospital

Lertlak Chaothawee, MD.[1]
Kittipan Visudharom, MD.[2]
Sucharath Warutama,MD.[1]
Pongpan Poonsawat, MD.[1]
Pradub Sukum, MD.[3]
Duddao Pantunurat.[1]
Yanipa Kaewlumhud.[1]
Darunee Jaiyong.[1]
Sangrawee Sri-ngam.[1]
Krittiya KhueanKhuab.[1]
Paweena Mapinta.[1]
Busakol Ngam-maung.[1]

[1] Cardiac Imaging Center, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[2] Division of Cardiothoracic and Vascular Surgery, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[3] Cardiovascular Medicine, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
256 MDCT angiography, Invasive coronary angiography (ICA), Calcium scoring, Coronary arterystenosis

OBJECTIVE. To study the accuracy of the 256 Multi-detector Computerized Tomography (MDCT) in detecting coronary artery stenosis.

MATERIALS AND METHODS. We retrospectively analyzed angiographic findings of patients who underwent both 256 MDCT and invasive coronary angiography (ICA). All epicardial arteries, regardless of calcium burden, were segmented into proximal, mid and distal part for comparative analysis. Significant coronary artery stenosis was defined as the reduction of luminal diameter being equal to or more than 50%. The diagnostic accuracy of 256 MDCT in coronary artery stenosis evaluation was assessed by comparing its' sensitivity, specificity, positive and negative predictive values to the gold standard ICA.

RESULTS. From January to December 2009, a total of 147 consecutive patients (124 male, 23 female, mean age of 60 ±12 years) underwent both MDCT and ICA were enrolled. Of total 1470 coronary segments (147 segments of LMA, 441 segments of the LAD, 441 segments of the LCx, 441 segments of the RCA), 98.9% were eligible to be assessed and only 1.1% (15/1470) were ineligible due to very high calcium clumps and severe motion artifacts. Compared to the ICA, the overall sensitivity of the 256 MDCT in detecting coronary stenosis was 88.3 %, specificity was 96.1%, positive predictive value was 88.1 % and the negative predictive value was 96.2% with an overall accuracy of 94.2% (p=0.20). In massive calcium scoring cases (calcium scoring ≥400 U), the sensitivity of 256 MDCT in detecting coronary artery stenosis was 90.3%, specificity was 96.1%, positive predictive value was 87.5% and the negative predictive value was 95.5%; the overall accuracy was 92.9%. In nonmassive calcium scoring cases (calcium scoring <400 U), sensitivity for classifying coronary stenoses was 89.2 %, specificity was 97.2%, positive predictive value was 88.7 % and the negative predictive value was 97.4 %; the overall accuracy was 94.9%.

CONCLUSION. The 256 MDCT, regardless of calcium burden, offers a reliable diagnostic accuracy in assessing coronary artery stenosis.

Nowadays, the 64 slice MDCT has become a reliable, standard tool for diagnosing coronary stenosis in mild to moderate risk patients. The overall reported sensitivity and specificity were reasonably accepted.[4,5] However, several limitations of the 64 MDCT existed, which included a long acquisition time, and the often required administration of beta-blockades to lower the motion artifacts from patients with high heart rates. With the new 256 MDCT, more data was collected within a shorter time, patients received reduced doses of radiation and the image quality was also much improved.

To verify the diagnostic accuracy of this new scanner in daily practice, we decided to perform the comparative study between the 256 MDCT and the standard ICA.

Materials and methods

From January-December 2009, a total of 1,707 patients, (regardless of having any cardiac arrhythmia including atrial fibrillation), had undergone coronary artery scanning by the 256 MDCT. Exclusion criteria included acute myocardial infarction, patients at risk for iodinated contrast agents, or elevated serum creatinine >1.5 mg/dl. Among those, 147 patients were requested to do an additional ICA by their cardiologists owing to indecisive degree of stenosis and/or divergent clinical presentations.

To verify the diagnostic accuracy of this new machine, we retrospectively compared the coronary images from the 256 MDCT with those from the standard ICA. All epicardial arteries were segmented according to the guidelines developed by the BARI investigators.[1,2] Significant coronary stenosis was defined as the reduction of luminal diameter ≥ 50% in comparison with an adjacent angiographically normal segment.[1,2] The degree of coronary stenosis was classified by severity of luminal reduction; mild (reduction of luminal diameter <50%), moderate (reduction of luminal diameter 50-69%) and severe (reduction of luminal diameter ≤70%). This study was approved by our institutional ethics committee and all participants gave their written informed consent.

CT coronary angiography (CTA)

CT studies were performed on 256 MDCT **(Brilliance ICT 256 MDCT, Philips, Netherlands)** scanner with a 0.27s rotation time. A bolus of iodinated contrast injection volume was calculated by the formula of scan time (5 sec. for coronary artery scanning) plus post threshold delayed time (~5 sec.) and multiplied by flow rate (4.5-6 ml./sec.) (Phillips company protocol). A contrast bolus was injected into brachial vein at a flow rate of 4.5-6 ml./sec. (Flow rate 6 ml./sec. of contrast injection was preferred if the patient's body weight >90 kg), followed by 50 ml. saline solution injection. The tracking position was placed at the ascending aorta and scan started automatically at 5.0 sec. after reaching the threshold (100-120 Hounsfield units, HU). Cardiac scan length covered from the tracheal bifurcation to 2-3 cm. below the diaphragm using the following parameters; X-Ray tube potential 120-140 KV, tube current 471 MA, slice collimation 128x0.625 mm^2, table speed of 44 mm/sec., and pitch 0.16. The mean coronary scan time was 5.0 sec. The retrospective electrocardiographic gating was routinely used for cardiac phase selection. The coronary scan data was completely obtained from two to three consecutive heart beats, the axial slices were recostructed and synchronized to the ECG. If the heart rate remained above 70 beats per minute, beta-blockade might have been administered if there were no contraindications.

The slice thickness was of 0.67 mm. The CT data was independently and blindly analyzed by three experienced cardiac CT specialists. The vessel analysis was assessed on at least two planes, one parallel and one perpendicular to the course of the vessel.

Invasive coronary angiography (ICA)

ICA was performed by standard technique via femoral approach. At least two orthogonal views were taken for each of the epicardial arteries. The angiograms were separately analyzed by experienced interventionists who had not done a prior review of the MDCT images. ICA was performed after cardiac CT scan if the results of cardiac scan showed significant coronary artery stenosis or showed controversial results relative to the patient's clinical signs. The coronary arteries (LMA, LAD, LCX, RCA) were segmental located (proximal, mid, distal) according to the guidelines as mentioned above.[1,2] The coronary segment was considered for significant stenosis by the same criteria as used in CT. Coronary artery dominance refers to the artery that supplies the posterior descending artery (PDA). Coronary artery lesions were described by their locations (proximal, mid and distal) and classified according to severity. Severity of coronary artery stenosis was estimated with percentage of stenosis defined as the ratio of reference luminal diameter divided by the reference diameter vessel measurement.[1]

Statistical analysis

By using ICA as the gold standard, images from CTA and ICA were compared and analyzed. The sensitivity, specificity and accuracy including positive andnegative predictive values were calculated.Chi-square test was used to an lyze observed differences, and p <0.5 was regarded as indicating a statistically significant difference.

Results

Of total 147 consecutive cases, 80% were men (124 male, 23 female) and the mean age was 60 ±12 years. Of total 588 coronary arteries, all 1470 coronary segments (147 segments of LMA, 441 segments of the LAD, 441 segments of the LCx, 441 segments of the RCA) were studied.

By ICA, as shown in Table 1, 73.2% (1076/1470) were angiographically normal, 18.9% (278/1470) had significant stenosis (luminal stenosis ≥50%) and the remaining 7.9% (116/1470) had non significant lesions.

By CTA, 98.9% (1455/1470) coronary segments were eligible for analysis. Only 1.1% (15/1470) of coronary segments were ineligible due to unusually high calcium clumps (n=13) and motion artifacts (n=2). Calcium scoring was calculated and the severity level was classified using Agaston system criteria.

Table 1: Distribution of coronary artery stenosis evaluation result using the gold standard ICA

Severity of coronary artery stenosis	Total coronary segments (%) n= 1470 (100%)	LM	LAD	LCx	RCA
70 - 100%	202 (13.7%)	5	80	50	20
50 - 69%	76 (5.1%)	7	30	24	15
<50%	116 (7.9%)	11	36	30	39
Normal	1076 (72.2%)	122	285	336	318

Table 2: Correlative findings of coronary artery stenosis between the CTA and ICA

Test	Disease present (ICA)	No disease (ICA)
Positive test (CTA)	318	43
Negative test (CTA)	42	1052

Table 3: Overall diagnostic accuracy of the 256 MDCT in diagnosing coronary artery stenosis comparing to the gold standard ICA

Result	(%)
Sensitivity	88.3
Specificity	96.1
Positive predictive value	88.1
Negative predictive value	96.2
Accuracy	**94.2**

Table 4.1: Correlative findings of coronary stenosis between the CTA and ICA in massive calcium score (CAC>400 U) subgroups

Test	Disease present (ICA)	No disease (ICA)
Positive test (CTA)	169	24
Negative test (CTA)	18	386

Table 5.1: Correlative findings of coronary stenosis between the CTA and ICA in non massive calcium score (CAC<400 U) subgroups

Test	Disease present (ICA)	No disease (ICA)
Positive test (CTA)	149	19
Negative test (CTA)	18	666

Table 4.2: Diagnostic accuracy of the 256 MDCT in diagnosing significant coronary artery stenosis comparing to the gold standard ICA in subgroup with massive calcium score (>400)

Result	(%)
Sensitivity	90.3%
Specificity	96.1%
Positive predictive value	87.5%
Negative predictive value	95.5%
Accuracy	**92.9%**

Table 5.2: Diagnostic accuracy of the 256 MDCT in diagnosing coronary arterystenosis comparing to the gold standard ICA in subgroup with non massivecalcium score (<400)

Result	(%)
Sensitivity	89.2%
Specificity	97.2%
Positive predictive value	88.7%
Negative predictive value	97.4%
Accuracy	**94.9%**

61 patients (41.2%) had calcium scoring >400 U Table 2 & 3 show correlative findings between ICA and CTA. Of a total 1455 segments, the agreement between ICA and CTA were 72.3% (1052/1455) for non-stenotic lesions and 21.2% (318/1455) for non significant and significant lesions. The discordant readings were 2.9% (43/1455) that appeared to have significant stenosis by CT only and 2.8% (42/1455) by ICA only.

Table 4.1 and 5.1 below delineated the correlative findings of coronary stenosis between ICA as a gold standard and CTA in massive calcium score (CAC >400 U) and non massive calcium score (CAC <400 U) subgroups respectively.

The overall sensitivity of the 256 MDCT in detecting coronary artery stenosis was **88.3%**, specificity was **96.1%**, the positive predictive value of MDCT was **88.1%** and the negative predictive value was 96.2% and the overall accuracy was 94.2% (p-value = 0.20) (Table 2-3). **In massive calcium scoring cases** (calcium scoring >400 U) sensitivity for detecting coronary artery stenosis was **90.3%**, specificity was **96.1%**. The positive and negative predictive values were 87.5% and 95.5% respectively with the overall accuracy of **92.9%** (Table 4.2).

In non massive calcium scoring cases (calcium scoring <400 U) sensitivity and specificity were **89.2%** and **97.2%** respectively. The positive predictive value was **88.7%** and the negative predictive value was **97.7%** and the overall accuracy was **97.4%** (Table 5.2). For CTA, 13 segments of 610 segments (2.1%) of massive calcium scoring (CAC >400) and 2 segments of 860 segments (0.002%) of non massive calcium scoring (CAC <400) subgroups were not be able to evaluate the degree of stenosis, owing to the blooming artifacts from severe calcification and motion artifacts respectively. The diagnostic accuracy of these two subgroups were not significant different (p=0.30). The total volume of iodinated contrast use was 60 ±10 ml for coronary artery scanning. The minimum and maximum value of calcium scoring were of 0 and 3506 U respectively (mean =275.5). Only 10 patients (0.007%) with a heart rate of more than 80 beats per minute were considered to be given beta blocker drugs before CT scanning.

Discussion

Currently, MDCT offers an alternative way to evaluate coronary artery stenosis without the risks of an invasive procedure. The overall diagnostic accuracy of the standard 64 MDCT ranged from **94-95%** of sensitivity, from **67-97%** of specificity and the positive and negative predictive values were **78-87%** and **92-97%** respectively.[4,5] However, several limitations existed including amount of contrast used, radiation exposure and motion artifacts from high heart rate.

Example

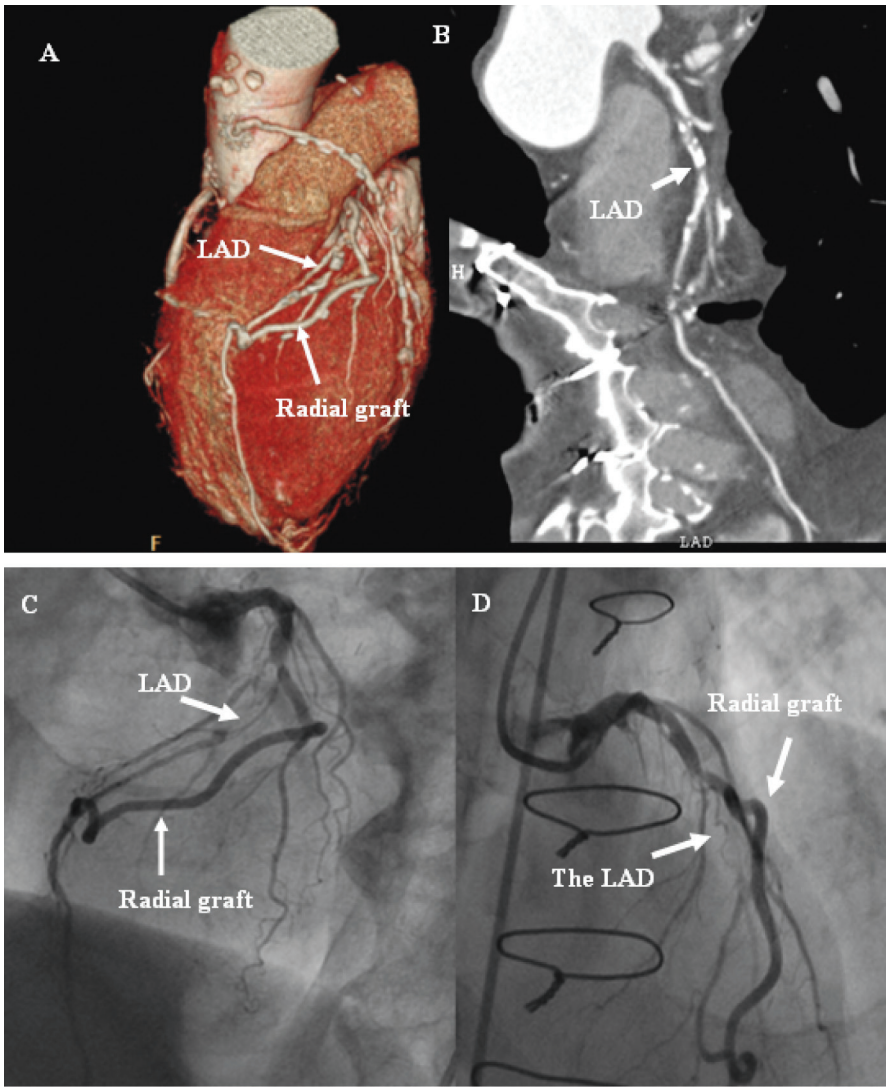

Figure 1: *The images of 256 MDCT coronary angiography and ICA of a 78 year old man with history of coronary bypass graft, who came to the hospital with chest pain. The CT scan showed* ***the total calcium volume to be more than 400 (539.8).***

By increasing number of detectors, the 256 MDCT could obtain sufficient data faster (within 2-3 heart beats) and was able to examine patients with higher heart rate without requiring them to take beta-blockade medicine. By cutting down the scan time, the average patient effective radiation dose equivalent was reduced from 15-21 mSV in 64 MDCT scanner[6,7] to around4-17 mSV (20-30% reduction) for coronary artery scanning and the iodinated contrast volume decreased by 30%.(We compared the radiation doses and contrast volumes with our initial experiences in the previous two years using 64 MDCT). However, the further investigation for clinical application in real world is still needed.

In daily practice, high risk cases of coronary artery disease (CAD) would go for invasive coronary angiography and only borderline or non high risk patients would be referred for CTA. In our study, total of 147 non high risk patients with clinically suspicious CAD were referred for CTA but their cardiologists still requested ICA owing to the positive or undetermined CTA results. By ICA, 80% of angiogram showed either normal or non-significant stenosis suggested the low risk population. By using ICA as a gold standard, the sensitivity of 256 MDCT was **88.3%** and the positive predictive value was **88.1%** which were acceptable compared to the ICA. In addition, the high specificity of 256 MDCT, **97.5%** made this machine very reliable for exclusion of CAD in low risk subgroups.

Blooming artifact effects remained a major limitation of CTA owing to massive calcium deposits. Our study showed non significant differences in the diagnostic accuracy between the massive calcium scoring (CAC >400) and non massive (CAC <400) calcium subgroups (**92.9% and 94.9%**, p=0.30). It indicates that high total calcium score seems not to have much effect on coronary artery assessment. However, the personal experiences of the reader might need to be taken into account. In addition, the negative predictive values of these two groups were impressive as 95.5% and 97.4% and could be use for exclusion of CAD in low risk candidates.

Finally, it is not only the non high risk patients who benefit from the new scanner. To verify graft patency in high risk patients who have undergone bypass surgery is another valid application. Without angle limitation, the patency and quality of graft especially at anastomotic site is well appreciated as delineated in Figure 1.

Study limitation

In addition to the relatively small number of subjects, our study represented the correlative findings between CTA and ICA of major epicardial arteries in only non high risk CAD suspicious patients which we believed would be the majority of CTA cases in daily practice. Unfortunately, we also do not have the long-term follow up with all patients. The future clinical outcome is of interest especially in the cases with nonsignificant lesion which could be subjected to acute plaque rupture.

Conclusion

The 256 MDCT offers a reasonably high diagnostic accuracy in detecting coronary artery stenosis in non high risk patients with clinically suspicious CAD. The shorter scan time of the 256 MDCT also benefits the patient who has contraindication to beta blocking drugs. High negative predictive values (regardless of calcium score) mean that the 256 MDCT could be confidently used for exclusion of CAD in low risk candidates.

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Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) Followed by Thoracotomies

Sawang Saenghirunvattana, MD.[1]
Vibul Jotisakulrata, MD.[1]
Chana Buakham, MD.[1]
Surapon Worapongpaiboon, MD., FCAP.[1]
Takahiro Nakajima, MD.[2]
Kazuhiro Yasufuku, MD., PhD, FCCP.[2]
Takehiko Fujisawa, MD.[2]

[1] Samitivej Hospital, Thailand. The Bangkok Hospital Group, Bangkok, Thailand.
[2] Department of Thoracic Surgery,Graduate School of Medicine, Chiba University, Tokyo, Japan.

Keywords:
Endobronchial ultrasound, Transbronchial needle aspiration, Lung cancer, Mediastinal lymph node biopsy, Thoracotomy.

OBJECTIVE. To evaluate sensitivity and specificity of EBUS-TBNA for aspiration biopsy mediastinal lymphadenopathy.

MATERIALS AND METHODS. A total of 150 patients were studied: the mediastinal lymph node was range 0.5-5.0 cm. under EBUS-TBNA.

RESULTS. The sensitivity was 97%.

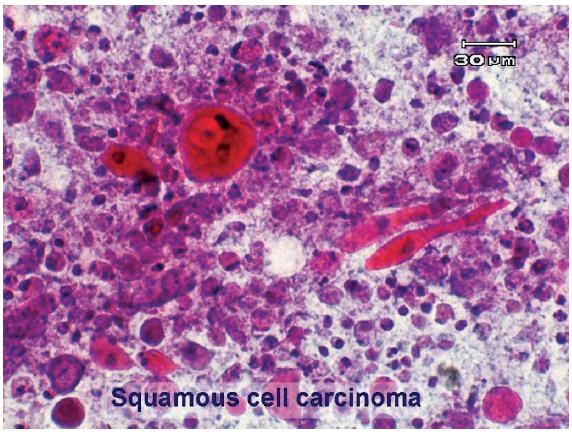
CONCLUSION. Given the high sensitivity, we conclude EBUS-TBNA may benefit the current diagnosis and staging of cancer.

We described our technique for performing Endobron chial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) upon 150 patients with mediastinal lympha-denopathy using a curved linear array ultrasonic bronchoscope that allowed for aspiration biopsy under real-time ultrasound imaging. EBUS-TBNA provided definitive diagnoses for benign diseases such as tuberculosis and accurate staging of lung cancer. The overall sensitivity was 97%. Seven patients with a lung nodule and mediastinal lymphadenopathy were recruited to proof the results of EBUS-TBNA by thoracotomies. There were 4 patients with lung cancer. Four lymph nodes with cancer metastasis were detected via EBUS-TBNA from 5 nodes iden-tified by surgery. Nine lymph nodes with no cancer invasion were confirmed by thoracotomy. The sensitivity was 80% and the specificity was 88.9%.

Endobronchial ultrasound guided TBNA (EBUS-TBNA) is a minimally invasive real-time procedure which has been shown to have a high yield for the evaluation of the mediastinum.[1-4] Here we report our experience of EBUS-TBNA for mediastinal lymphadenopathy.

Materials and Methods

Patients whose computer scan of the chest revealed mediastinal lymphadenopathy were considered to undergo endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Patients with bleeding tendency, active pulmonary tuberculosis, or on respiratory support with positive end expiratory pressure were excluded. Informed consent was obtained in all patients. Six patients with a lung nodule and mediastinal lymphadenopathy were recruited to proof the results of EBUS-TBNA by thoracotomies.



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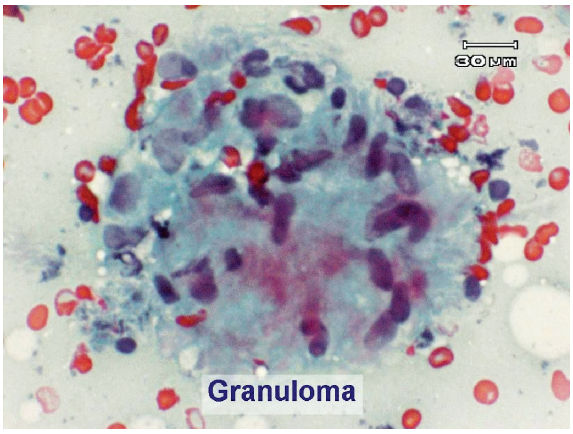

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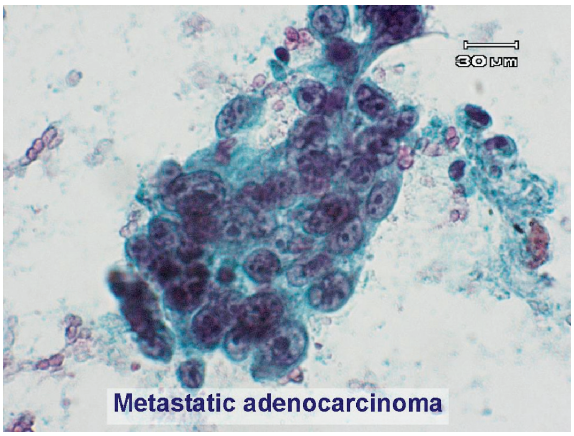

C

Figure A-C: *revealed pathology of squamous cell carcinoma (A), granuloma (B) and adenocarcinoma (C)*

Results

Three patients were excluded, one had active tuberculosis, and the other two had bleeding tendency. One hundred and fifty patients underwent EBUS-TBNA. There were 68 females and 82 males. Their ages ranged from 22 to 75 years old. One hundred and nineteen were Thai, twenty-five were Japanese: there was also one patient from each of the following countries: Cambodia, Kenya, Dubai, France, England and Canada.

EBUS-TBNA successfully sampled lymph node tissue from 145 out of 150 patients (97%). The average of the short axis diameter of the mediastinal lymph nodes was 1.2 cm. (range 0.5 cm - 5 cm). There were no complications during any of the procedures.

There were fifty-six cases of tuberculosis, fifty-six cases of adenocarcinomas, ten of squamous cell carcinoma; two of metastatic carcinoma and two were malignant lymphoma. Normal lymphoid tissues were obtained from twenty patients. Four patients were diagnosed with sarcoidosis. Seven patients with a lung nodule and mediastinal lymphadenopathies were recruited to proof the results of EBUS-TBNA by thoracotomies.

There were 4 patients with lung cancer. Four lymph nodes with cancer metastasis were detected via EBUS-TBNA from 5 nodes identified by surgery. Nine lymph nodes with no cancer invasion were confirmed by thoracotomy. The sensitivity was 80% and the specificity was 88.9%.

Discussion

The sensitivity of EBUS-TBNA was 97% in our current study. This high degree of effectiveness clearly indicates advantages in managing patients with mediastinal lymphadenopathy, in terms of making accurate diagnoses and staging of lung cancer. EBUS-TBNA was very helpful in a patient who developed carcinoma in situ at the carina with a 2-cm. short axis diameter subcarinal node.The subcarinal lymph node was disclosed to be tuberculosis via EBUS-TBNA. Electrocautery technique was employed to destroy the carcinoma in situ completely. The patient's diagnosis of inoperable lung cancer due to carinal involvement and likely to be stage 4, turned out in fact, to be a curable lung cancer with tuberculosis of mediastinal lymph node. Without this definite diagnosis, she may have undergone a chemotherapy program treatment and may have suffered from spreading of tuberculosis.

Three months later, following the anti-tuberculous drugs, the mediastinal node had completely disappeared. EBUS-TBNA has been reported to be useful in the diagnosis of sarcoidosis with the diagnosis yield of 91.8%.[5] In our current series we experienced 4 cases of sarcoidosis. In one patient, who presented with blurred vision due to uveitis, mediastinal lymphadenopathy was present. EBUS-TBNA revealed non-caseous granuloma.

Lymphoma was detected in only two cases. The disease is quite difficult to diagnose: only 50% of the cases could be proved by EBUS-TBNA.

Conclusion

The sensitivity of our EBUS-TBNA was 97%. The technique offered correct tissue diagnosis and staging of lung cancer. Potentially operable patients with clinically nonmetastatic, non-small cell lung cancer may benefit from pre-surgical EBUS-TBNA biopsies and staging.

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Case Report

VMAT for early pancreatic adenocarcinoma in case where surgery is contraindicated

Cholakiet Khorprasert, MD.[1]
Prasert Lertsanguansinchai, MD.[1]
Napapat Amornwichet, MD.[1]
Wirote Loasoontornsiri, MD.[1]
Supranee Supanunt [1]
Krittiya Chantharawanitkul [1]
Kriangdate Boonlerluk [1]
Chulee Vannavijit [1]
Wutthichai Boonrat [1]
Patcharapa Trikaewcharoen [1]
Puncharat Sakthumjaroen [1]

[1] Department of Radiation Oncology, Wattanosoth Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
VMAT, Inoperable pancreatic adenocarcinoma, IGRT, IMRT

There are several methods for managing pancreatic cancer. Surgical resection gives the best chance for a possible cure in the early stages of the disease. However only 10-20% of patients present with potentially resectable pancreatic cancer. Chemotherapy is the treatment of choice for the advanced metastatic disease. For locally advanced, inoperable pancreatic cancer, combined chemotherapy and radiation is the preferred treatment.[1] In the case of patients who have contraindications for surgery, concurrent chemoradiation may be chosen[2]. The patient in this study, was a case of adenocarcinoma at the pancreatic head, stage $T_1N_0M_0$, with underlying heart disease; she thus was contraindicated for a major operation. The treatment plan was chemoradiation, using VMAT radiotherapy technique with a radiation dose of 45Gy in 25 fractions and oral Xeloda.

Case report

A 82-year-old female presented with obstructive jaundice. A CT scan of the upper abdomen revealed a 1.3 cm. soft tissue mass at distal common bile duct (CBD) and periampullary region causing compression and dilatation of common bile duct and pancreatic duct. The endoscopic ultrasound and fine needle aspiration together with Metallic stent placement was done. The pathologic findings showed malignant cells comparable with adenocarcinoma of the pancreas. The patient underwent further investigations which included a F18-FDG-PET/CT scan. (Figure 1) The scan demonstrated a hypermetabolic mass at the pancreatic head with a SUV of 4.9. Neither Distant metastasis nor regional nodal spread was detected. The patient was then treated with concurrent chemoradiation. Surgery was not a priority treatment, due to her heart condition.

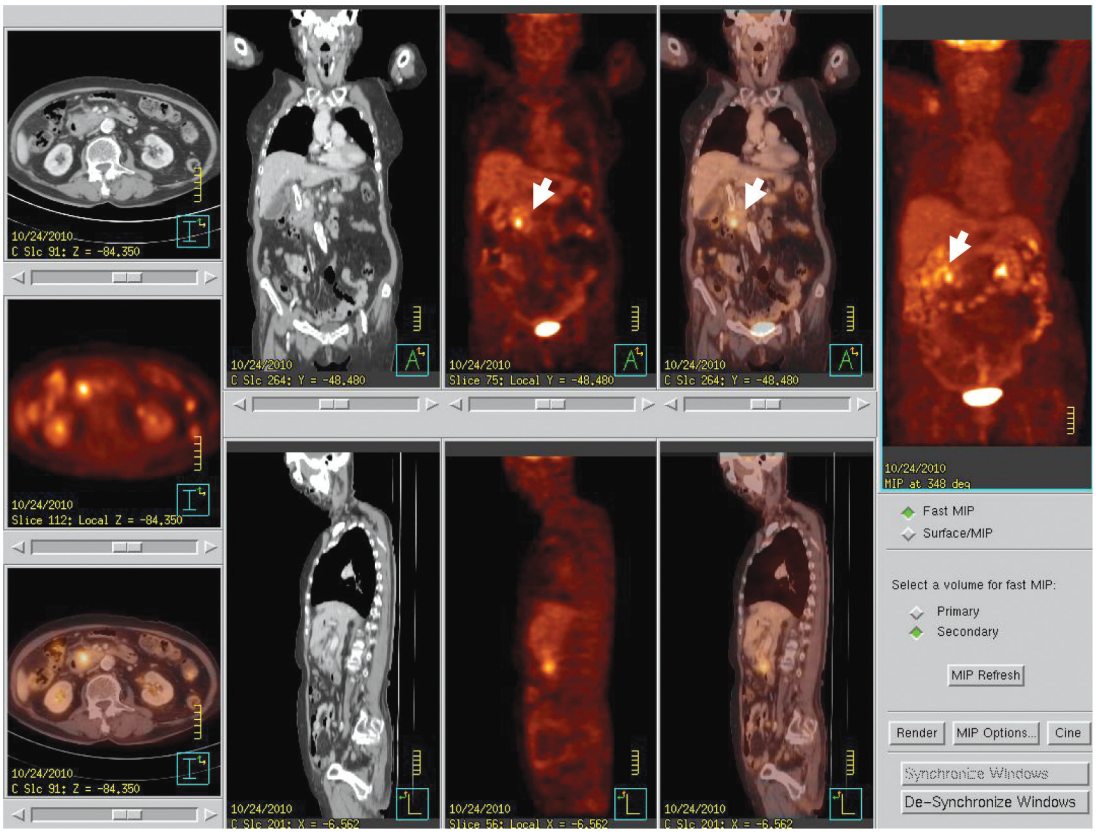

Figure 1: *PET/CT images show 1.3 cm. hypermetabolic mass at pancreatic head (arrow), without regional node and distant metastasis (stage $T_1N_0M_0$)*

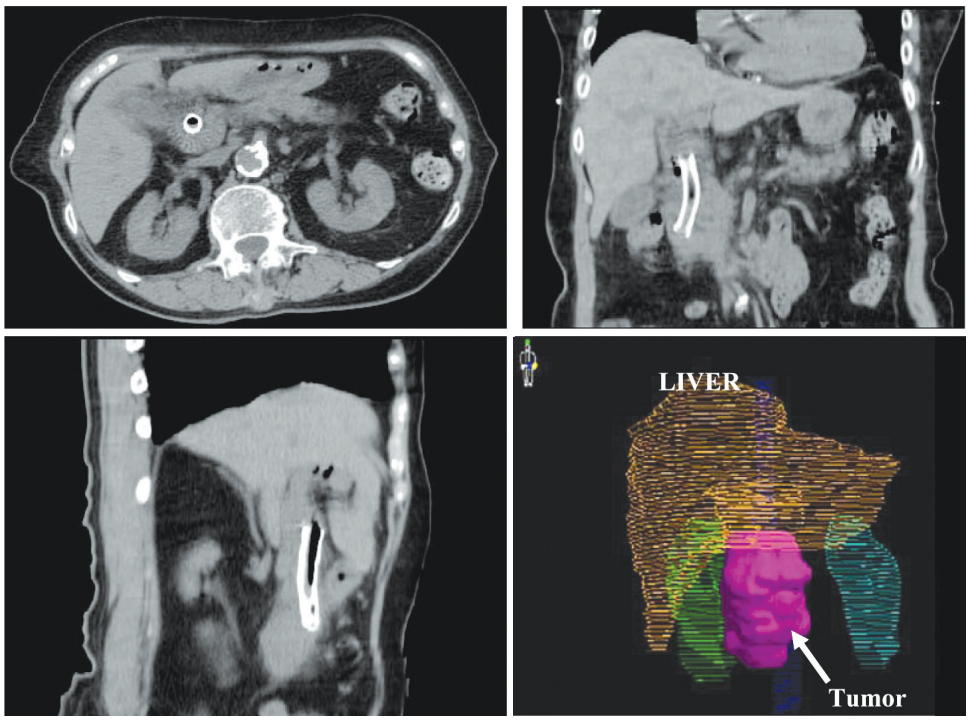

Figure 2: *CT images show the tumor in 3 plane and 3 Dimensional imaging of tumor (pink colour), OAR Liver (yellow), right kidney (green), left kidneys (blue). There is metabolic stent placement in common bile duct.*

Treatment planning

A single arc VMAT, planned by CMS Monaco® treatment planning system, version 2.03 (Elekta Group St. Louis, MO), was used for radiation treatment. We compared the results of the VMAT plan with conventional IMRT plan (5FIMRT) planned with the same TPS (CMS Monaco®). The total number of monitor units (MU) per fraction decreased from 543 to 494 MU and significantly reduced treatment time from 15-20 minutes to 5 minutes, due to a higher dose rate and continuous beam on during modulated arc radiation.

The total prescribed dose of radiation for this case was 45 Gy with a total of 25 fractions. The PTV volumes covered by at least 95% of the prescribed dose were 98.91% and 99.62% respectively, for the VMAT and IMRT plan. In terms of critical organ sparing, V20 (the volume received 20 Gy dose) for the liver in VMAT plan was reduced from 13.20% to 7.75%, V20 for the right kidney was reduced from 3.24% to 1.49% and V20 for the left kidney and the spinal cord dose was comparable to IMRT plan (Table 1). The 2D dose distributions for transverse, sagittal, and coronal planes are shown in Figure 3.

Treatment QA

VMAT plan QA was performed in both 2D and 3D QA analysis, using MatriXX Evolution ionization chamber array and Compass 3D verification software (IBA Dosimetry, Schwarzenbruck, Germany). 3D and 2D planar dose QA were analyzed with Omnipro IMRT software. The 3D dose distribution reconstructed in the patient's anatomy (Figure 4), showed that the difference between TPS calculation and the measurement in terms of the average dose and average gamma in PTV was 0.43% and 0.37 respectively. The 2D dose distribution for coronal plane was measured and compared, the agreement between the measured and calculated dose distribution was within 98% using gamma criteria 3%/3mm. (Figure 5) The point dose was measured with 0.125 cc. ion chamber (PTW Freiburg, Germany), the difference was less than 3% (-2.79% in this study). These results indicated the VMAT plan could be delivered accurately using Elekta Synergy VMAT linear accelerator.

Table 1: Comparison of IMRT and VMAT plan

%Tumor Coverage (D95)		Critical Organs	%V20	
IMRT	VMAT		IMRT	VMAT
99.62	98.91	Liver	13.20	7.75
		Right kidney	3.24	1.49
		Spinal cord	31.66	28.54

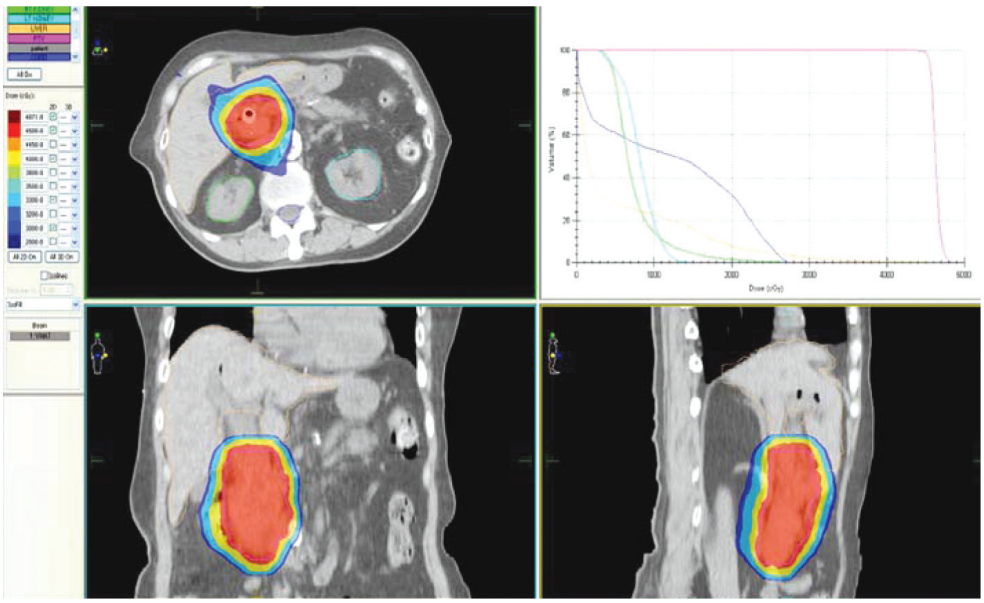

Figure 3: *The 2D distributions for transverse, sagittal, coronal planes and Dose Volume Histograms (DVHs) of VMAT plan*

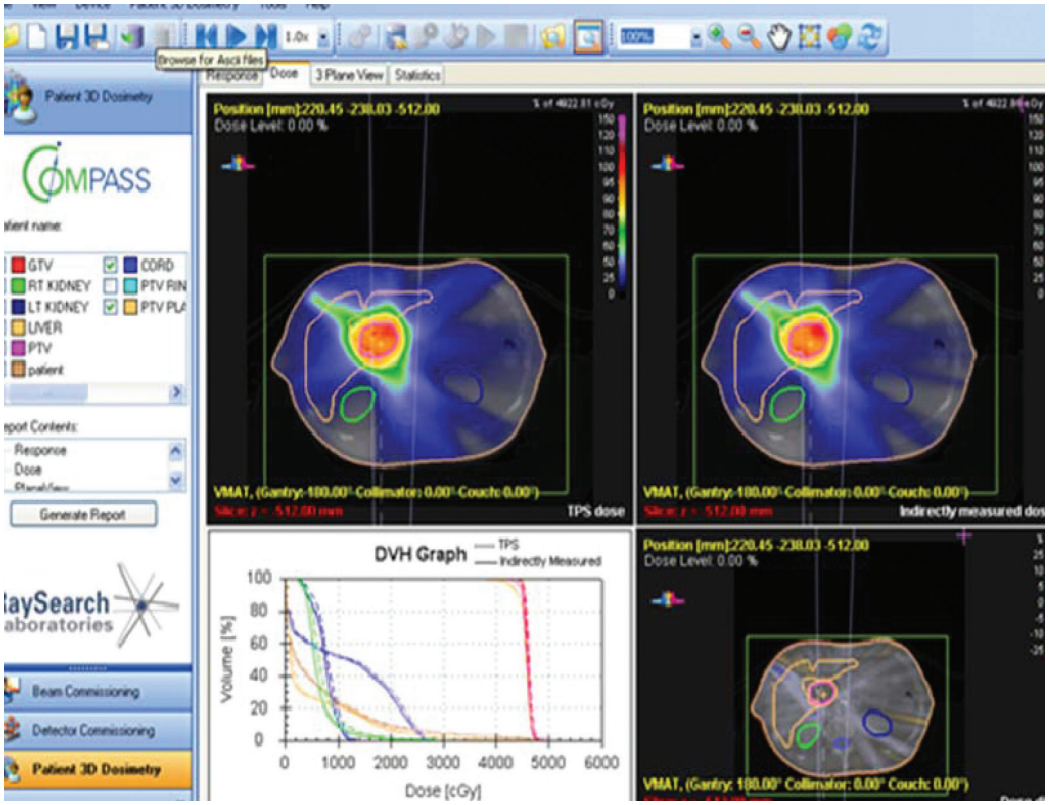

Figure 4: *Shows the result of COMPASS 3D QA for VMAT plan*

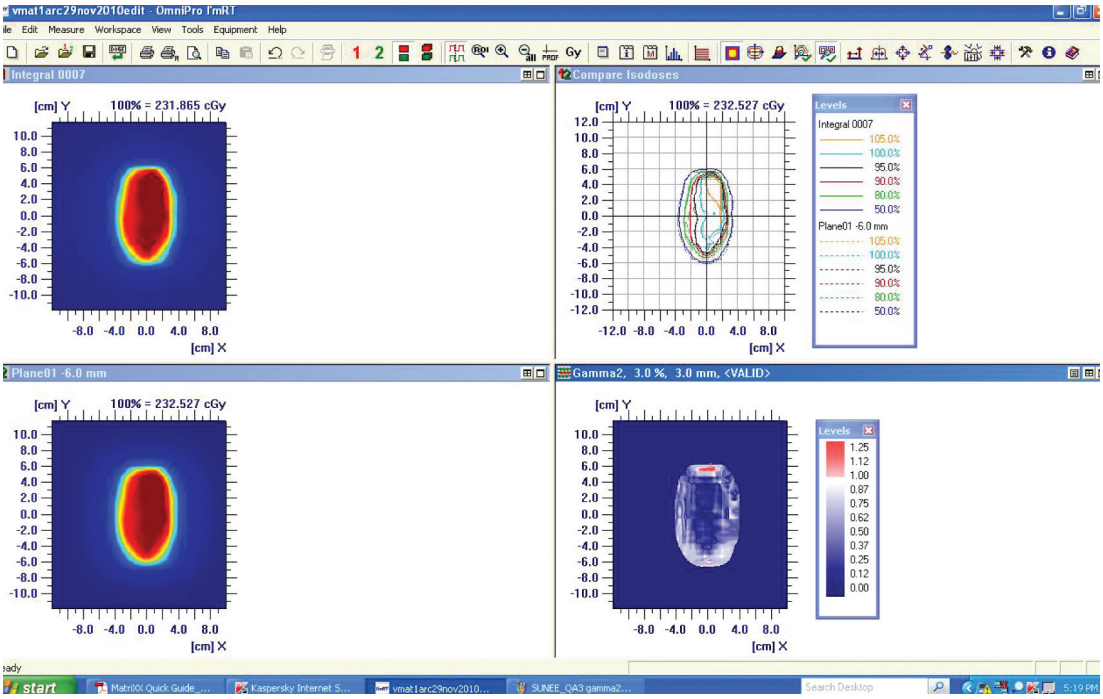

Figure 5: *Shows the result of 2D QA for VMAT plan with Omnipro IMRT*

Image Guidance

The verification of patient and target position used Elekta IGRT technique, XVI® cone beam CT. The patient underwent XVI® image guidance daily for the first three days of treatment and then once a week. The result for mean systemic/random setup error in translation direction for this patient was -0.1±0.07 SD, 0.36±0.19 SD and -0.24±0.16 SD in x/(R-L), y/(S-I) and z/(A-P) respectively. The position correction is neglected if less than 0.5 cm error in any direction. The total irradiation time for VMAT 1 arc is 5 minutes for 494 MU.

Outcome and follow-up

After the completion of the treatment, the patient was free of disease during the 6 months follow up period. The liver function test appeared normal, bilirubin declined to normal levels: $C_{19\text{-}9}$ decreased from 626.50 units/ml. to 178.40 units/ml.

Discussion

The treatment of pancreatic cancer depends on stage, patient status and co-morbidity, but usually requires multi-modality of treatment. One combined treatment method is concurrent chemoradiation therapy; the treatment has been demonstrated not only to palliate symptoms but also to improve patient survival. Nowadays, radiation therapy plays an important role in cancer treatment, using high energy x-rays or other types of radiation to kill cancer cells or keep them growing. The challenge of radiation treatment is the acute radiation side effects on surrounding critical organs, such as kidney, liver or the spinal cord.

Radiation therapy began to be used for cancer treatment more than 100 years ago[3]. The radioactive source, Radium was employed and later, Cesium and Cobalt 60 were also used. Between 1948 and 1953 the first linear accelerators (Linac) were used as sources of radiation.

A total radiation dose is typically divided into multiple sessions (fractionation). As such, there is a need to repeatedly place the radiation beam accurately and reproducibly on the target volume. This has been achieved through a variety of image guidance techniques. Treatment planning is the process used to define the incident angles, shapes and intensities of the Radiation beams used to irradiate the tumor. The development of two-dimensional computed tomography (CT) enabled radiation oncologists and neurosurgeons to directly visualize tumors. Without these early treatment planning systems, the ability to define the tumor using only two-dimensional images was limited and it was impossible to visualize.

Computerization has led to immense leaps in radiation therapy and is now an invaluable tool, in parallel with the great developments in imaging technology and radiation technologies.

The linear accelerators are now standardly used in radiation therapy, and innovations have enabled their increased precision and efficiency, in particular with regard to:

- The incorporation of imaging devices on digital linacs to more accurately locate tumors and plan and deliver radiation doses
- The use of 3D volume imaging to help visualize a tumor in true 3D
- An optimum 3D dose distribution delivered quickly and accurately to the target tumour area, at the same time as reducing unnecessary radiation to the surrounding healthy tissues.

The fast development of advanced imaging and radiation therapy have enabled new state of the art treatment techniques, namely IMRT (intensity modulated radiation therapy) IGRT (image guided radiation therapy) and then VMAT (volumetric modulated arc therapy) (Figure7)

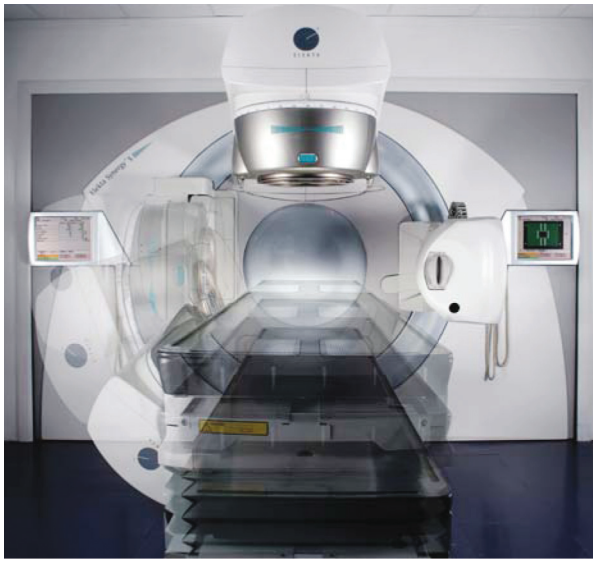

Figure 7: *The Elekta Synergy® combines VMAT&IMRT and image guided radiation therapy (IGRT), XVI®*

Definitions:

– ***3D volume imaging.*** This technology enables visualization of soft tissue detail in any area of the body

– ***IGRT (Image guided radiation therapy).*** The integration of tumor imaging into radiation therapy enabling accurate delivery of radiation through on-line 3D volume imaging

– ***IMRT (Intensity modulated radiation therapy).*** A method of accurately modulating the radiation intensity to areas of the tumor

– ***VMAT (Volumetric modulated arc therapy).*** Rapidly delivers radiation in arcs, whose intensity can be continuously modulated without switching the beam off

Time line showing major innovations in radiation therapy and stereotactic radiosurgery at Bangkok Hospital

Three dimensional conformal and IMRT (Intensity Modulated Radiation Therapy) treatment is currently used to reduce acute short term side effects. IMRT represents one of the technical innovation in modern radiation therapy which uses non-uniform intensity patterns with computer aided optimization to achieve superior dose distribution.

Recently, the sophisticated and advanced radiation therapy technique called Elekta VMAT (Volumetric Modulated Arc Therapy, which was installed in Bangkok Hospital in March 2010) has become an alternative choice for pancreatic cancer treatment in unresectable cases or where surgery is contraindicated. VMAT allows a similar or more precise dose distribution and faster dose delivery than IMRT.

VMAT produces irradiation with simultaneously varying dose rates, gantry speed, collimator, and leaf positions. It's integration with IGRT technology (XVI®, X-ray Volume Imaging), provides three dimensional volume imaging to increase precision, accuracy of target position and therefore clinical confidence. This case study of treating pancreatic cancer with Elekta VMAT planning, shows the dose distribution to the tumor is comparable to IMRT technique but with better organ preservation, whilst also significantly shortening treatment time.

Conclusion

In our case study, the patient with cancer at the head of the pancreas stage $T_1N_0M_0$ was treated with VMAT for curative dose and normal organs such as liver, spinal cord and kidney tolerated the procedure very well. VMAT is thus an important development in treatment options when radical surgery is contraindicated.

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Case Report

Melioidosis and Pandemic Influenza

Paithoon Boonma, MD.[1]

Secondary bacterial pneumonia complication after influenza viral infection is the major caused of death in pandemic influenza of an out break in 1918 and multiple subsequent epidemic and inter-epidemic periods.[1]

The bacteria commonly reported complication after influenza are *Streptococcus pneumonia, Staphylococcus aureus and Haemophilus influenzae*.[2,3] Occasionally other bacterials reports varied to the endemic pathogens. The report 2 cases of probable melioidosis complicated after influenza viral pandemic 2009 are presented.

Case 1

[1] Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.

A 78-year-old man presented with history of relapsed fever after he was treated for influenza A viral infection. About 7 days before this admission, he developed an acute febrile illness with coryza symptoms and body pain. He came to Bangkok Hospital and the screening viral influenza A from nasal secretion was positive. He was treated with Oseltamivir for 5 days. His symptoms was rapidly improved. 2 days prior to admission, he had fever with coughing and progressive right chest pain.

Keywords:
Melioidosis, Pandemic Influenza

The chest x-ray revealed patchy infiltration at right lower lung (Figure 1a). Total White blood cell count (WBC) had increased to 18,800 cell/mm^3 with 90% of Polymorphonuclear (PMN). He was treated as bacterial pneumonia complicated after influenza A viral infection with Amoxicillin/Clavulanic acid and Moxifloxacin.

During the first 3 days of hospitalization, fever persisted and chest pain was not improved. The follow up chest x-ray revealed progressive patchy infiltration with right plural effusion (Figure 1b).

Sputum culture grew *E.coli* and *Staphylococcus aureus* which they were all susceptible to the antibiotics therapy.

Because of his clinical deterioration of clinical pneumonia, antibiotic had changed to Imipenem/Cilastation and Co-trimoxazole. By the time, the results of melioidosis titer showed rising from < 1:80 to 1:320. (Table 1) His clinical was gradually improved with the new antibiotics therapy. Fever gradually subsided and less chest pain. Follow up chest x-ray showed almost clear infiltration and right pleural effusion (Figure 1c)

Antibiotics had switched to oral Amoxicillin/Clavulanic acid for another 2 months.

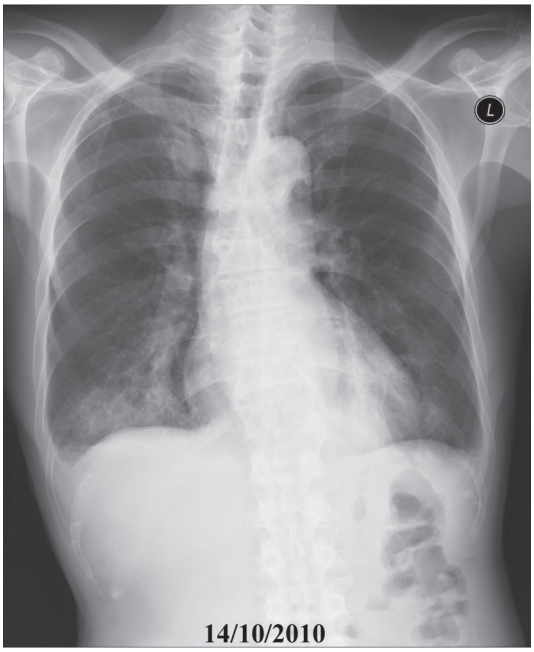

Figure 1a: *The chest x-ray shows patchy infiltration at right lower lung.*

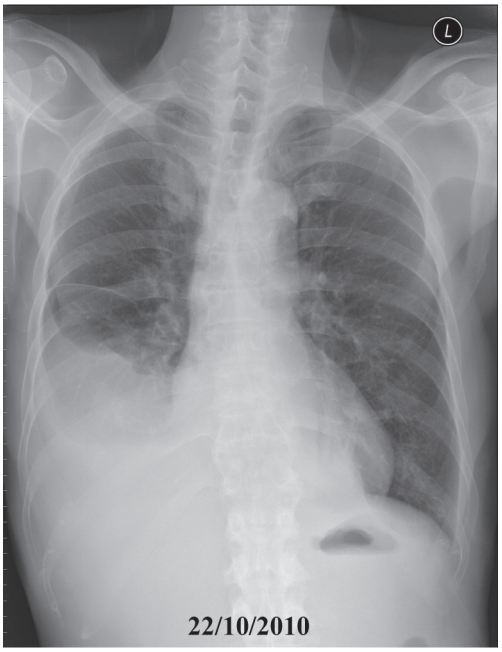

Figure 1b: *The chest x-ray shows progressive patchy infiltration with right pleural effusion.*

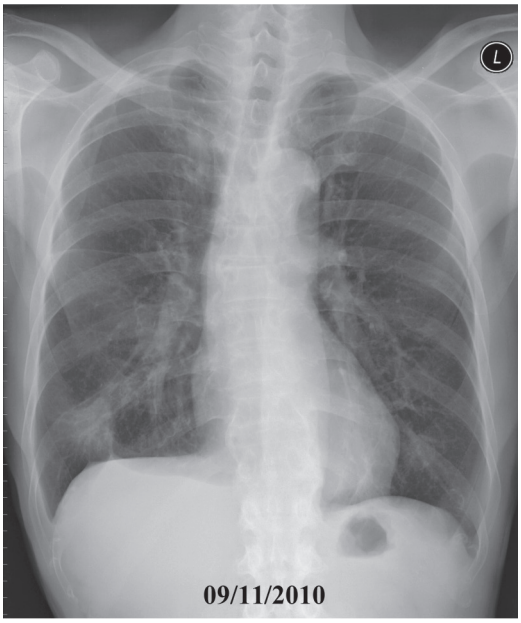

Figure 1c: *The chest x-ray shows almost clear infiltration and right pleural effusion.*

Table 1: Results of Total WBC, melioidosis titer and C reactive protein (CRP) related to antibiotic(s) therapy.

Date	WBC (cell/mm^3)	Melioidosis titer	CRP	Antibiotic therapy
14/10/2010	18,880	<1:80	-	Amoxicillin/Clavulanic acid + Moxifloxacin
19/10/2010	26,350	<1:80	194.3	Imipenem/Cilastation, Co-trimoxazole
21/10/2010	15,610	1:320	-	
25/10/2010	9,050	1:80	-	Amoxicillin/Clavulanic acid
05/11/2010	5,330	<1:80	1.75	

Case 2

A 22-year- old obese young man (body weight 110 kg., height 178 cm.) was transferred to Bangkok Hospital for proper management of severe influenza A pneumonia.

About 5 days prior to this admission, he was sick from acute fever, sore throat, malaise and body aching for 2 days. He admitted in a hospital and investigations of nasopharyngeal secretion was positive for influenza A H1N1 2009. Chest x-ray revealed minimal interstitial infiltration at lower lungs. Initially he was treated with Oseltamivir but the fever persisted and clinical deterioration to progressive dyspnea in 2 days. Empirical antibiotics were added with Cefepime and Levofloxacin. The patient transferred to Bangkok hospital and was admitted in an intensive care unit. He was clinically ill with dyspnea and orthopnea. The oxygen saturation at room air was only 85%. He was on BIPAP ventilator with 100% oxygenation.

Septic work up for caused of pneumonia associated with influenza A was done. Chest x- ray revealed progressive diffuse pulmonary infiltration (Figure 2a).

The echocardiogram revealed good Left ventricular contraction (EF = 63%), no left ventricular hypertrophy and normal heart valves. No pericardial effusion. Because the patient had a criteria of high body mass index (31.9 hg/m^3) that would develop severe influenza A complication, antibiotic empirical therapy started immediately with Oseltamivir, Ceftazidime and Dalacin C. Those regimen would coverage most possible pathogens for his pneumonia. The patient had good clinical responded from the treatment that could observed in the first 24 hours. The patient could wean off BIPAP ventilator and transferred to regular ward in 3 days. For results of septic work up, there was no significant pathogen found except the high serology of melioidosis titer = 1:640 and the titer had rising to 1:1280 in a week later (Table2). Oseltamivir prescribed for 10 days. Antibiotic had switch to oral Amoxicillin/Clavulanic acid and Co-trimoxazole on discharged hospitalization day.[7] The chest x-ray during follow up period showed decrease pulmonary infiltration (Figure 2b) and after treatment about a month, chest x-ray showed completely clear. (Figure 2c)

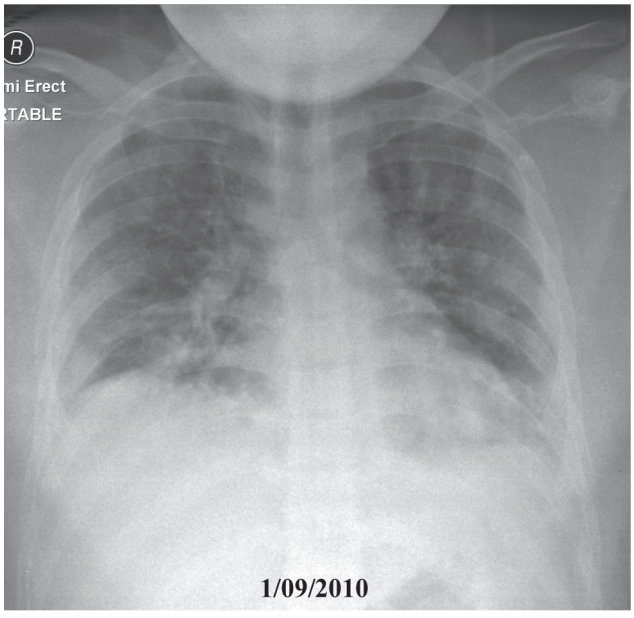

Figure 2a: *The chest x-ray reveals progressive diffuse pulmonary infiltration.*

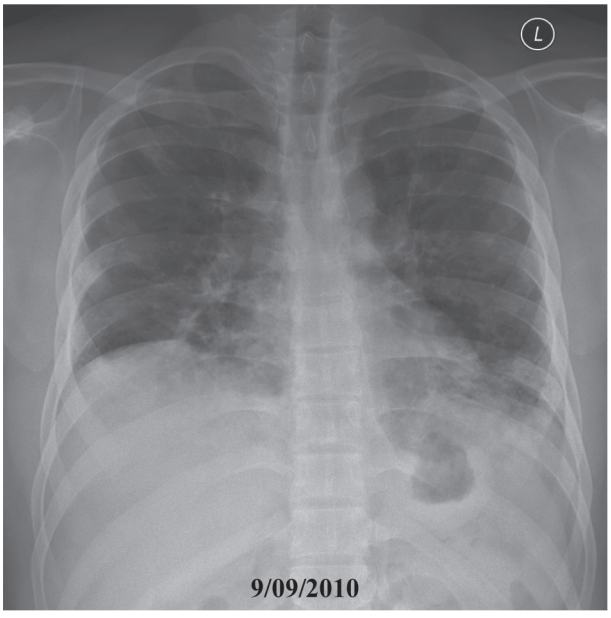

Figure 2b: *After Treatment; chest x-ray shows decrease pulmonary infiltration.*

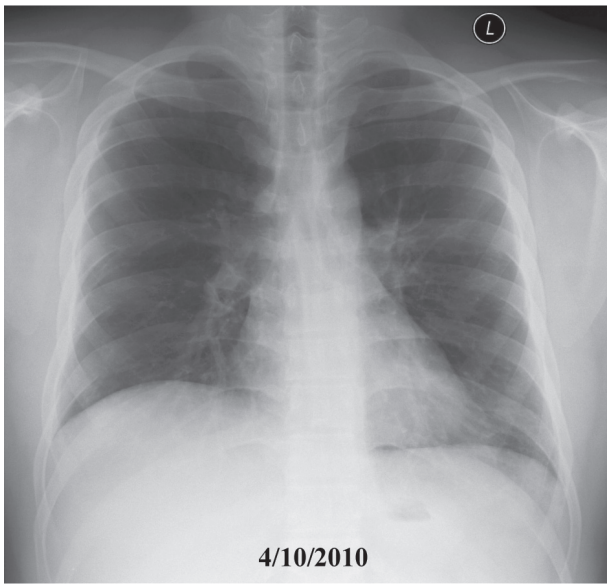

Figure 2-3: *After Treatment about 1 month; Chest x-ray shows completely clear.*

Table 2: Result of Total WBC, melioidosis titer and C reactive protein (CRP) related to antibiotic(s) therapy.

Date	WBC (cell/mm^3)	Melioidosis titer	CRP	Antibiotic therapy
30/08/2010	4,660	1:640	44.98	Ceftazidime, Dalacin C
03/09/2010	6,840	1:640	-	Imipenem/Cilastation
09/09/2010	10,520	1:1,280	-	Co-trimoxazole + Amoxicillin/Clavulanic acid
25/10/2010	11,210	1:1,280	24.30	

Discussion

Melioidosis caused by the bacteria *Burkhoderia pseudomallei*. The organism presents in soil and surface water in endemic area of South East Asia an Northern Australia. Infection usually follows percutaneous inoculation or inhalation of the causative organism.[4,5,6]

Clinical presentations varied from asymptomatic, subacute and chronic infection to an acute disseminated septicemia which has high mortality rate up to 80-90%.[7] Infection can occur long after exposure to endemic area many years later.[8,9] About 60% had underlying disease e.g. Diabetes mellitus, chronic kidney and chronic liver disease.

Pulmonary infection is the most common site of more than 50% of patients. The disease has high prevalence during many season.[5,6]

Interestingly, melioidosis is rarely reported to be complicated after influenza viral infection particularly in the endemic area. This might be that influenza viral is rarely tested for inpatient whom admitted with community acquired pneumonia.

Since the pandemic influenza A H1N1 2009 outbreak during 2009-2010, physicians were informed early detection of this viral outbreak and therefore, beware of it's complication particularly in high risk patients.

To my knowledge, only one case reported of melioidosis had complicated after influenza A infection.[8] The disease activation occurred long after exposure to a known endemic area in Vietnam six years ago. This case demonstrates the potential of melioidosis to appear long after departure from endemic area and recrudescence had been reported in associated with a variety of stressful event such as thermal injury, after surgery, diabetic ketoacidosis and infection associated e.g. pneumococcal pneumonia, dengue hemorrhagic fever, Mycobacterial disease[4] and influenza A.[8]

Most antibiotic recommended for treatment community acquired pneumonia[10] do not have broad activity to coverage sever melioidosis. Ceftazidime and Imipenem/ Cilastation have well been on clinical control trials that could decreased mortality rate in severe septicemia melioidosis more than 50 percent.[11,12,13,14]

2 cases report, demonstration that melioidosis might also be one of the pathogens complication after influenza A infections. Through, the organism could not detection from the clinical specimen, their serologic study, melioidosis titer had rising significantly. They could be diagnosed probably melioidosis.[7]

Therefore melioidosis should be considering particularly cases of pneumonia from endemic area which was not responded to those antibiotics commonly used for community acquired pneumonia.

Conclusion

Report 2 cases of influenza A viral infection and developed pneumonia complication from probable melioidosis. They had good clinical responded to antimelioidosis-antibiotic treatment.

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Diffuse pulmonary neuroendocrine cell hyperplasia with tumorlets and elevated serum CEA

Prawat Nitiyanant, MD.[1, 4]
Vitoon Pitiguagool, MD.[2]
Chirotchana Suchato, MD.[3]
Rergchai Varatorn, MD.[3]

[1]N Health Pathology Department, National Healthcare System, Bangkok Hospital Group, Bangkok, Thailand.
[2]Division of Cardiothoracic and Vascular Surgery, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[3]Imaging Center, Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[4]Department of Pathology,Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Bangkok, Thailand.

Keywords:
Pulmonary tumorlets, CEA, F18-FDG-PET/CT, (DIPNECH).

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a generalized proliferation of scattering single cells, small nodules (neuroendocrine bodies) or linear proliferations of neuroendocrine cells of lung. They may be confined to the bronchial and bronchiolar epithelium, include local extraluminal proliferation (tumorlets), or progress to the development of carcinoid tumor. Sometimes DIPNECH is accompanied by intra- and extraluminal fibrosis of the involved airways.[1,2] It is rare and presents typically in the fifth or sixth decades and is more common in woman.

The great majority of pulmonary tumorlets are found incidentally and show no clinical consequence. Only rare occasions bronchopulmonary lymph node metastasis were reported.[3,4,5] DIPNECH and tumorlets may associated with Cushing syndrome,[6,7] elevated serum CEA.[8]

Case report

A 60-year-old asymptomatic Thai female with history of mild hyperglycemia, hyperlipidemia and hyperuricemia had high and rising serum CEA levels (Figure 1). The chest x-ray and tomosynthesis (Figure 2a-b) showed subsegmental atelectasis and reticular infiltration at the right middle lobe. CT Chest (Figure 3) showed small pulmonary atelectasis at right middle lobe.

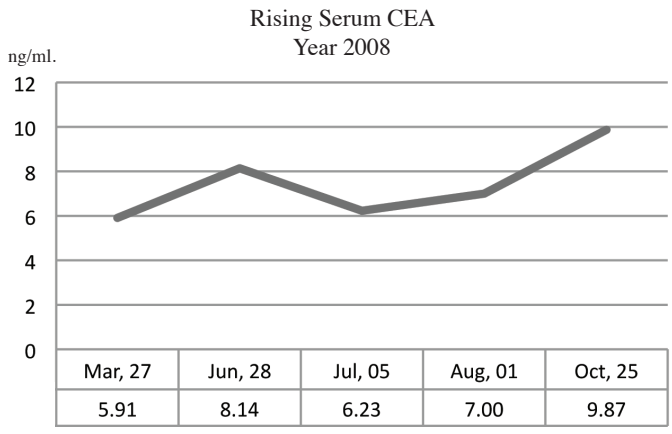

Figure 1: *Graph shows rising serum CEA*

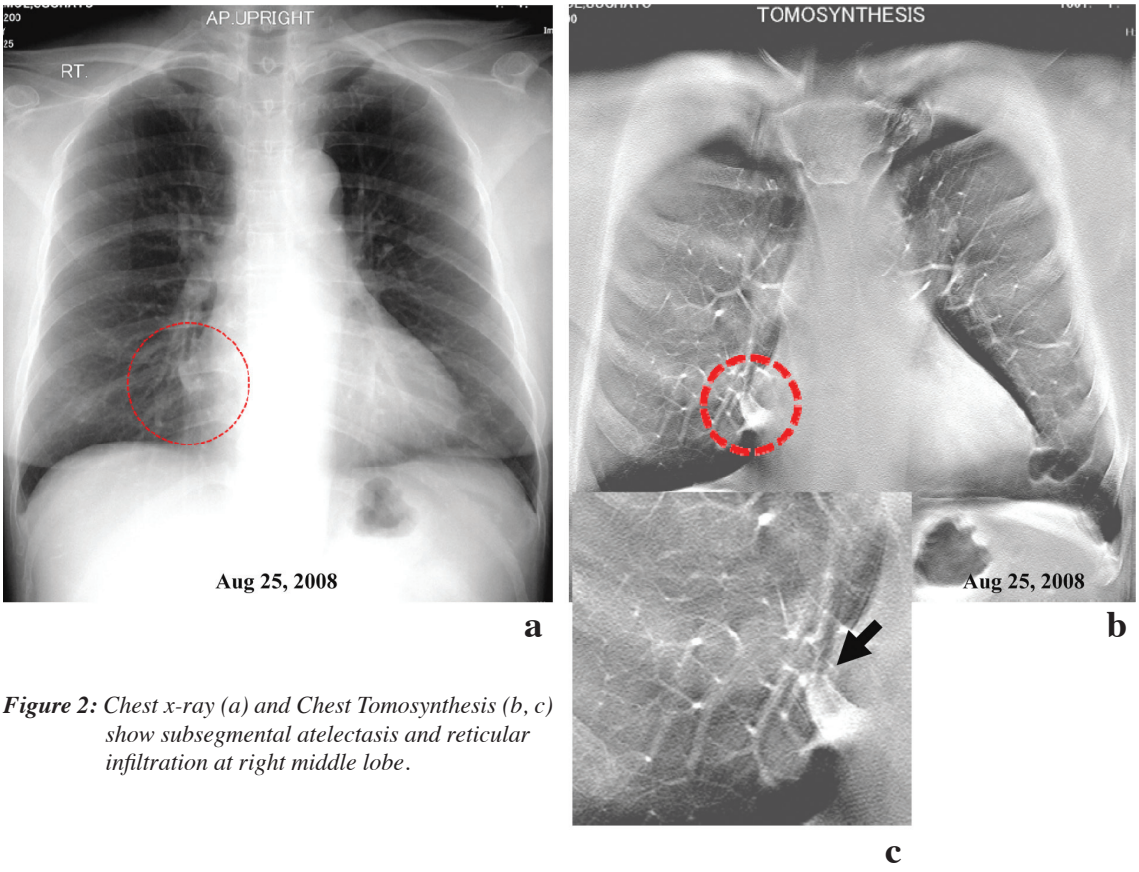

Figure 2: *Chest x-ray (a) and Chest Tomosynthesis (b, c) show subsegmental atelectasis and reticular infiltration at right middle lobe.*

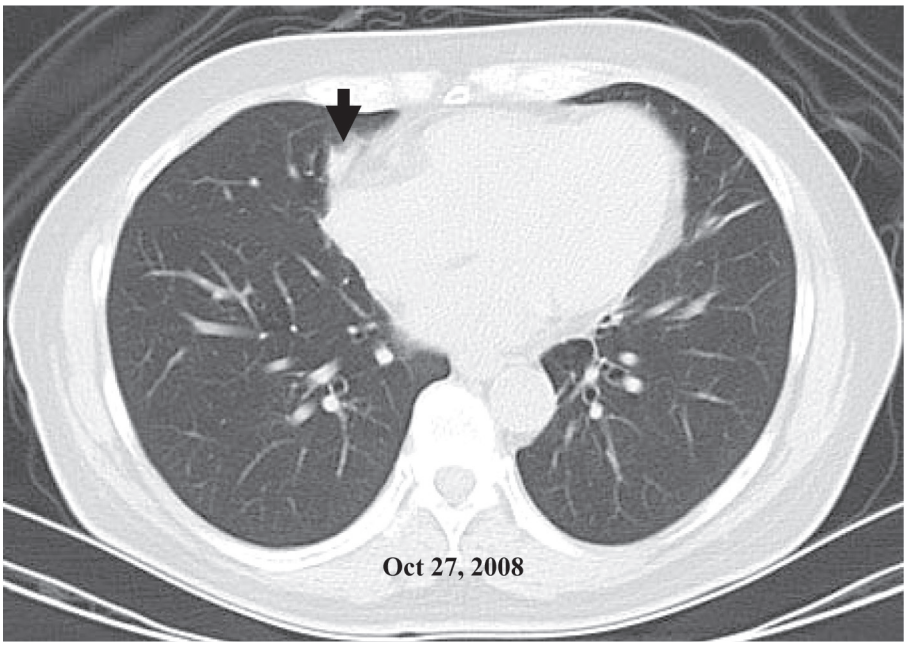

Figure 3: *CT Chest shows small pulmonary atelectasis at right middle lobe.*

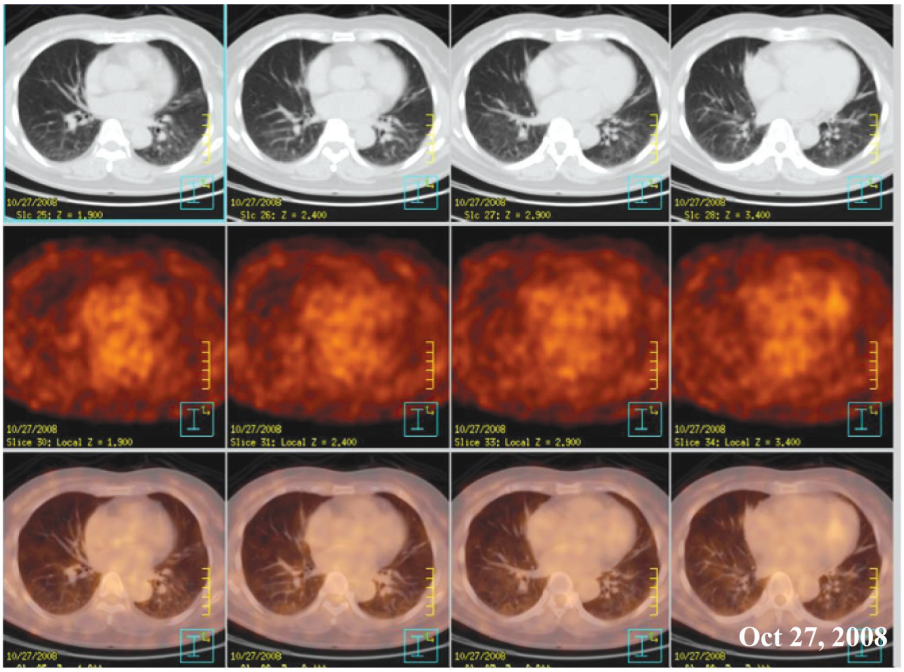

Figure 4: *The F18-FDG-PET/CT show non-FDG avid lesion in right middle lobe, which could be a benign lesion. Pulmonary tumorlets and bronchioalveolar carcinoma may also be non-FDG avid lesion.*

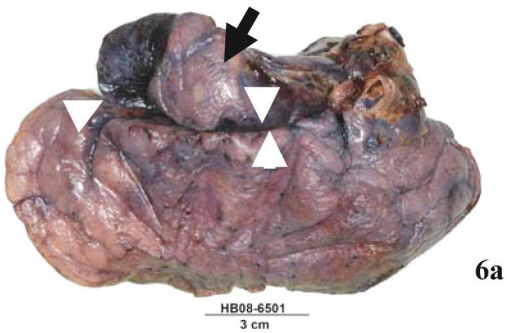

Figure 6a: *The right middle lobe shows one accessory lobe (arrow) superior to a minor fissue (arrow head)*

Figure 6c: *The accessory lobe shows areas hemorrhage, atelectasis and clusters of dilated brochi.*

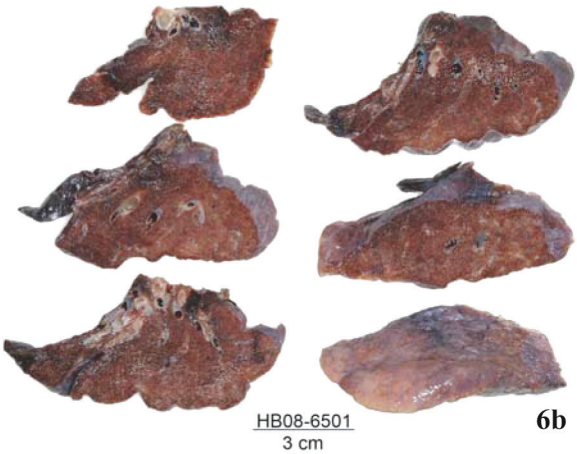

Figure 6b: *Serial near horizontal sections of the right middle lobe show no visible tumor nodule.*

The F18-FDG-PET/CT (Figure 4) showed non-FDG avid lesion in the right middle lobe, which could be a benign lesion. But pulmonary tumorlets and bronchioloalveolar carcinoma may also be non-FDG avid lesion.

On gross examination, the right middle lobe of lung showed one minor fissure and one small accessory lobe at the superior part of the lateral segment (Figure 6a). There is no tumor nodule seen in the lung parenchyma. (Figure 6b). One pale tan brown rubbery firm atelectatic area, measuring 2x1x0.8 cm. with clusters of dilated bronchi is noted in the central part adjacent to the minor fissure, extending from the middle lobe bronchus to the peripheral part of lung. The remaining accessory lobe is grey brown and firm. The lung parenchyma is tan brown, focally black and soft. Some dilated blood vessels filled with blood and few brown black nodules of 3 to 4 mm. are noted. (Figure 6c).

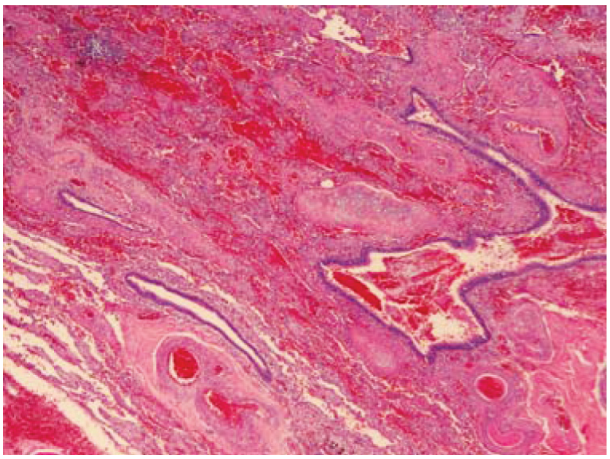

Figure 7: *Lung shows areas of hemorrhage, several blood vessels, focal fibrosis and dilated bronchi (HE x20).*

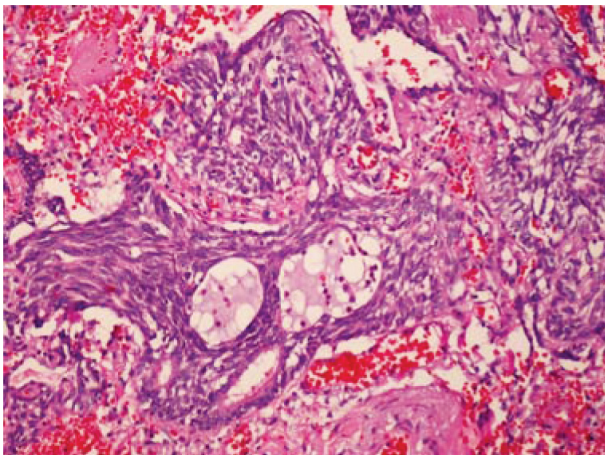

Figure 8a: *Lung tissue shows three microscopic tumorlets with hemorrhage and mild focal fibrosis in the stroma. (HE x100).*

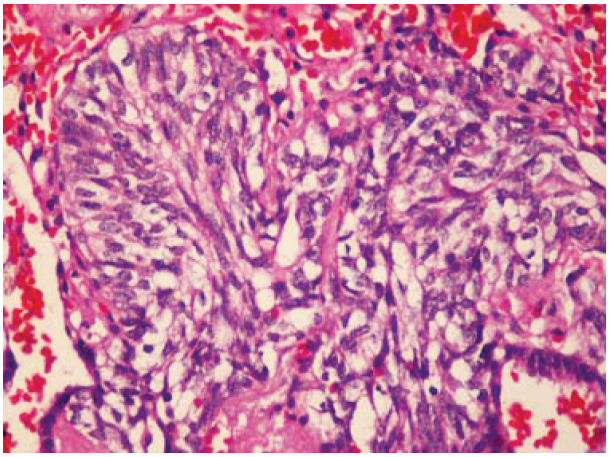

Figure 8b: *One tumorlet composing of spindle, polyhedral to oval shape tumor cells with scanty to clear, vacuolated cytoplasm and elongated to oval nuclei with speckled chromatin (HE x200).*

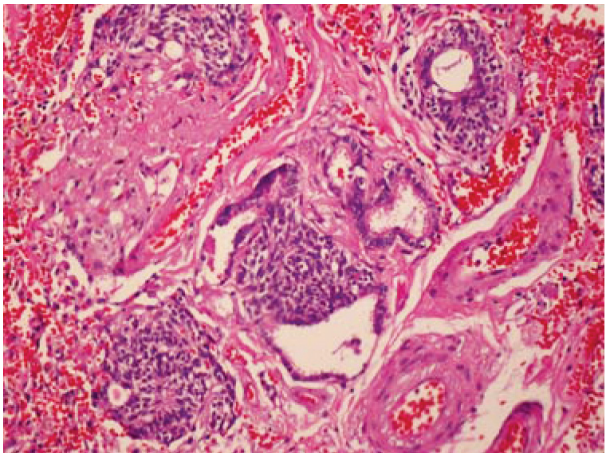

Figure 8c: *In this fibrotic, hemorrhagic and vascularized area, there are four terminal bronchi showing neuroendocrine cell hyperplasia (HE x100).*

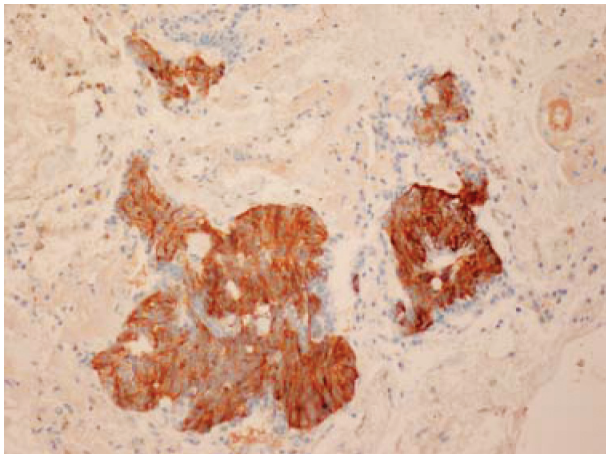

Figure 8d: *One tumorlet and three terminal bronchi show neuroendocrine cell hyperplasia (chromogranin A x100).*

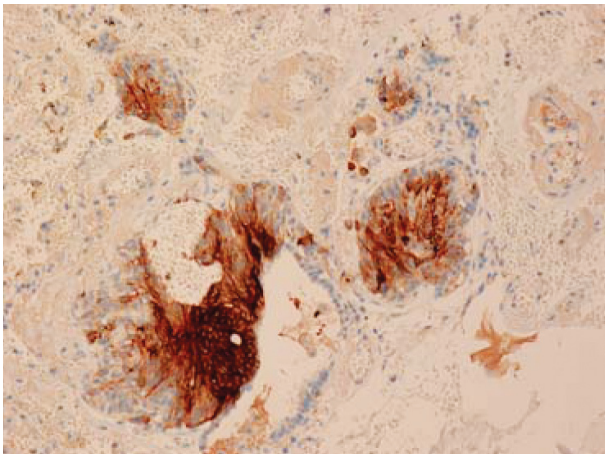

Figure 8e: *The tumorlet and foci of neuroendocrine cell hyperplasia are also CEA positive (CEA x100).*

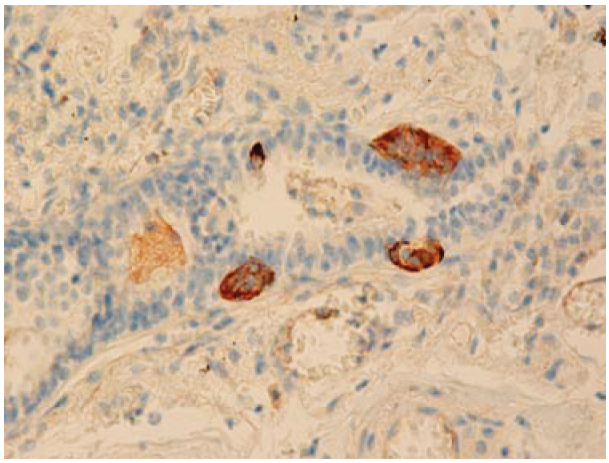

Figure 9: *Single, small clusters and one small nodule of chromogranin A positive neuroendocrine cells in the mucosa of one small brochus (Chromogranin A x200).*

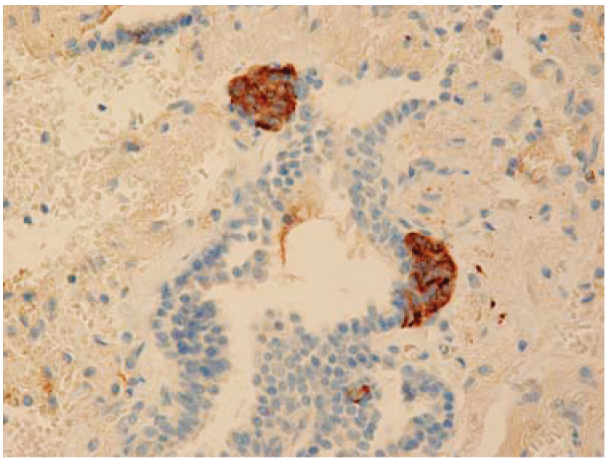

Figure 10: *Two small nodules of neuroendocrine cells (neuroendocrine bodies) in the bronchiolar mucosa (chromogranin A x200).*

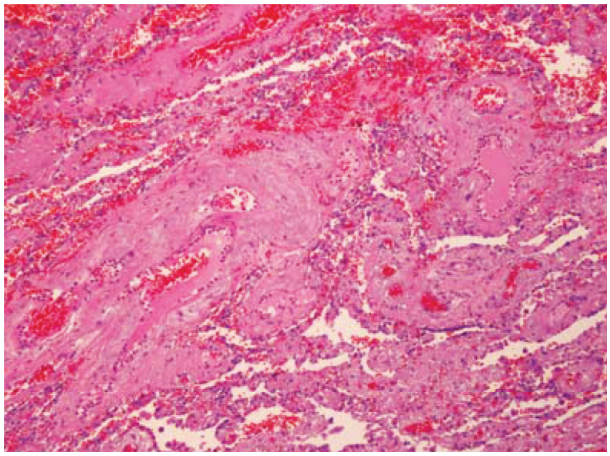

Figure 11: *Lung tissue shows areas of vascular malformation and mild hemorrhage (HE x100).*

The microscopic examination of the lung revealed areas of severe hemorrhage with several vaious sizes blood vessels, foci of fibrosis (Figure 7), dilated bronchi, multiple small foci of lymphoid cells infiltration and multiple clusters or nests of spindle, polyhedral, oval to round tumor cells with scanty cytoplasm and oval to elongated nuclei with speckle chromatin and few perceptable nucleoli (Figure 8a-e).These cells are TTF1 +ve; chromogranina A +ve; CEA +ve but CK 20 –ve. Few tumor cells are CK 7 +ve. There are few mitoses noted. They are tumorlets or carcinoid tumorlets of lung. Many dilated bronchi show mild chronic inflammation and focal fibrosis. Some dilated bronchi in the hemorrhagic areas show occasional thick wall blood vessels and some areas of dilated capillaries and small lymphatics in the lamina propria of the mucosa. Many small bronchi and bronchioles show scattering single, small clusters and nodules of chromogranina A and CEA positive cells in the mucosa (Figure 9-10). The finding are compatible with diffuse pulmonary neuroendocrine cell hyperplasia. Several small blood vessels in the hemorrhagic areas show hyalinization of the wall with occasional foci of increased elastic fibers. Some larger blood vessels show acidophilic areas and increased elastic fibers in the wall. Few blood vessels show mixed aterial and venous walls (Figure 11). The lung parenchyma inferior to the minor fissure shows congestion, occasional foci of hemorrhage, mild emphysematous changes and occasional small foci of mild anthracosis.

Discussion

Diffuse Pulmonary neuroendocrine cell hyperplasis (DIPNECH) and pulmonary tumorlets can be found in lungs with little to no scarring or less common in lungs severely scarred by bronchiectasis or other inflammatory process.[1-5] They may be associated with Cushing syndrome[6,7] High CEA (33ng/ml) was found in one case of DIPNECH in associations with an adenocarcinoma of a mixed subtype with partial neuroendocrine differentiation of the right upper lobe. The tumor was strongly positive for CK7;CK18; TTF1 and SPA and focally positive for

CEA, NSE and chromogranin A. The proliferation rate (Ki67) was 20-30%. The cells of multiple tumorlets and DIPNECH were strongle positive for CD56; synaptophysin, NSE and chromogranin A and focally positive for CK7,CK18, TTF1 with proliferation rate (Ki67) of 1-2%[8] Tumorlets were found in one case of pulmonary sequestration with elevated serum progastrin-releasing peptide.[9] Tumorlets and carcinoid secondary to congenital broncho-esophageal fistula were also reported.[10]

The right middle lobe in our case showed one accessory lobe with vascular malformation, hemorrhage and bronchiectasis. These may be suggestive of a minor malformation (?sequestration) The DIPNECH and tumorlets found mainly in the accessory lobe showed positive chromogranin A, CEA and CK7. The serum CEA in her postoperative and follow up period are still elevated and rising. Bronchioloalveolar carcinoma (BAC) less than 5 mm. with rather low number of tumor cells is possible false negative by F18-FDGPET/CT. Slow growing pulmonary neuroendocrine neoplasms with low metabolic activity are often negative F18-FDG-PET/CT.[11] These may explained the negative imaging results in our case. Pulmonary tumorlets should be included in the differential diagnosis of a subcentrimeter pulmonary nodule.[12]

Tumorlets developed from hyperplastic neuroendocrine cells (Kulchitsky cells) in the bronchial and bronchiolar mucosa.[13] The natural history is unknown. The mechanism of progression may involve critical genetic alteration. There are some reports of Cushing syndrome associated with pulmonary tumorlets. The tumorlets are benign condition but rarely they show lymp node metastasis. Since the pulmonary neuroendocrine cells in this patient also secrete CEA (evidence by immunohistochenical study), postoperatively rising serum CEA may be suggestion of remaining neuroendocrine cells proliferation so recurrent DIPNECH and tumorlets should be aware. On routine CT scan shows small subsegmental atelectasis or small nodule. The other study F18-FDG-PET/CT show no increase uptake. All investigation could not rule out malignant process. Therefore the thoracotomy for lesion removal is recommended. This report is a good teaching case for the pulmonary innfiltration or small nodule which all imagings and laboratory findings do not show the definite diagnosis. The removal of the lesion is indicated.

Conclusion

This case illustrates the difficulty in the preoperative diagnosis of DIPNECH and tumorlets, the definite diagnosis can be made by pathologic examination.

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Takotsubo-like syndrome, the role of IABP in Neurosurgical Patients

Nanthasak Tisavipa, MD.[1]
Denchai Laiwattana, MD.[1]
Decha Kintorn, MD.[1]
Vikrom Srisukh, MD.[2]
WitayaJongsupangkarat, MD.[2]
Akkapong Nitisingh, MD.[3]
Parunut Itthimatin, MD.[3]

[1] Neurosurgery Department, Bangkok Neuroscience Center, Bangkok Hospital Group, Bangkok, Thailand.
[2] Cardiovascular Medicine, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[3] Neurosurgical Unit, Department of Surgery, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Keywords:
Intracerebral hemorrhage, Subarachnoid hemorrhage, Takotsubo syndrome

The associations between cardiac problems and neurological problems are common. The most well known one is EKG changes in patients with subarachnoid hemorrhage (SAH). EKG changes can be seen as much as 50-100% in acute stage of SAH.[1,2] The echocardiography also reveals the abnormalities in left ventricular (LV) function in these patients. Many neurological conditions can result in transient LV dysfunction which can be demonstrated clearly by echocardiography with or without EKG change. This finding was first reported as "Takotsubo syndrome" in 1991 by Satoh.[3] We report cases of intracerebral hemorrhage with low ejection fraction without EKG change.

Case 1

A right handed male patient aged 46 years, without prior serious medical history came to the hospital with symptoms of dysarthria, right facial palsy and right hemiparesis. CT scan revealed large left parietal intracerebral hematoma. The preoperative EKG showed nonspecific ST-T change. The patient underwent echocardiography on the first day of onset. The echocardiogram revealed dilated left ventricle and global poor contraction in which ejection fraction (EF) was 35-40%. No blood clot was seen. No other abnormality was seen. He underwent the cranial surgery uneventfully and no cardiac event occurred during intraoperative period. Post operative period was uneventful. The follow up echocardiogram performed on the 2nd day after surgery revealed normal LV size, fair to good contraction, EF=50%. The exercise stress echo was also negative. The echocardiogram was performed again, two years later. The results were normal LV size, normal contraction, EF 51%.

Case 2

A 56-year-old, right handed female patient who was otherwise healthy, suffered from sudden onset of severe headache and loss of consciousness 4 hours before arrival. CT scan showed the subarachnoid hemorrhage with brain edema. CT scan showed Fisher grade III. (Figure 1) She underwent the 4 vessels cerebral angiogram and was diagnosed as having a ruptured anterior communicating artery. (Figure 2-3) Her chest film showed pulmonary edema. (Figure 4) Her blood pressure dropped to 80/40 mmHg. The EKG showed normal sinus rhythm. The echocardiography (Figure 5) showed dilated left ventricle, poor left ventricular systolic function (EF=33%), akinesia of anterior, anteroseptal and anterolateral wall, therefore her diagnosis was congestive heart failure. Although the inotropic drug, dobutamine, was maximally infused, her systolic blood pressure remained under 100 mmHg. The intraaortic balloon pump (IABP) was inserted to augment the heart to maintain the systemic blood pressure. She did well with the IABP. The aneurysm was successfully coiled.

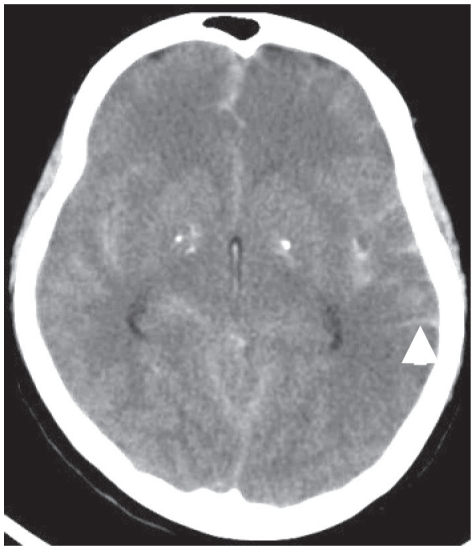

Figure 1: *Subarachnoid hemorrhage in non contrast CT scan (see arrow head)*

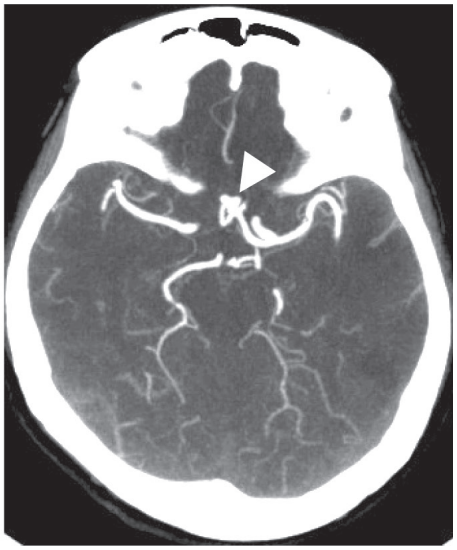

Figure 2: *CTA shows anterior communicating artery aneurysm. (see arrow head)*

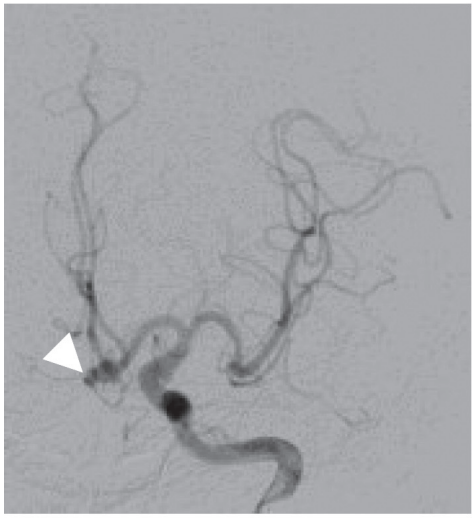

Figure 3: *Left ICA angiogram shows anterior communicating artery aneurysm. (see arrow head)*

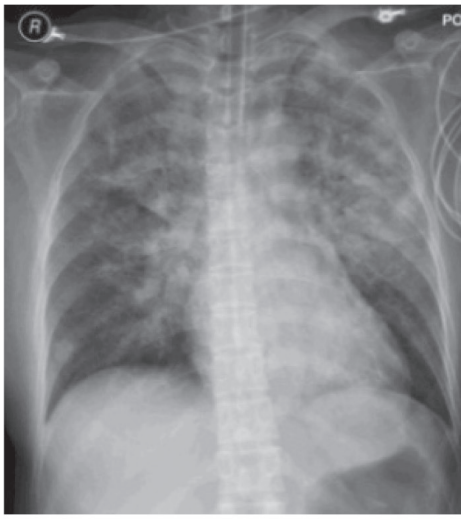

Figure 4: *The Chest x-ray shows pulmonary edema*

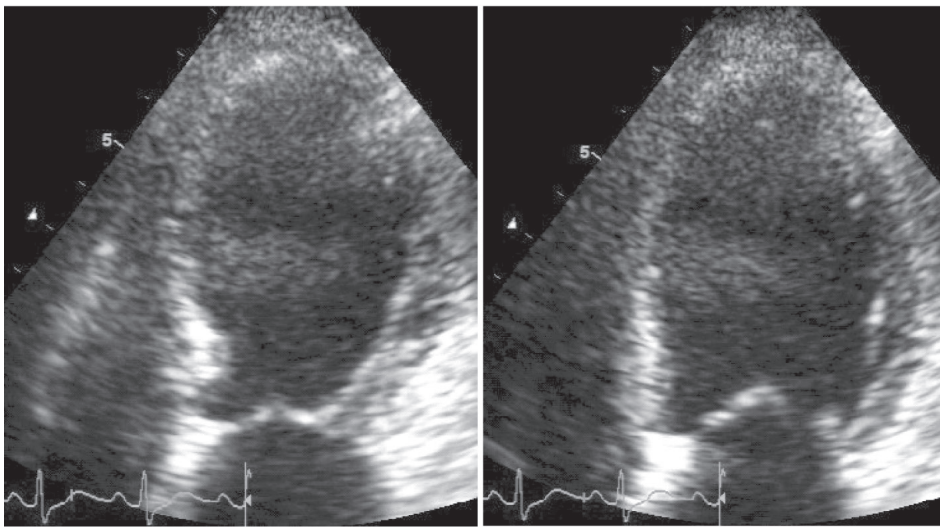

Figure 5: *Echocardiograms show dilated left ventricle, poor left ventricular systolic function.*

Discussion

Although the mechanism of neuro-cardiac syndrome is not well understood, there have been many reported cases concerning this particular syndrome. The most well known syndrome is Takotsubo syndrome. The name Takotsubo originates from the shape of the left ventricle, which resembles a Japanese octopus-trapping pot.

The classic Takotsubo syndrome is characterized by transient, often severe left ventricular dysfunction and EKG changes that might mimic acute myocardial infarction in the absence of significant obstructive coronary disease.[4] Since being first described in 1991, there were more than 789 cases reported as of May 2008.[4] Elderly women are most commonly affected.

We present cases of LV dysfunction in the intracerebral hemorrhage and subarachnoid hemorrhage patients. The clinical findings of these patients were similar to Takotsubo syndrome. The EKG changes in our patients were non-specific ST-T changes. The cardiac enzyme did not change; therefore the coronary angiogram was not performed. However the echocardiogram revealed the LV dysfunction which spontaneously resolved. As for the first case, the recovery of the heart was evidenced at 6 months after initial echocardiogram. There was no period of systemic circulation problem during his admission.

The other case was more severe and quite complex. The patient suffered from a ruptured anterior communicating artery aneurysm and pulmonary edema. Her systemic blood pressure could not be maintained, despite inotropic drugs being maximally administered. The IABP was introduced to maintain her systemic blood pressure. In subarachnoid hemorrhage, the main rationales of treatment are to avoid cerebral vasospasm and maintain cerebral perfusion pressure (CPP) which can be calculated by the subtraction of intracranial pressure (ICP) from mean arterial pressure (MAP) [CPP=MAP-ICP]. The options of treatment include triple-H therapy which consists of hypervolemia, hypertension, and hemodilution. In the patient with signs of congestive heart failure, the volume control is crucial. Accompanying the hypertensive goal, the IABP played more than one role for this particular patient.

Incidence and Demographics

The incidence of Takotsubo syndrome in intracerebral hemorrhage patients remains as yet unknown. [5] N. Banki, et al., in his large prospec-tive studies of LV dysfunction after SAH, reported 28% of 173 patients had evidence of regional LV dysfunction and 15% had global LV dysfunction, with an LVEF less than 50.[6] However, due to its similarity to atherothrombosis-mediated acute coronary syndromes and its unfamiliar diagnosis, it is likely under-reported. The mean age of patients presenting with this syndrome is approximately 62–75 years of age.[28] Approximately 85–100% of patients diagnosed with Takotsubo are women.

Pathophysiology

Although the mechanism of Takotsubo is unknown, several theories regarding the cause for this syndrome have been proposed. The relationship between stressful events and the onset of symptoms was observed in several reports. Increasing of catecholamines has been reported in many patients following Takotsubo cardiomyopathy. Elevated catecholamine levels have been shown to cause direct myocyte injury via an increase in intracellular calcium and oxygen-free radicals. This pathologic process is seen in catecholamine-induced cardiomyopathy (i.e., secondary to a pheochromocytoma) which histologically and morphologically results in abnormalities similar to Takotsubo.

It is hypothesized then that excessive activation of cardiac catecholamine receptors may be the origin of the cardiomyopathy.[7,8,9] The unique distribution of sympathetic nerves and receptors on LV contributes to this hypothesis.[10,11] The catecholamine receptors on left ventricle are composed of $\beta 1$,$\beta 2$ 85%, and $\alpha 1$,$\alpha 2$ for the rest.[3] This causes hypercontractility of the affected left ventricle. In addition, there is a possible loss of elasticity following extreme expansion together with the presence of a thinner layer of myocardium at the apex as compared to other regions of the LV.[12] This explains why the syndrome affects the LV apex and result in apical ballooning. Direct myocyte toxicity due to calcium overload, microvascular dysfunction due to excessive catecholamines or primary metabolic abnormalities are also possible mechanisms.[4]

Temporary occlusion of a variant left anterior descending (LAD) due to ruptured atherosclerotic plaque is another hypothesis.[29] Although this coronary anatomy was not observed in all patients, it has been suggested as an alternative explanation in some cases.

The most common affected segments were the basal portions of the anteroseptal and anterior walls and the middle ventricular portions of the anteroseptal, inferoseptal, anterior, and anterolateral walls.[6]

Clinical feature and diagnosis

Patients often present with chest pain, and/or dyspnea, after suffering acute physical or emotional stress. Patients' symptoms may range from mildly symptomatic to critically ill. Bybee et al. have proposed criteria for the diagnosis of this syndrome (Table 1)

Table 1: Proposed Mayo Criteria for the Diagnosis of Takotsubo Cardiomyopathy*[14]

1. Electrocardiographic abnormalities (ST-segment elevation followed by T-wave inversion)
2. Transient apical and mid-ventricular wall motion abnormalities (akinesis or dyskinesis)
3. Absence of obstructive coronary artery disease or evidence of acute plaque rupture
4. Absence of the following:
a. Recent significant head trauma
b. Intracranial hemorrhage
c. Pheochromocytoma
d. Another etiology of myocardial dysfunction (myocarditis or hypertrophic cardiomyopathy)

**Patients must fulfill all four characteristics*

Management

The management of Takotsubo syndrome is primarily empirical and should be individualized depending on the LV function. There is emerging data which supports the role of β-blocker, propanolol, in decreasing peak gradients in midventricular obstruction.[12,13] β-blockers decrease LV contractility and increase the diastolic filling time which augmented LV end diastolic volume (EDV).[14,15] In the patients with coronary artery vasospasm, dihydropyridine calcium channel blockers are recommended instead of β-blocker.[14,16] Dobutamine is contraindicated in this kind of patient.[16,17,18] Phenylephrine may represent an alternative approach in patients presenting with outflow tract obstruction and severe hypotension. In hemodynamically unstable patients, early administration of intra-aortic balloon pump counterpulsation should be considered.[32]

Generally, Takotsubo syndrome is a quite benign and self-limiting condition. But if systemic blood pressure cannot be maintained, Intra-Aortic Balloon Pump is an effective treatment option. In rare situations Takotsubo syndrome can progress into refractory cardiogenic shock with limited therapeutic options available. Bonacchi M, et al. reported their application of Extracorporeal life support in order to rest the heart, sustain circulation and end-organ perfusion. They concluded that ECLS might be the selected treatment and seems to be an effective and useful ultimate therapeutic strategy for preventing death.[33]

Management of Takotsubo syndrome after subarachnoid hemorrhage

In patients with subarachnoid hemorrhage who need hypervolemia and permissive hypertension, the low EF can reduce the cerebral perfusion and cause brain damage. Although the systemic blood pressure can remain in normal acceptable range, this patient group almost always needs a mild to moderate degree of hypertensio in order to treat the vasospasm. When Takotsubo syndrome occurs, even maximized inotropic agents could not raise the systemic blood pressure high enough to correct vasospasm.

The author used IABP in conjunction with inotropic agents in order to sustain circulation and promote potential ventricular recovery. The IABP can maintain the systemic blood pressure and allows additional space for volume infusion. As mentioned earlier, Takotsubo syndrome is a self-limiting condition, therefore within or two weeks, the patient will no longer need IABP.

Prognosis

Takotsubo syndrome does not cause permanent myocardial damage. Contrast enhanced MRI scan of heart shows no residual scaring, although there is severe residual regional wall dysfunction. In addition, the myocardial changes seen in myocardial biopsy are also completely normalized after functional recovery.[19] Therefore the Takotsubo syndrome is generally a benign condition, mortality rate is less than 1% in hospitalized patients[13,16] and recurrence rate is no more than 10%.[31] Complete recovery of contractile function has been documented in nearly all cases and usually resolves within a few weeks.[30] Only 5% of the patients with Takotsubo syndrome have the significant finding on coronary angiogram and rarely develop fulminant myocardial infarction (<1% of all acute myocardial infarction).[20,21]

Conclusion

Takotsubo cardiomyopathy differs from common cardiac dysfunction in its reversible nature. This characteristic must be taken into consideration when treating patients with intracerebral hemorrhage to avoid misclassification of the disease. Takotsubo syndrome is now a known complication in the severe neurological condition such as subarachnoid hemorrhage. Physicians taking care of these patients should become familiar with it. Both IABP and ECLS have a role in more severe scenarios or in the patient who needs systemic blood pressure augmentation such as vasospasm.

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Review Article

Off-Pump All Arterial Coronary Artery Bypass Grafting

Permyos Ruengsakulrach, MD., PhD, FRCST, FCCP [1]

[1] Division of Cardiothoracic and Vascular Surgery, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Coronary artery disease, Coronary artery bypass grafting, Off-pump coronary artery bypass grafting, Cardiopulmonary bypass, Arterial graft.

There is growing acceptance of the long-term durability of using coronary artery bypass grafting (CABG) for the treatment of coronary artery disease (CAD). The idea is to give an antegrade flow to the coronary artery circulation, thereby relieving angina. CABG as used in clinical practice since the 1960s, is arguably the most intensively studied surgical procedure ever, while percutaneous coronary intervention (PCI), used for over three decades, has been subjected to more randomized clinical trials (RCTs) than any other interventional procedure. In comparison with CABG, PCI unfortunately has a higher rate of reintervention. In 2009, the American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Thoracic Surgeons (STS), American Association for Thoracic Surgery (AATS), American Heart Association (AHA), and the American Society of Nuclear Cardiology (ASNC) jointly launched appropriateness criteria for revascularization.[1] Appropriateness criteria are based on current understanding of the technical capabilities and potential patient benefits of the procedures examined. Coronary revascularization is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure. The methods of revascularization depend mainly on symptoms, clinical presentations and coronary artery anatomy. Generally, surgery is mostly appropriate except for certain situations, for example, prior bypass surgery with native triple vessel disease, and failure of multiple bypass grafts with patent left internal thoracic artery (LITA) to the native coronary artery, depressed left ventricular ejection fraction. Percutaneous coronary intervention (PCI) has many uncertainties and may be inappropriate in the following conditions: left main (LM) coronary artery disease; multivessel coronary artery disease associated with diabetes, and depressed left ventricular function.

In 2010, the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI) developed a new guideline for myocardial revascularization.[2] Some of the recommendations were (1) Non-emergent high-risk PCI procedures, (including those performed for distal LM disease, complex bifurcation stenosis involving large side branches, single remaining coronary artery, and complex chronic total occlusion recanalization) should be performed by adequately experienced operators at centers that have access to circulatory support and intensive care treatment, and have cardiovascular surgery on site. (2) For patients with stable CAD and multivessel or LM disease, all relevant data should be reviewed by a clinical/noninvasive cardiologist,

a cardiac surgeon, and an interventional cardiologist to determine the likelihood of safe and effective revascularization with either PCI or CABG. PCI is more preferential for one or double vessel disease - non-proximal LAD. The recommended risk stratification score to be used in candidates for percutaneous coronary intervention is the SYNTAX score. The SYNTAX score was derived from the combined angiographic anatomic classifications of each significant lesion from the SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) trial.[3] The SYNTAX score has been shown to be an independent predictor of major adverse cardiac events in patients treated with PCI. For example, patients with triple vessel complex lesions, incomplete revascularization achievable with PCI and SYNTAX score >22 should have CABG rather than PCI. Patients with LM and double vessel or triple vessel disease and SYNTAX score ≥33 should also have CABG in preference to PCI.

The most common risk models for CABG are The Society of Thoracic Surgeons (STS) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE). In contrast with the SYNTAX score, STS score and EuroSCORE were calculated from clinical variables rather than angiographic anatomy. STS risk models are based upon clinical data from The Society of Thoracic Surgeons National Adult Cardiac Surgery Database, one of the oldest and largest of all specialty registries.[4] The EuroSCORE, developed in 128 centers in eight European states, aims to predict 30-day mortality of patients undergoing cardiac surgery.[5] It has been validated with good results in European, North American and Japanese populations.[6-8] It has also been used to predict other useful endpoints including long-term mortality[9], intensivecare unit stay,[10] complications and costs of cardiac surgery.[11] Both the STS and EuroSCORE risk algorithms are good predictors of early mortality from offpump coronay artery bypass grafting (OPCAB) or Onpump coronary artery bypass grafting (ONCAB).

Compared with PCI, however, CABG presents a greater immediate risk of mortality and morbidity, as well as higher initial costs. When these 2 procedures have been compared longitudinally over several years, however, the total costs become similar, due to the greater need for reintervention after PCI. Off-pump coronary artery bypass grafting (OPCAB) has been developed and re-popularized over the past decade, in order to reduce morbidity and mortality due to conventional CABG or on-pump coronary artery bypass grafting (ONCAB), which cardiopulmonary bypasses and cardioplegic arrests require. Cardiopulmonary bypass (CPB) is associated with an acute phase reaction of protease cascades, leucocyte, and platelet activation that result in tissue injury.[12] This largely manifests as subclinical organ dysfunction, which produces a clinical effect in those patients that exhibit an excessive inflammatory response, or in those with limited functional reserve. The risks of myocardial ischemia/reperfusion, (otherwise associated withaortic crossclamping, and cardioplegic arrest), and systemic inflammatory response or wider organ dysfunction, are known to be elicited by cardiopulmonary bypass (CPB). OPCAB was developed precisely in order to alleviate and minimize complications from CPB and cardioplegic arrest; therefore complete revascularization can be achieved with excellent long-term results and reduction of morbidity and/or mortality.

In addition to the CPB, the quality of conduits for CABG also determines the clinical outcome and more importantly, patients' long-term survival after CABG. The objectives of this review are to (1) compare the rationale and outcome of OPCAB and ONCAB, and (2) compare the results of arterial conduits and vein grafts.

Off-Pump Coronary Artery Bypass Grafting (OPCAB) vs. On-Pump Coronary Artery Bypass Grafting (ONCAB)

"Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future"

Theodor Billroth

Concepts of surgical treatment of CAD have been developed since 1880.[13] Interestingly, the idea of surgical revascularization was first suggested when Langer observed the interconnections within the coronary system, and between coronary vessels and surrounding extracardiac structures such as the diaphragm, bronchi, and the pericardium. In 1898, Pratt suggested that coronary sinus blood flow could be reversed by the insertion of an artery into the myocardial venous system thereby enhancing myocardial blood flow. Much of the early surgical treatment of CAD however, was primarily concerned with relieving the discomfort of angina, rather than with revascularizing the myocardium. In 1899 for example, Parisian Professor of Physiology, Charles Emile Francois Franck, suggested treating angina by performing sympathetic ganglionectomy of the upper thoracic ganglia to divide the afferent pain fibres.[14] Another palliative approach for treating angina, namely thyroidectomy, emerged from Kocher's observation in 1902 that a patient with angina became asymptomatic after total thyroidectomy.[15] Finally, Wearn, who had found connections between the cardiac chambers and the myocardial sinusoids, suggested in 1928 that "if coronary flow was occluded, flow in the Thebisian vessels could be reversed, thus supplying blood from the ventricular cavities to the myocardium". Many surgeons experimented with these ideas. In 1930, Claude Beck championed early attempts at increasing the blood supply to the myocardium by inducing pericardial scarring and thereby encouraging neovascularization.

Several other operations (cardiopneumopexy, cardiojejunopexy, cardiogastropexy, cardiolienopexy) and revascularization of the heart by tubed pedicle graft of skin and subcutaneous tissue were also developed. Other indirect coronary revascularizations were (1). coronary sinus arterialization using brachiocephalic, subclavian, and innominate arterial grafts, (2) increasing left heart volume by created a surgical communication between the pulmonary artery and left atrium in patients in an effort to increase left heart volume and thus antegrade coronary artery blood flow, (3) increasing coronary collateral by the bilateral ligation of the distal internal thoracic arteries would shunt flow through branches of the pericardiophrenic arteries back through the heart via vascular anastomoses within the epicardium, (4) increasing pulmonary collaterals by ligating the lingular vein and then suturing the lingula to the epicardium. However none of these gave good clinical outcomes. Transmyocardial laser which was clinically employed in 1983 was also developed by indirect revasculaization concept. In 1946, Vineberg developed a procedure involved tunneling of the internal thoracic artery (ITA) into the left ventricular myocardium as a form of indirect myocardial revascularization.

The idea of operating directly on the coronary arteries was conceived as early as the first decade of the twentieth century when Alexis Carrel's experiments grafting both arteries and veins in animals paved the way for the development of direct CABG in humans. He developed a technique of vascular anastomosis (applicable to either small or large arteries and veins) which achieved a watertight suture without narrowing the caliber of the vessel. His experimental results of anastomosing the innominate artery of one dog into the distal coronary artery of another were reported in 1910. He also performed the first CABG using a free carotid artery graft anastomosed between the descending thoracic aorta and left coronary artery. In addition, he first performed vein bypass grafting by anastomosing a vein into a transected aorta. At this time, this operation was performed with difficulty and carried a high mortality rate. In 1912, Carrel was awarded the Nobel Prize in Medicine or Physiology for his work on transplantation and vascular grafting.[16] Myocardial revascularization by anastomosing the ITA to the coronary artery was advocated by Demikhov[17], who undertook a canine study of this technique in 1952; 4 of his dogs survived for more than 2 years with patent grafts. Robert H. Goetz performed the first successful clinical CABG on May 2, 1960.[18] He used a non-suture technique to connect the right ITA to the coronary artery by means of a modified Payr's cannula made of tantalum.[19] The patency of the anastomosis was demonstrated angiographically and the patient remained free of angina pectoris for 1 year. Kolessov, a Russian surgeon, performed the first successful human CABG in 1964 when he anastomosed an ITA to a coronary artery through a left thoracotomy without the use of CPB.[20,21] (Table 1) This was achieved almost simultaneously and independently by Gordon Murray in Canada.[22]

The development of coronary arteriography by Sones[23] in the early 1960s at the Cleveland Clinic enabled for the first time accurate identification of the location and degree of coronary stenoses to help direct CABG, and work there subsequently focused on direct endarterectomy with patch-graft reconstruction.[24] Several years later, Favaloro at the Cleveland Clinic refined the technique of CABG using the greater saphenous vein (SV) as a conduit, the operation became more widely accepted and appreciated.[25]

Table 1: The First Clinical Coronary Artery Bypass Operations

Date	Surgeon	Graft	Technique	Follow-up
May 2, 1960	Goetz	RITA	Tantalum ring	No angina at 1 year Pt. died of AMI 1.5 years later
April 4, 1962	Sabiston[26]	SV	Suture	Pt. died 3 days later (This case first reported in 1974)
Feb 25, 1964	Kolesov	LITA	Suture	No angina at 3 years' follow-up
Nov 23, 1964	Garrett Dennis DeBakey[27]	SV	Suture	No angina at 7 years' follow-up (This case first reported in 1973)
Mar 22, 1967	Kolesov	LITA	Stapling	No angina at 3 years' follow-up
May 9, 1967	Favaloro[25]	SV	Suture	Successful
Feb 29, 1968	Green[28]	LITA	Suture	Successful

AMI = acute myocardial infarction; LITA = left internal thoracic artery; RITA = right internal thoracic artery; SV = saphenous vein.

The heart-lung machine was developed at the same time as indirect and direct coronary revascularization techniques became established. Initial investigations into systemic hypothermia and inflow occlusion began at the University of Minnesota. Such a heart-lung machine would first require a safe method of anticoagulation that could be reversed at the end of the operation; second, it would require a method of pumping blood without destruction of red blood cells; and third, there would have to be a method to oxygenate blood and dissipate carbon dioxide during the time that the heart and lungs were temporarily at rest. The first 2 requirements were easily met. Heparin and protamine were readily available, and there were several pumps being used in the dairy and food industry that could be adapted. The real problem was to develop an artificial oxygenator. This turned out to be difficult. Then, in 1937, Dr John Gibbon began work on a pump oxygenator that he finally put into clinical practice on May 6, 1953.[29] His technical achievements were astounding; however, when compared with today's knowledge and technology, they appear rudimentary, and indeed, after having only 1 survivor in his first 6 cases, he essentially abandoned its use. Although during the same period, C. Walton Lillehei at Minnesota was poised to begin a clinical trial in which the oxygenator would be either the mother or father of the patient, a technique called cross circulation. He did 45 operations using cross circulation and had 28 survivors. Although there was great interest in this technique, it was not adopted by other surgical groups. The risk of injury of the parent acting as the donor was a major concern.[30]

Finally, at the Mayo Clinic, John Kirklin and his colleagues were building a heart-lung machine based on the Gibbon design that used a vertical film oxygenator and roller pumps. It was called the Mayo-Gibbon heart-lung machine. This is the first truly commercial heart-lung machine, which was used in 1950s and early 1960s. The heart-lung machine was used routinely in operations for ischemic heart disease in the late 1960s. In 1959 Dubost et al. became the first to perform a coronary artery operation in a human using heart-lung machine or cardiopulmonary bypass (CPB) when they performed coronary ostial reconstruction on a patient with syphilitic aortitis.[31] On April 4, 1962, David Sabiston, Jr, performed the first saphenous vein–coronary artery bypass grafting procedure without using CPB in the world.[32] After 1968, CABG with CPB was widely adopted. Favaloro et al. at The Cleveland Clinic subsequently popularized the use of autologous saphenous vein segments as bypass grafts.[25,33] The major advance of 1968 was the implementation of ITA grafting by several groups. Though Goetz and Kolesov had performed the first such human operations, it was only in 1968 that broad use of the procedure began. Bailey was the first to perform the procedure that year[34], followed soon by Reed, who became the first to perform the operation using CPB and fibrillation. Further application of the ITA occurred with the work Spencer[35] and Green, of the group at New York University. During the next 10 years, after the first operation using CPB, the operative mortality for open heart surgery rapidly decreased each year. Better oxygenators, better surgical techniques, better cardiology, and many other improvements brought the risk of death down to single-digit levels. The current heart-lung machine is now simplified and adoption of its use is widespread (Figure 1).

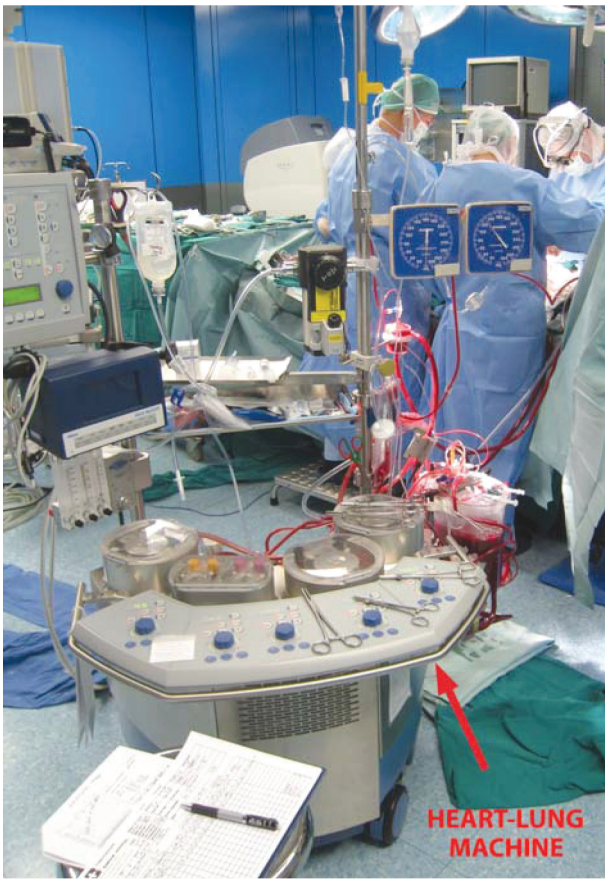

Figure 1: *Heart-Lung Machine at the Bangkok Heart Hospital*

CPB however does have some specific drawbacks, with several potentially harmful effects on normal homeostatic physiology which include (1) the effects of hypothermia, (2) the physiologic derangements caused by contact of blood with artificial surfaces, (3) the need for anticoagulation, and (4) the alterations in perfusion mechanics to organ systems. Hypothermia during CPB causes alterations in drug metabolism and distribution, and adverse effects on coagulation through both the intrinsic and extrinsic pathways and

inhibition of platelet function. Enzymatic reactions are delayed, and vasomotor changes result in reduced organ perfusion and redistribution of blood away from the heart. When blood comes into contact with artificial surfaces, several inflammatory responses are initiated through activation of the complement cascade, coagulation pathways, and the kallikrein cascade.[36] The coagulation cascade is activated and clotting occurs. Therefore the anticoagulant, heparin needs to be given during CPB. Despite the reversal of the heparin effect by using protamine at the end of CPB, postoperative bleeding occasionally occurs because of platelet dysfunction and fibrinolysis. Neutrophil activation plays a major role in the systemic inflammatory response and organ dysfunction. At the beginning of CPB, neutrophil counts measured in both atria increase. Once blood flow is restored to the lungs, however, neutrophil counts continue to increase only in the right atrium, as opposed to a decline in the left atrium, due to trapping within the pulmonary capillaries. Proteolytic enzymes are released and free oxygen radicals are produced, both of which lead to extensive endothelial cell damage, increased vascular permeability, and capillary leak. For many patients, it is a subclinical event, but in some it may advance to a life threatening, fulminant condition, similar to adult respiratory distress syndrome (ARDS), otherwise known as noncardiogenic pulmonary edema. Both fluctuations in arterial pressure and the absence of pulsatile blood flow with CPB may lead to transient hypoperfusion to the organs. The kidneys in particular are susceptible, and impairments in baseline (or preoperative) renal function may lower the threshold for postoperative renal dysfunction or failure. In addition, it is thought that splanchnic hypoperfusion, resulting in circulating endotoxins, causes activation of macrophages and monocytes, and is responsible for the direct relationship between the duration of CPB and the level of tumor necrosis factor-alpha (TNF-α) in the blood. The side effects of CPB are summarized in Table 2.

Table 2: The side effects of cardiopulmonary bypass

Inflammatory responses
• Plasma protease cascades
• Cellular response and tissue injury
• Cytokine response
Clinical organ dysfunction
• Myocardial injury
• Renal injury
• Pulmonary injury
• Neurological injury

The clinical benefits possible in avoiding the CPB's side effects became the driving force for many of cardiac surgeons to develop OPCAB techniques. Furthermore techniques of myocardial protection during induced temporary cardiac arrest and types/ routes of cardioplegic solution delivery play also important roles for outcome of ONCAB. While the basic pathobiology of myocardial ischemic injury and reperfusion has been determined over the last 50 years, there are important, unresolved, or at least not completely elucidated, issues in the field. These include the relative contributions of different modes of cell injury and death to evolving myocardial infarcts; interactions of phenomena produced by reperfusion including stunning and preconditioning. Promising new cardioprotective strategies for reducing lethal reperfusion injury are discussed, including ischemic postconditioning, activators of the reperfusion injury salvage kinase pathway, inhibitors of protein kinase c-delta, and inhibitors of the mitochondrial membrane permeability transition pore.[37] Complex multiple coronary reconstructions in high risk patients requiring long periods of aortic cross-clamping are particularly associated with high rates of morbidity and mortality because of damage to the myocardium.[38]

In the late 1980s, general surgeons began to develop and expand the practice of less invasive surgical techniques. The trend established by laparoscopic removal of the gallbladder rapidly spread to other abdominal and retroperitoneal operations, encouraged by the reports of faster recovery without sacrificing quality outcomes. In the present time, the laparoscopic cholecystectomy has become a standard surgical procedure for gallbladder surgery. For cardiac surgery, several North American surgeons became interested in using the coronary stabilizer for OPCAB in 1997. In 1998, Jansen et al. reported the design, experimental evaluation, and the first clinical use of this novel suctionbased mechanical coronary artery stabilizing system. After federal approval of the device, they began clinical application of this stabilizer. Early experience with the device was limited to vessels on the anterior surface of the heart, which were easily bypassed with excellent stabilization. Lateral and posterior vessels presented technical challenges because hemodynamic tolerance to the cardiac displacement necessary for exposure was poor. After experimental evaluation of the hemodynamic consequences of vertical cardiac displacement, techniques were developed and shared and gradually more surfaces of the heart could be approached safely. In the early 1990s, another sternotomy-sparing approach was used for CABG. A short, transversely placed, several-centimeter left anterior thoracotomy incision was used to access to the anterior surface of the heart which the LITA could be harvested and anastomosed to the LAD. This minimally invasive direct coronary artery bypass (MIDCAB) operation accomplished the goal of avoiding a sternotomy; however, CPB could also be avoided, and the concept of an off-pump approach gained greater acceptance. Most surgeons believed that avoiding of

CPB was the major advantage of minimally invasive surgery rather than changing skin incision. Three major developments that make multivessel OPCAB possible are (1) cardiac displacement/ exposure, (2) stabilization and (3) instruments for clearing surgical view for coronary artery anastomosis (Figure 2). The sequence of steps, anastomotics techniques, pharmacologic manipulations need to be changed from the traditional ONCAB. Dr. Visudharom K. (Kit Arom), former director of the Bangkok Heart Hospital and Chief of Cardiovascular & Thoracic Surgery, was one of the pioneers in USA who developed the OPCAB techniques. OPCAB was later adopted well as a standard CABG at the Bangkok Heart Hospital.[39-46] One of the concerns in adopting off-pump techniques is abandoning the safety net provided by CPB. Crashing in the middle of an OPCAB procedure is particularly difficult, both because of the lack of planning, as well as the often-dangerous hesitancy to use CPB and abandon one's goal of performing the operation offpump. Therefore, it is important for surgeons to know how to prevent rapid hemodynamic deterioration and how to respond when it occurs. The conversion rate from OPCAB to ONCAB at the Bangkok Heart Hospital has decreased year by year. The conversion rate in the past year was close to zero even the OPCAB had been used in 99% of cases.

The numbers of OPCAB patients and surgeons who perform OPCAB are increasing over the years. The potential benefits of OPCAB are (1) zero mortality, (2) less morbidity, (3) less blood transfusion, (4) reduced inotropic requirements, (5) reduced myocardial injury, (6) faster recovery, (7) short hospitalization, and finally (8) reduction of costs. The evidence of improvement are several, both at the molecular level and with regard to clinical outcomes.[47-53] Monocyte activation plays a key role in amplifying both inflammatory and coagulopathic sequelae in patients undergoing ONCAB. Greilich PE. et al. showed that activationdependent increases in monocyte surface changes (CD11b expression and monocyte-platelet conjugate formation)

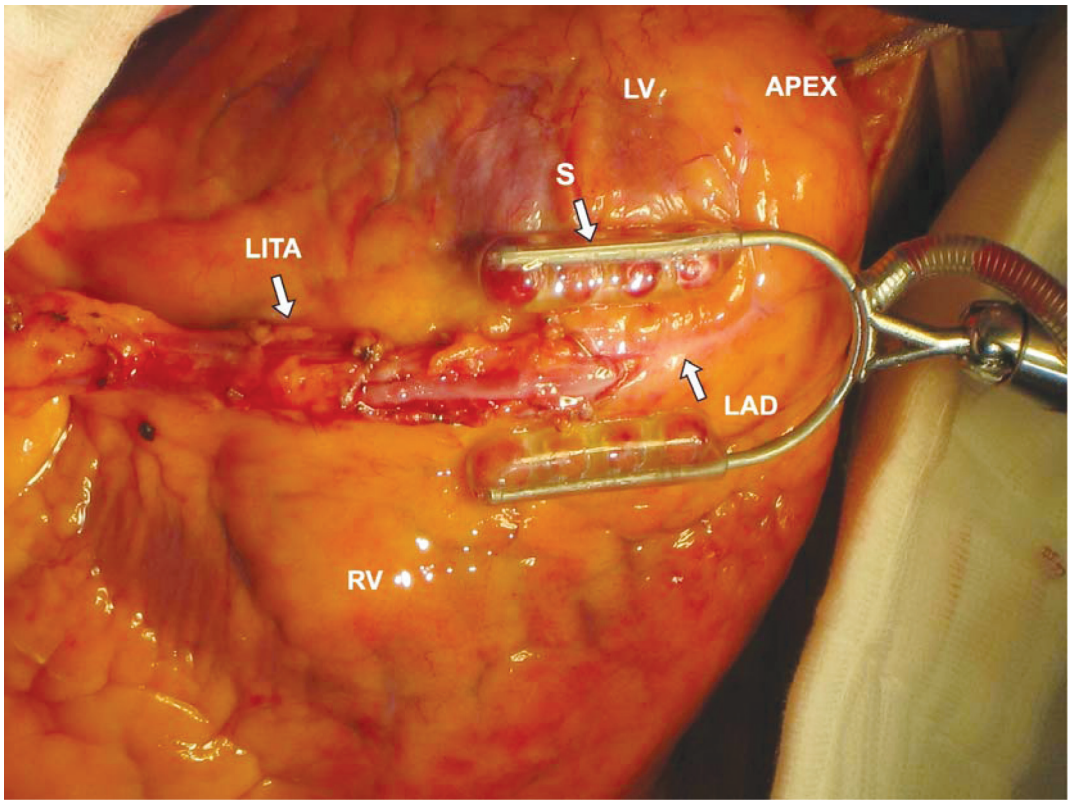

Figure 2: *The left internal thoracic artery was anastomosed to the left anterior descending artery with off-pump technique. Stabilizing arm with suction foot is on the area of anastomosis of the left anterior descending artery.*

LV = Left ventricle, **S** = Stabilizer, **LITA** =Left internal thoracic artery,
LAD = Left anterior descending artery, **RV** = Right ventricle

associated with ONCAB are abolished when performed OPCAB. The plasma increases in the monocyte-secreted cytokines IL-6, IL-8 and IL-10 were both delayed, and their amounts diminished when CABG was performed off pump.54 The use of CPB in ONCAB contributes to the postoperative inflammatory response. The molecular chaperone heat-shock protein (HSP) 70 may be induced by ischemia, and has been detected both in the myocardium and in the circulation after CABG. In vitro, extracellular HSP70 may activate both innate and adaptive immunity. Dybdahl B. et al. demonstrated that significantly more HSP70 is released after ONCAB than after OPCAB, possibly indicating a difference in inflammatory responses, cellular stress or damage, between the two procedures.[55]

Talpahewa SP. et al. studied the changes in cortical cerebral oxygenation during ONCAB using the Near infrared spectroscopy.[56] They found that ONCAB is responsible for deterioration in [O_2Hb], and cerebral blood volume, which peaks at 40-60 min following initiation of CPB. The changes in [O_2Hb] are reversible whereas the reduction of cerebral blood volume persists to the end of the surgery. This suggests a transient impairment in the autoregulatory mechanisms controlling cerebral blood flow following discontinuation of CPB. Lee et al. performed a prospective RCT, demonstrating that ONCAB was associated with more cerebral microemboli and significantly reduced cerebral perfusion (post-op) to the bilateral occipital, cerebellar, precunei, thalami, and left temporal lobes than was the case with OPCAB.[57] Compared with base line, OPCAB patients performed better on the Rey Auditory Verbal Learning Test (total and recognition scores) at both 2 weeks and at 1 year whereas ONCAB performances were statistically unchanged for all cognitive measures.

One major concern for OPCAB is graft patency, which may be compromised because of poor visualization during anastomosis. Angelini GD. et al. compared long-term outcomes in patients randomized to OPCAB or ONCAB, who were followed up for 6 to 8 years after surgery.[58] Patency was studied in 199 of 349 survivors. There was no evidence of attrition bias. The likelihood of graft occlusion was no different between OPCAB (10.6%) and ONCAB (11.0%) groups (odds ratio, 1.00; 95% confidence interval, 0.55-1.81; $p > .99$). In addition to concern about the graft patency, surgeons who use ONCAB might be worried by evidence that surgeons perform fewer grafts with OPCAB compared with ONCAB. However, the absolute difference reported by a systemic review of 22 RCTs was only 0.2 grafts fewer with OPCAB. Incomplete coronary revascularization is not a problem in our experience, even with small coronary arteries in diabetic patients.[59] The advantages of OPCAB perhaps demonstrate better in high risk patients with several comorbidities. Generally for OPCAB experienced surgeons, the outcomes are excellent comparable to the ONCAB (Table 3).[60-62]

However, there were also negative studies that did not demonstrate the benefit of OPCAB; even those showing worse outcomes than ONCAB.[63-65] Several problems were raised in these studies. General limitations of the randomized controlled trials include study design, patient selection, and inadequate sample sizes. For example, a prospective randomized study detecting statistically significant differences in 30-day mortality (2.9% ONCAB versus 2.4% OPCAB) requires the randomization of 15598 patients in each treatment group ($\alpha = 0.05$, power = 0.8). Meta-analysis is a useful tool for formally summarizing the available information and creating hypotheses that may be tested in future trials. However limitations are flawed methods of each study, publication bias, variation of concomitant treatments (co-interventions) and heterogeneity of studies. The other common factor is surgical experience.[58] OPCAB is a new technique and it requires a lot of practice to be able to do an efficient coronary anastomosis in all areas of the left ventricle.

Arterial Grafts vs. Venous Grafts

Long-term patency of a bypass graft is an important determinant in reducing morbidity and increasing survival after CABG. Problems in graft patency study include (1) lack of uniform definitions of graft failure, (2) most studies were of symptomatic angiogram (many graft failures cause no symptom), (3) exact time of graft failure was unknown, and (4) the use of appropriate statistical models for analysis. The traditional conduits are left internal thoracic artery (LITA) and saphenous vein graft (SV). Kaplan–Meier (K-M) estimates of patency suggest that about 85–92% of LITA grafts are patent at 15 years. Unfortunately K-M estimates of patency of SV at 10 and 20 years are only 60% and 20% respectively.[76, 77] Mechanisms of SV graft failure could be divided into (1) intrinsic causes and (2) extrinsic causes. The intrinsic causes include poor vein quality, missed valve/ branch (in situ), branch ligature placement, intimal flaps, intimal hyperplasia, accelerated atherosclerosis, aneurysmal dilatation. The extrinsic causes are anastomotic problems, inflow tract stenosis or occlusion outflow tract stenosis or occlusion, thromboembolism and mechanical compression of graft. The pathology of SV graft disease consists of thrombosis, neointimal hyperplasia, and atherosclerosis. Therapeutic strategies to prevent SV graft disease include external stenting, pharmacotherapy, and gene therapy. However the successes of laboratory studies have not been replicated in the clinic yet.[78, 79] Because of the growing evidence of the benefits of arterial grafts, the right internal thoracic artery (RITA), right gastroepiploic artery (RGEA) and radial artery (RA) have been investigated and used more frequently. There was a survival benefit and a lower reintervention rate in favour of bilateral over single ITA grafting in a wide range of patients that continued into the third decade after surgery.[80]

Table 3: Summary of the randomized controlled trials comparing off-pump (OPCAB) and on-pump (ONCAB) surgery

Study	No. of Patients		Results
	OPCAB	ONCAB	
van Dijk[66, 67]	142	139	No. of anastomosis - no diffference Blood products and Release of creatine kinase muscle-brain isoenzyme - less in OPCAB Complications - no differences Survival free cardiovascular events - no differences OPCAB - no effect on 5-year cognitive or cardiac outcomes
Angelini[68]	200	201	OPCAB significantly lowers in-hospital morbidity without compromising outcome in the first 1-3 years after surgery compared with ONCAB.
Puskas[69]	100	100	OPCAB achieved similar completeness of revascularization, similar inhospital and 30-day outcomes, shorter length of stay, reduced transfusion requirement and less myocardial injury.
Muneretto[70]	88	88	OPCAB could be successfully used for total arterial grafting without compromising the completeness of revascularization. Avoidance of CPB significantly decreased mechanical ventilation support and length of intensive care unit and postoperative stay.
Khan[71]	54	50	OPCAB was as safe as ONCAB and caused less myocardial damage. The graft-patency rate was lower at three months in the OPCAB than in the ONCAB.
Legare[72]	150	150	There were no significant differences between the OPCAB and the ONCAB in mortality, transfusion, perioperative myocardial infarction, permanent stroke, new atrial fibrillation, and deep sternal wound infection. The mean time to extubation was 4 hours, the mean stay in the intensive care unit was 22 hours, and the median length of hospitalization was 5 days in both groups.
Al-Ruzzeh[73]	84	84	OPCAB showed similar patency of grafts, better clinical outcome, shorter hospital stay and better neurocognitive function than ONCAB.
Fattouch[51]	63	66	OPCAB reduced early mortality and morbidity in patients with STsegment elevation myocardial infarction in respect to the ONCAB. OPCAB showed better results than ONCAB in patients who underwent surgery within 6 hours from the onset of symptoms and in patients with cardiogenic shock.
Moller[74]	176	163	No significant difference was found in the composite primary outcome (i.e., all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention) after 30 postoperative days, nor were any of the individual components of the primary outcome significantly different.
Hueb[75]	155	153	No difference was found between groups in the primary composite end point (death, myocardial infarction, further revascularization or stroke) at 5-years follow-up.

Buxton B. et al. advocated the use of RITA for grafting coronary arteries with a high grade stenosis or occlusion, for grafting left rather than right coronary arteries, and using in situ rather than free ITA grafts. Passing the RITA to the left, either anterior to the aorta or through the transverse sinus, did not influence patency.[81]

The RA initially was used as a conduit for coronary artery bypass grafting by Carpentier and associates in 1973.[82] In contrast to other arterial conduits, the RA appeared to offer a highly promising alternative for a number of technical reasons. It is easily harvested and handled during the surgery. It is similar in length and size to the ITA, its diameter is closer to the size of the coronary artery than that of the SV. However, despite these potential advantages, Curtis and colleagues reported in 1975 that the failure rate of RA grafts in a group of 79 patients was 64.7% at 6 to 12 months after operation.[83] This represented a significantly higher failure rate than that of the SV and ITA grafts used in the same patients. Furthermore, one of the histologically normal RA grafts removed at reoperation revealed marked concentric intimal hyperplasia. This shed considerable doubt upon the viability of the RA as an alternative graft. In 1976 Chiu suggested that the thick-walled RA appeared to depend more on vasa vasorum for its integrity than the thin-walled vein. The vasa vasorum of free RA graft, which disrupted at both ends, cannot regenerate readily from the adjacent tissue and may have been more vulnerable to intimal hyperplasia and occlusion than either SV or ITA grafts.[84] In 1976 Fisk and colleagues reported results from 48 RA grafts. After 1 to 24 weeks, only 50% of RA grafts were patent compared with 77% of SV grafts. These authors suggested that the RA should not be used. As a result of these poor results the RA fell out of favor, and only recently has been rediscovered as a viable conduit.

The early 1990s witnessed a revival of interest in the RA. During this period, Carpentier and associates were contacted by a patient who had been part of their trial conducted in the 1970s. This patient's RA graft was thought to have occluded soon after surgery. However, to their surprise, an angiogram 18 years later indicated that the RA was in fact patent and free from disease. This discovery led to Acar and colleagues to reinvestigate the use of the RA for CABG.[86]

Several studies confirmed its suitability. Ruengsakulrach P., et al. studied cadaver's hand and found that a complete (classic) superficial palmar arch was found in 10% of hands, and a classic complete deep palmar arch was found in 90% of hands.[87] Although the superficial palmar branch of the ulnar artery was continuous with the radial artery in only 34% of hands, every hand had at least one major branch connecting the radial and ulnar arteries. Therefore in the absence of vascular disease, harvesting the radial artery should be regarded as a safe procedure.

Intimal hyperplasia which was thought to be cause of graft failure occurs as a consequence of physiologic stimuli, constituting an attempt by the tissue to maintain normal conditions of flow and/ or wall tension. Regions of the intima with adaptive increases in thickness differ functionally from adjacent, thinner regions. Excessive lipoprotein in the plasma tends to accumulate preferentially in the hyperplastic intima causing atherosclerosis.[88] From the histopathology study, the RA is more likely to have atherosclerosis, intimal hyperplasia, and medial calcification than the ITA.[89] The ITA is elastic artery as compared to the RA which is muscular artery and the ITA has more internal elastic lamina layers than the RA. This may be one of the reasons that the RA has higher incidence of atherosclerosis than does the ITA.[90] Since the RA is a muscular artery therefore it is a vasoreactive conduit which has high tendency of vasospasm than the ITA and is reason that the ITA and is reason that postoperative calcium blocker may be indicated. The incidence of medial calcification (Monckeberg's calcinosis) in the RA was 13.3%.[89] Medial calcification of an artery, even when extensive, is not necessarily associated with extensive intimal changes and the lumen of the artery is not to be compromised by the medial change. On the contrary, vessels with marked calcification often show less intimal involvement than is average for that age. The degree of intimal hyperplasia in the RA was due to increasing age, diabetes, history of smoking, and peripheral vascular disease.[89] The use of RA in these patients should be carefully considered.

The prevalence of the RA calcification (intimal or medial) detected by preoperative assessment of the RA by ultrasound in patients who were scheduled for CABG was 24.7%. Echogenic plaques were found in 6.8% and the overall incidence of RA abnormality (calcification or echogenic plaques) was 31.5%.[91] Older or male patients or those with carotid artery disease are at a high risk for RA calcification alone; those who have carotid disease or peripheral vascular disease tend to have a higher risk of any RA abnormality.

There were two randomized trials regarding the RA patency namely "the radial artery patency and clinical outcomes (RAPCO) trial" [92, 93] and "the radial artery patency study (RAPS) trial".[94] The RAPCO demonstrated that there are no clinical or angiographic differences between RA and free RITA or the SV graft at 5 years follow up. The RAPS found the failure rate of RA was 8.2% versus failure rate of SVG 13.6% ($p = 0.009$). They concluded that the RA was superior to the SV. However if the seven RA conduits which had the "string-sign" were considered failures, instead of patent, the results were almost identical. The trials need to be followed for another 5 years, since vein graft disease rapidly progresses after 5 years of grafting. Table 4. summarizes the graft patency according to the 2010 recommendations by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).[2]

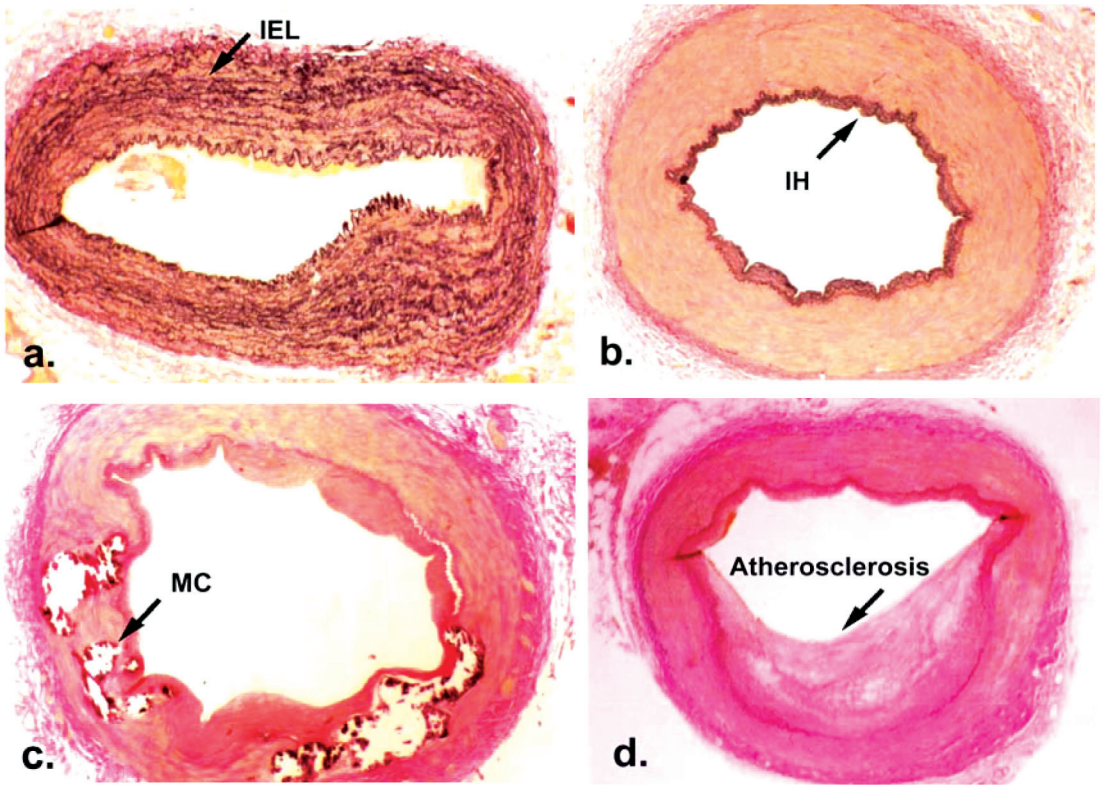

Figure 3: *Histopathology of the internal thoracic artery (ITA) and radial artery (RA), (a.) The ITA demonstrates internal elastic lamina (IEL). [Verhoeff Van Gieson's elastin ´ 20 (original magnification)] (b.) The RA demonstrates intimal hyperplasia (IH). [Verhoeff Van Gieson's elastin ´ 20 (original magnification)] (c.) The RA demonstrates medial calcification (MC) in the media of the arterial wall. [Haematoxylin-eosin´25 (original magnification)] (d) The RA demonstrates atherosclesosis. [Haematoxylin-eosin´25 (original magnification)]*

ITA = internal thoracic artery; RA = radial artery; IEL = internal elastic lamina;
IH = intimal hyperplasia; MC = medial calcification

Table 4: Graft patency after coronary artery bypass grafting (%)

Graft	Patency at 1 year	Patency at 4-5 years	Patency at 10-15 years
SV 95, 96	>90	65-80	25-50
Radial artery 94, 96	86-96	89	Not reported
Left ITA 96, 97	>91	88	88
Right ITA 96	Not reported	96	65

ITA = internal thoracic artery; SV = saphenous vein.

To expand the use of the RA and avoid aortic cross clamping during proximal inflow graft anastomosis, composite graft (T or Y graft) has been introduced. (Figure 4) Muneretto C. et al. performed a prospective randomized study compared composite arterial graft (LITA-RA, n=80) with a standard aortocoronary graft with SV (LITA and SV, n = 80).[98] They found a lower incidence of stroke, graft occlusion and recurrent angina in the composite arterial graft group.

For RGEA, two large studies of about 1000 cases have indicated 5-year patencies of 62% and 86%.[99, 100] A current reviews indicated RGEA performance was similar to that of the SV. Low-grade stenosis of the target coronary artery proximally or competitive flow is a major cause of early RA and RGEA graft failure.

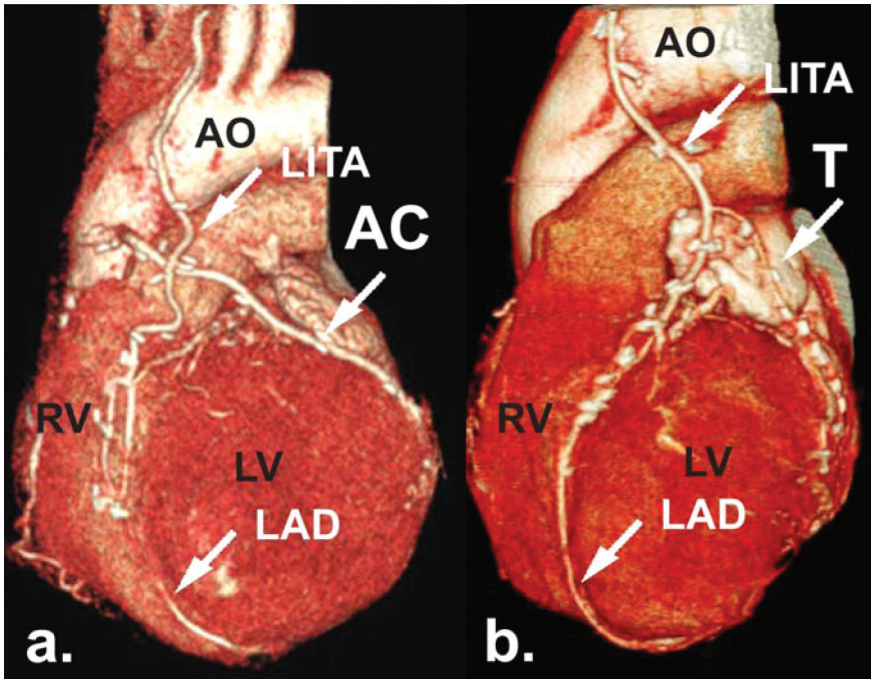

Figure 4: 256 slice computed tomography volume-rendering image in the left anterior oblique projection. (a.) the radial artery (aortocoronary graft) to the obtused ***marginal branch of the left circumflex artery (b.) the radial artery (T graft from the left internal thoracic artery) to the obtused marginal branch of the left circumflex artery.***

T	=	T graft	LV	=	Left ventricle
AO	=	Aorta	LITA	=	Left internal thoracic artery
AC	=	Aortocoronary graft	LAD	=	Left anterior descending artery
RV	=	Right ventricle			

Table 5: Technical recommendations for coronary artery bypass grafting

Technical	Class [a]	Level [b]
Procedures should be performed in a hospital structure and by a team specialized in cardiac surgery, using written protocols.	I	B
Arterial grafting to the left anterior descending artery system is indicated.	I	A
Complete revascularization with arterial grafting to non-LAD coronary systems is indicated in patients with reasonable life expectancy.	I	A
Minimization of aortic manipulation is recommended.	I	C
Graft evaluation is recommended before leaving the operating theatre.	I	C

[a]**Class of recommendation.**
Class I = Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
[b]**Level of evidence.**
Level A = Data derived from multiple randomized clinical trials or meta-analyses.
Level B = Data derived from a single randomized clinical trial or large non-randomized studies.
Level C = Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Off-Pump All Arterial Coronary Artery Bypass Grafting

Logical thinking: "if the CABG performs with off-pump and all arterial grafts, it should give both short and long-term excellent outcomes. Balacumaraswami L, et al. compared intraoperative transit-time flow measurements in all ITA, RA, and SV in patients undergoing OPCAB and ONCAB.[101] In comparison with OPCAB, the overall mean graft flow and flow/pressure ratio were significantly higher and mean arterial pressure significantly lower for all grafts in the ONCAB. These findings are probably a result of vasodilatation resulting from CPB and reactive hyperemia resulting from a period of ischemia. There was no difference in the mean graft flow and flow/pressure ratio of arterial grafts, which were significantly less than for SV. Therefore where unstable patients and graft flow are concerned, OPCAB with SV graft should be considered.

Kobayashi J. et al. randomly assigned patients to undergo multiple arterial OPCAB (n=81) or ONCAB (n=86).[47] The number of arterial grafts performed per-patient were 3.3±1.0 for OPCAB and 3.4±0.9 for ONCAB. The completeness of revascularization, hospital mortality, perioperative complications and early graft patency (within 3 weeks after the operation by angiography) were found to be similar in both groups. The operative was significant shorter in OPCAB group. Table 5. summarizes the technical recommendations for CABG from the 2010 guidelines on myocardial revascularization.[2]

Bangkok Heart Hospital Experiences

Between Jan 2005 and Dec 2010, 816 patients underwent isolated OPCAB at the Bangkok Heart Hospital. All arterial OPCAB was used in 581 patients (71%). LITA, RITA, RGEA, left RA and right RA were used in 97.4% (566/581), 18.2% (106/581), 20.5% (119/581), 85.9% (499/581) and 26.9% (156/581), respectively. Male was 84.0% (488/581). Mean age was 60.7±10.3 yrs. 68.7% (399/581) had hypertension and 41.8% (243/581) had diabetes. 29.6% (172/581) had significant left main coronary artery disease. Mean preoperative left ventricular ejection fraction was 57.1±13.2 %. Average number of grafts was 4.1±1.3. The clinical outcomes were improved over the year even for high risk patients. The 30-day mortality was 0% and there was no perioperative myocardial infarction, reoperation for bleeding, deep sternal wound infection and stroke in the year 2010 (Society of Thoracic Surgeons score: mean 1.09 ±0.94%, median 0.80% and European system for cardiac operative risk evaluation score: mean 2.13±1.81%, median 1.30%).

Conclusion

Patients may achieve an excellent outcome with either type of procedure. Older patients with more co-morbidities and more advanced atherosclerotic disease will probably derive greater benefit from OPCAB. The long-term benefit of CABG is maximized with the use of arterial grafts, specifically ITA. Using RA increases the number of arterial anastomoses beyond the use of both ITAs. The side-to-side anastomosis eliminates an aortic anastomosis, decreases amount of graft required, and increases total graft flow (a higher patency rate). All arterial conduits provide superior long term graft patency in general. However the choice of graft depends also on individual patient risk factors and coronary artery anatomy, target vessel size and degree of stenosis.

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Review Article

Current Treatments for Carotid Artery Disease

Kosin Thupvong, MD. FACS[1]
Permyos Ruengsakulrach, MD. PhD, FRCST, FCCP[1]

[1] Division of Cardiothoracic and Vascular Surgery, Bangkok Heart Hospital, The Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Carotid artery disease,
Carotid atherosclerosis,
Carotid Sclerosis carotid stenting,
Staging endarterectomy

Carotid artery disease is one of the main causes of stroke, apart from other cardiac causes or disease of the brain itself. About 80% of all strokes are ischemic and approximately 25-50% of these are caused by an unstable carotid artery plaque.[1] The risk factors for carotid stenosis are similar to those for atherosclerosis and include hypertension, diabetes, cigarette smoking and dyslipidemia. Prevention of stroke caused by carotid bifurcation stenosis can be achieved by accurate identification and evaluation of patients at risk. Pathophysiology of carotid atherosclerosis is similar to that in other vascular beds. However, atherosclerosis in the carotid artery is usually unifocal, and 90% of lesions are located within 2 cm. of the internal carotid artery (ICA) origin. Extracranial internal carotid artery stenosis accounts for 15 to 20% of ischemic strokes, depending on the population studied. The degree of carotid stenosis is associated with the degree of stroke risk. Carotid atherosclerosis can produce retinal and cerebral symptoms by way of 1 of 2 major mechanisms. progressive carotid stenosis leading to insitu occlusion and hypoperfusion (less common), or intracranial arterial occlusion resulting from embolization (more common). Embolism from unstable plaque is the major mechanism of stroke in carotid atherosclerosis.[2,3] Stroke is more likely to be due to embolism rather than hypoperfusion even in patients with >70% carotid stenosis, and the risk of stroke may be lower in patients with >90% stenosis, due to post-stenotic narrowing in the distal ICA, which reduces flow and risk of embolism. Patients presenting with carotid distribution cerebral ischemia should be thoroughly evaluated for treatable causes, including sources of emboli from the carotid arteries, heart, and aortic arch. Patients with or without carotid stenosis may also develop symptomatic cerebral hypoperfusion from systemic causes.

A carotid bruit is the most common clinical finding, although its positive predictive value is only about 60 to 70 percent. A carotid bruit is identified in 4% to 5% of patients age 45 to 80 years, and should be heard in the majority of patients with carotid stenosis greater than or equal to 75%. However, a bruit may be absent if there is slow flow through a severe stenosis.

Muluk et al. in 1999 studied serial duplex scans in 1701 carotid arteries in 1004 asymptomatic patients over a 10-year period.[4] The risk of progression of ICA stenosis increased steadily with time (annualized risk of progression, 9.3%). With multivariate modeling, the four most important variables that affected the progression were baseline ipsilateral internal carotid artery (ICA) stenosis ≥50%, baseline ipsilateral external carotid artery (ECA) stenosis ≥50%, baseline contralateral ICA stenosis ≥50%, and systolic pressure more than 160 mm Hg. Ipsilateral neurologic ischemic events (stroke/transient ischemic attack) occurred in association with 14%

of the carotid arteries that were studied. The progression of ICA stenosis correlated with these events, but baseline ICA stenosis was not a significant predictor.

Three treatments for this problem are (1) medical therapy (2) carotid stenting (CS) and (3) carotid endarterectomy (CE). CE, surgical removal of the carotid atherosclerotic plaque, has formed the mainstay of surgical treatment. Endovascular angioplasty (with/without stenting) for carotid stenosis, less invasive technique for carotid artery revascularization, has been proposed as a viable alternative to carotid endarterectomy. Current guidelines for CE in symptomatic carotid stenosis are based on two randomized; controlled trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both from the 1990s.[5-7] In both trials, the degree of stenosis, estimated from a catheter angiogram, was the major criterion for recommending CE. According to these trials, the benefit from CE is greatest in patients with 70-99% stenosis with a 5-year absolute risk reduction of 15.3%, less, only 7.8% in those with 50-70% stenosis and minimal in those with <50% stenosis. Since then there were several clinical trials published.

The objectives of this review are (1) to provide evidences of benefit/risk of each treatment and (2) to create recommendation for patients.

Five different aspects should be considered as to the treatment of patients with carotid disease:

1. Neurological symptomatology [patients are classified as symptomatic if they have a carotid distribution transient ischemic attack (TIA: a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction[8]), or non-disabling stroke in the preceding 6 months (originally 4 months in NASCET)].
2. Degree of carotid stenosis [NASCET calculated the degree of stenosis using the site of maximal narrowing as the numerator, divided by the distal ICA diameter where the vessel walls became parallel and beyond any area of post-stenotic dilatation.[9] ECST calculated the degree of stenosis using the diameter at the site of maximal narrowing divided by the estimated diameter of the normal carotid bulb.[10] This means for a given level of stenosis, the percentage narrowing would be lower using the NASCET method compared to the ECST method. For example, a NASCET 70% stenosis corresponds to an 82% ECST stenosis.[11, 12] The recommendation is that carotid duplex should be a bilateral scan and include a basic assessment of the vertebral arteries. All results and calculations to refer to the NASCET method of measurement.[12]]
3. Medical co-morbidities
4. Vascular and local anatomical features
5. Carotid plaque morphology

Traditional imaging methods of carotid artery disease include angiography, duplex ultrasound and computed tomography angiography (CTA). These methods mainly focus on anatomic features of the plaque; however, some techniques are also able to detect morphologic characteristics of plaque vulnerability such as ulceration, a large lipid or necrotic core and a thin fibrous cap. Angiography was the gold standard in the NASCET and ECST to determine degree of stenosis. Duplex ultrasonography and CTA are also being used to determine the degree of stenosis in carotid artery disease. With regard to plaque morphology, several studies have compared the imaging results to histopathological findings as the gold standard. Angiography was able to detect ulceration with a sensitivity and specificity of approximately 45% and 75%, respectively.[13, 14] CTA has also shown to identify plaque ulceration, calcification and lipid cores with an overall agreement of about 75% between CTA findings and histology.[15, 16] Among the current clinically available imaging modalities, MRI seems the most accurate method to image plaque morphology in carotid artery disease. Various advanced imaging methods are available, such as high-resolution magnetic resonance imaging, single photon emission computed tomography (SPECT), positron emission tomography (PET) and near-infrared fluorescence. Radionuclide and fluorescent tracers that identify inflammation, apoptosis and proteolysis, are promising.[17] A combination of activity of molecular processes and detailed anatomic information can be obtained, providing a powerful tool in the identification of the vulnerable plaque. With these developments, we are entering a new era of imaging techniques in the selection of patients for carotid surgery.

In routine clinical practice, the indication to treat using invasive techniques is usually based on 1 and 2, while the choice between carotid endarterectomy (CE) and carotid artery stenting (CS) is mainly based on 3, 4 and 5.

The following are definitions of the classification of the evidence (Class I-IV) and classification of recommendation (A, B, C and U) used in this article.

Definitions

Classification of Evidence

Class I: Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) clearly defined.
b. Exclusion/inclusion criteria clearly defined.
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.

d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT in a representative population that lacks one criterion a-d.
Class III: All other controlled trials (including welldefined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Classification of Recommendation
A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)
C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Medical Therapy

Atherosclerosis is a progressive systemic disease with strong relationships in the prevalence of plaques in different sites of arterial system. Carotid intima-media thickness (IMT) is a validated measure of atherosclerosis burden and is most reproducibly evaluated in the far wall of the distal common carotid artery[18] moreover, carotid atherosclerosis is a risk factor for several chronic diseases, including coronary artery disease[19] and stroke[20]. Carotid atherosclerotic plaque rupture is thought to cause transient ischemic attack and ischemic stroke. Pathological hallmarks of these plaques have been identified through observational studies.

Statins showed anti-atherosclerosis through pleiotropic effects.[21, 22] Statin significantly reduces the progression of early, preintrusive atherosclerosis. A trend for reduction in carotid IMT was shown after only 6 months of therapy.[23] Aggressive statins were more –0.063 mm/y of reduction in annual progression of carotid atherosclerosisthan conventional statins therapy.[24] The latest recommendations for primary prevention of stroke from the European Stroke Organization are that blood cholesterol should be checked regularly; high cholesterol (e.g., LDL cholesterol >3.9 mmol/L [150 mg/dL]) should be managed with lifestyle modification (class IV, level C) and a statin (class I, level A). In secondary prevention of stroke, statin therapy is recommended for patients with non-cardioembolic stroke (class I, level A).[25] In secondary prevention of stroke, evidence-based data from the only available trial were obtained with a high dose of atorvastatin (80 mg per day[26]); post-hoc analysis of the subgroup of patients with Heart Protection Study (HPS) who had a previous stroke found no effect on stroke recurrence with simvastatin 20–40 mg per day.[27] An analysis from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that lowering of LDL cholesterol concentrations to less than 1.8 mmol/L compared with more than 2.6 mmol/L (70 vs 100 mg/dL) was followed by a 28% reduction in relative risk for stroke.[28] This result was obtained post-hoc and, therefore, is hypothesis generating. The next step would be to show that, in patients with a stroke or transient ischaemic attack, an LDL cholesterol concentration of less than 1.8 mmol/L (70 mg/dL) is associated with a lower incidence of recurrent stroke or other major vascular events than is a concentration of less than 2.6 mmol/L (100 mg/dL).[29]

β-blocker can reduce the rate of carotid intima media thickness progression in clinically healthy, symptomfree subjects with carotid plaque[30], the results suggest that the autonomic nervous system may be an important role in atherosclerosis development in otherwise healthy people with carotid plaque. Secondary stroke prevention after transient ischemic stroke or minor stroke is of major importance in order to avoid recurrent cerebrovascular events and decrease morbidity and mortality.

For patients with non-cardioembolic stroke, antiplatelet agents are the treatment of choice. Aspirin (81 to 325 mg) plus extended-release dipyridamole and clopidogrel are more effective than aspirin and should be used in patients with a high risk of recurrent stroke.[31] Oral anticoagulations are highly effective in patients with a cardiac source of embolism. Medical therapy alone is preferred for patients in whom the risk of revascularization outweighs its benefits, including patients who are at low risk for stroke with medical therapy (symptomatic stenosis less than 50%, asymptomatic stenosis less than 60%), and those with a highrisk of procedure-related stroke or death due to clinical or technical factors. Patients with transient ischemic attack (TIA) / minor stroke should be seen as soon as possible in dedicated centers that offer single visit imaging. All patients should start taking their risk factor medications as soon as possible and patients with a 50 – 99% ipsilateral internal carotid artery stenosis should be transferred to the Vascular clinic for further managements.

Carotid artery stenting

Carotid angioplasty and stenting (CS) has steadily developed over the preceding decade. The main advantages of CS over CE are that the procedure is less invasive, performed under local anaesthesia, and is less influenced by the co-morbidities of the patient, while the outcomes are determined mainly by anatomical or procedural variables.[32-34] The disadvantages of CS are (1) it is not suitable if there is a contrast allergy, severe aortic arch atheroma, highly tortuous arteries or lumenthrombus (2) femoral artery puncture is required, which may cause a cutaneous or femoral nerve injury, and a wound haematoma which may become infected or compress vital groin structures (3) higher total procedural costs due to more expensive devices used for endovascular treatment (4) it may cause a stroke, as a result of arterial dissection, late embolization of thrombus on damaged plaque, hypotension (carotid sinus stimulation), aneurysm formation, or arterial puncture (5) uncertain durability over many years in preventing ipsilateral carotid ischemic stroke. Although no randomized study has compared carotid angioplasty vs. stenting, virtually all endovascular carotid procedures currently performed are stentbased. Carotid stents are self-expanding and the vast majority of them are made of nitinol.

Patients undergoing CS are commonly pre-treated with aspirin and clopidogrel. Aspirin is continued lifelong and clopidogrel given for at least 1 month after the procedure. The concept of dual antiplatelet therapy came from the coronary experience and was immediately embraced by part of the interventional community also for the endovascular treatment of the carotid arteries. Small randomized trials comparing single with double antiplatelet therapy for CS followed but had to be prematurely terminated due to high stent thrombosis and neurological event rates in the aspirinonly group.[35]

The first randomized trial comparing endovascular and surgical treatments for carotid stenosis patients, CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study)[36], which was published in 2001, included 504 patients enrolled between 1992 and 1997 and was designed to compare balloon angioplasty alone versus CE. Stents, when they became available, were incorporated as well but only accounted for 26% of cases. The CAVATAS trial demonstrated no statistically significant difference between endovascular and surgical treatment in the rate of disabling stroke or death within 30 days (6.4% CS vs. 5.9% CE) and no significant difference in the 3-year ipsilateral stroke rate. These early encouraging results generated a great deal of interest in CS, and further studies were undertaken. The long-term effectiveness of endovascular treatment of this trial reported in 2009.[37] Patients who were randomly assigned in CAVATAS and completed treatment for carotid stenosis (200 patients had endovascular treatment and 213 patients had CE) had prospective clinical follow-up at a median of 5 years and carotid duplex ultrasound at a median of 4 years. Severe carotid restenosis (≥70%) or occlusion occurred significantly more often in patients in the CS than in patients in the CE (adjusted hazard ratio [HR] 3.17, 95% CI 1.89 – 5.32; p<0·0001). The estimated 5-year incidence of restenosis was 30.7% in the CS and 10.5% in the CE. Patients in the endovascular arm who were treated with a stent (n=50) had a significantly lower risk of developing restenosis of 70% or greater compared with those treated with balloon angioplasty alone (n=145; HR 0.43, 0.19–0.97; p=0·04). Current smoking or a history of smoking was a predictor of restenosis of 70% or more (2.32, 1.19–4.54; p=0·01) and the early finding of moderate stenosis (50 – 69%) up to 60 days after treatment was associated with the risk of progression to restenosis of 70% or more (3.76, 1.88 – 7.52; p=0·0002). There were more patients with non-perioperative ipsilateral stroke or transient ischaemic attack (HR 1.29, 95% CI 0.78 – 2.14) and more patients with non-perioperative ipsilateral stroke (1.22, 0.59 – 2.54) in the endovascular arm than there were in the endarterectomy arm during follow-up, although these differences were not statistically significant. The increase in events in the endovascular arm might be partly explained by the high incidence of restenosis after endovascular treatment.

Hassan Murad M., et al. in 2008 performed systemic review and meta-analysis compared CE vs CS for carotid artery stenosis.[38] Ten randomized controlled trials (RCTs) with 3182 participants proved eligible, provided low to moderate quality evidence. At 30 days and compared with CE, CS was associated with a nonsignificant reduction in the risk of death in five studies (RR, 0.61; 95% CI, 0.27-1.37; I^2 = 0%); a nonsignificant reduction in the risk of nonfatal MI in 3 studies (RR, 0.43; 95% CI, 0.17-1.11; I^2 = 0%); and a nonsignificant increase in the risk of any stroke in 5 studies (RR, 1.29; 95% CI, 0.73-2.26; I^2 = 40%). When only major and disabling strokes were included in the analysis, a similar nonsignificant increase in the risk of stroke was noted in patients who received CS in 4 studies (RR, 1.06; 95% CI, 0.32-3.52; I2 = 45%). When only Q-wave myocardial infarctions (MIs) we reincluded in analysis, data were very limited and precluded meaningful analysis (1 Q-wave MI in the CS group vs 4 in the CE group). These results came from only two trials, because the other trials did not differentiate between Q and non-Q wave MI. These analysis limitations are blind of data in each study and half of the trials were stopped early and yielded imprecise results on the outcome of stroke, which is the main outcome these two procedures are primarily intended to prevent. Finally, both procedures appear equivalent on their effects on death and nonfatal MI; the difference in risk of strokes between procedures remains inconclusive, with a trend toward superiority favoring CE.

The American College of Cardiology Foundation (ACCF) Task Force on Clinical Expert Consensus Documents (CECD), and was cosponsored by the Society for Cardiovascular Angiography and Interventions (SCAI), the Society for Vascular Medicine and Biology (SVMB), the Society of Interventional Radiology (SIR), and the American Society of Interventional & Therapeutic Neuroradiology (ASITN) published a guideline for carotid artery stenting (CAS) in 2007.[39] The European Society for Vascular Surgery (ESVS) again brought together a group of experts in the field of carotid artery disease to produce updated guidelines for the invasive treatment of carotid disease in 2009.[40]

The available level I evidence suggests that for symptomatic patients, surgery is currently the best option [A]. Mid-term stroke prevention after successful CS is similar to CE [A]. CS should be offered to symptomatic patients, if they are at high risk for CE, in highvolume centers with documented low peri-procedural stroke and death rates or inside an RCT [C].

CS is a reasonable alternative to CE, particularly in patients at high risk for CE. The concept of a high-risk patient is very controversial. It appears that when patients meet North American Symptomatic Carotid Endarterectomy Trial (NASCET) / the Asymptomatic Carotid Atherosclerosis Study (ACAS) exclusion criteria, they are automatically defined as high risk.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE) is the only randomized trial comparing CS and CE performed with the systematic use of Embolic Protection Devices (EPDs).[41] The trial included symptomatic and asymptomatic patients at high risk for surgery and wasdesigned to prove the noninferiority of the endovascularapproach. According to the SAPPHIRE trial, a high-risk patient with medical co-morbidities has one of the following features:

1. congestive heart failure (New York Heart Association class III/IV) and/or a known severe left ventricular dysfunction;
2. open heart surgery needed within 6 weeks;
3. recent MI;
4. unstable angina (Canadian Cardiovascular Society class III/IV); or
5. severe pulmonary disease.

Barbato J. E., et al. in 2008 performed a prospective, randomized, single-center study of CS with or without a distal cerebral protection filter.[42] A 1:1 scheme was used to randomize 36 carotid artery stenting procedures in 35 patients. Diffusion-weighted magnetic resonance imaging 24 hours after stenting was used to assess the occurrence of new embolic lesions. Four strokes occurred (11%), two in each group, in patients aged 75, 80, 82, and 84 years. They concluded that the use of filters during CS provided no demonstrable reduction of microemboli. However Garg N., et al. in 2009 performed a random effects meta-analysis of studies with concurrently reported data on protected and unprotected CS.[43] Initial database queries resulted in 2485 articles, of which 134 were included in the final analyses (12,263 protected CAS patients and 11,198 unprotected CS patients). Using pooled analysis of all 134 reports, the relative risk (RR) for stroke was 0.62 (95% CI 0.54 to 0.72) in favor of protected CS. Subgroup analysis revealed a significant benefit for protected CS in both symptomatic (RR 0.67; 95% CI 0.52 to 0.56) and asymptomatic (RR 0.61; 95% CI 0.41 to 0.90) patients ($p<0.05$).

Zarins C. K., et al. in 2009 reported a prospective, nonrandomized comparative cohort study of a broad-risk population of symptomatic and asymptomatic patients with carotid stenosis namely "Carotid revascularization using endarterectomy or stenting systems" (CaRESS).[44] There were 397 patients enrolled (254 underwent CE and 143 underwent protected CS). More than 90% of patients had >75% stenosis; two thirds were asymptomatic. The risk of death or nonfatal stroke 4 years following CS with distal protection is equivalent to CE in a broad category of patients with carotid stenosis. There were no significant differences in stroke or mortality rates between high-risk and nonhigh-risk patients and no differences in outcomes between symptomatic and asymptomatic patients. After 4 years, CS had a 2-fold higher restenosis rate compared to CE. The risk of death/stroke or death/stroke/MI appears to be higher following CE than CS among patients <80 years of age, yet there is no statistically significant relationship between death, stroke, or MI among octogenarians.

Asymptomatic Carotid Surgery Trial-2 (ACST-2) is a randomized clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. At least 5000 patients with asymptomatic carotid stenosis are thought to be needed to participate. It will provide important evidence comparing the immediate and long-term safety and efficacy of CE and CS in patients with asymptomatic carotid stenosis.

Carotid Endarterectomy

Generally, treatment for symptomatic carotid stenosis is settled with interventions such as either CS or CE. However treatments for asymptomatic carotid stenosis are controversial. Symptomatic patients with moderate stenosis of the carotid artery (50-69% stenosis), or intraplaque hemorrhage demonstrated by MRI is a good indicator of recurrent ipsilateral stroke and TIA and may be used to improve patient selection for carotid surgery.[45]

In the Asymptomatic Carotid Surgery Trial (ACST), the annual risk of stroke after CE (0.55%) was much less than the annual risk with the Best Medical Treatment (BMT) alone (1.9%).[46] Both the Asymptomatic Carotid Atherosclerosis Study (ACAS) and ACST studies compared CE plus BMT versus BMT alone, and both studies demonstrated a decreased risk of stroke by approximately 50% at 5 years.[47] The current guideline recommendation Table 1) for asymptomatic patient is to perform CE in asymptomatic men with <75 years of age with 70–99% stenosis, if the perioperative stroke and death rate is <3%. CE should be considered in younger, fit women. When CE is used in combination with BMT and performed well, it can have life-long protective effects against stroke-related death and disability for patients with asymptomatic carotid stenosis. Several trials compared "best medical treatment (BMT)" vs CS vs CE.[48-50]

Abbott was one of the first to observe that the annual risk of stroke in medically treated patients has declined significantly over the last 20 years and the latest meta-analysis concludes that non-interventional therapy is the safer option, whilst also being more costeffective.[48] A second (smaller) meta-analysis published in 2010 included natural history data from three studies recruiting after 2000 and found that the average annual risk of ipsilateral stroke in 1635 medically treated patients was 0.5%.[53] Abbott and others have attributed this decline in stroke risk to improvements in BMT, especially through the use of high dose statins.[54, 55] Not surprisingly, this has elicited the inevitable counter-argument, primarily because some studies in Abbott's meta-analysis included patients with 50–99% as opposed to 60–99% stenoses.

Since there is a trend of reduction of incidence of stroke over the years after improvement of medical treatments, we need to undertake an adequately powered randomized trial which includes treatment arms for CE, CS and BMT. This should make it possible to test algorithms for identifying 'high risk for stroke' subgroups (e.g., transcranial Doppler embolisation, silent infarction on CT, incomplete circle of Willis, computerised plaque morphology, biomarkers).

The CE is absolutely indicated in symptomatic patients with >70% (NASCET) stenosis [A] and probably with >50% (NASCET) stenosis [A]. The perioperative stroke/death rate should be <6%. CE is contraindicated for symptomatic patients with less than 50% stenosis [A]. CE should be performed within 2 weeks of the patient's last symptoms [A].

There is still considerable controversy with regard to the role of prophylactic CE in coronary artery bypass grafting (CABG) patients with coexistent carotid artery disease. In many centres around the world, the detection of a carotid stenosis greater than 70% (irrespective of neurological symptom status) will prompt either synchronous or staged CE plus CABG. A 2003 systematic review of 8972 patients undergoing synchronous or staged CEA and CABG identified three studies (99 patients) where in CE was performed immediately prior to off-pump coronary artery bypass grafting (OPCAB) with a reported 30-day death/stroke rate of 1.0%.[56, 57] This was considerably less than comparable reported risks for patients undergoing synchronous CE plus On-Pump CABG [30-day death/stroke 8.7% (95% confidence interval (CI): 7.7–9.8)], staged CE–CABG [30-day death/stroke 6.1% (95% CI: 2.9– 9.3)] and reverse-staged On-Pump CABG–CE [30-day death/stroke rate 7.3% (95% CI: 1.7–12.9)].[58]

In relation to the peripheral vascular disease, the prevalence of internal carotid artery stenosis of 70% in patients with peripheral vascular disease was 24.7%.[59] Age, smoking quantity and a carotid bruit were independent risk factors associated with severe carotid stenosis. Routine duplex screening is recommended in patients with peripheral vascular disease, particularly in male, elderly smokers.

Table 1: Guidelines from various organizations for carotid endarterectomy of asymptomatic carotid stenosis.

Society / Association	Recommnedation
American Heart Association (1998)	Stenosis 60-99%. CE indicated when it can be performed with less than 3% stroke and death rate.[51]
American Academy of Neurology (2005)	Stenosis 60-99%. CE can reduce future stroke rate if the perioperative complication rate is kept low.[5]
Society for Vascular Surgery (2008)	Stenosis 60-99%, CE plus BMT, if the perioperative risk is low.[52]
European Society of Vascular Surgery (2009)	CE recommended in asymptomatic men with <75 years of age with 70-99% stenosis, if the perioperative stroke and death rate is <3%. CE should be considered in younger, fit women.[40]

Contraindications to CE are carotid stenosis at surgically inaccessible sites, recurrent stenosis after previous endarterectomy, and stenosis after irradiation. Cervical irradiation is a known risk factor for accelerating carotid stenosis progression. Carmody et al. demonstrated a 22% prevalence of >70% carotid stenosis in patients with previous neck radiotherapy compared with 4% in controls.[60] Eighty percent of patients with significant stenosis in the irradiated group were symptomatic. CE in these patients is hindered by previous surgical reconstructions and radiation-induced fibrosis that obliterates the endarterectomy plane and, as a result, is often associated with interposition graft placement. CE in these patients is not associated with a greater risk of stroke; however, a higher incidence of arterial damage, cranial nerve palsy, prosthetic infection, anastomotic breakdown, restenosis, and an increased rate of wound complications have been reported.[61]

Octogenarians alone are not a contraindication for CE. Octogenarians undergoing CS had a 3.46-times higher absolute risk of stroke than those undergoing CE. CS in octogenarians using current technology should be avoided in favor of CE or possibly medical management unless a stroke rate of less than 3% can be achieved.[62]

Bangkok Medical Center's Experience

The incidence of carotid artery stenosis in Thailand is currently unknown; however we estimated it would increase together with the increasing incidence of coronary artery disease in Thailand. The number of patients who underwent CE at the Bangkok Medical Center has increased over the year since K.T. started a CE program.

The following are MRA (Figure 1), endarterectomy specimen (Figure 2 a, b) and CE with vein patch (Figure 3) in one of our patients. This patient recovered well without any complication; however he would face a higher risk of stroke if CS was performed.

Major Recommendations

1. Carotid endarterectomy (CE) is established as effective for recently (within previous 6 months) symptomatic patients with 70 to 99% internal carotid artery (ICA) angiographic stenosis (**Level A**). CE should not be considered for symptomatic patients with less than 50% stenosis (**Level A**). CE may be considered for patients with 50 to 69% symptomatic stenosis (**Level B**) but the clinician should consider additional clinical and angiographic variables (**Level C**, see below). It is recommended that the patient have at least a 5-year life expectancy and that the perioperative stroke/death rate should be <6% for symptomatic patients (**Level A**). Medical management is preferred to CE for symptomatic patients with <50% stenosis (**Level A**).

2. It is reasonable to consider CE for patients between the ages of 40 and 75 years and with asymptomatic stenosis of 60 to 99% if the patient has an expected 5-year life expectancy and if the surgical stroke or death frequency can be reliably documented to be <3% (**Level A**). The 5-year life expectancy is important since perioperative strokes pose an up front risk to the patient and the benefit from CE emerges only after a number of years.

3. No recommendation can be provided regarding the value of emergent CE in patients with a progressing neurologic deficit (**Level U**).

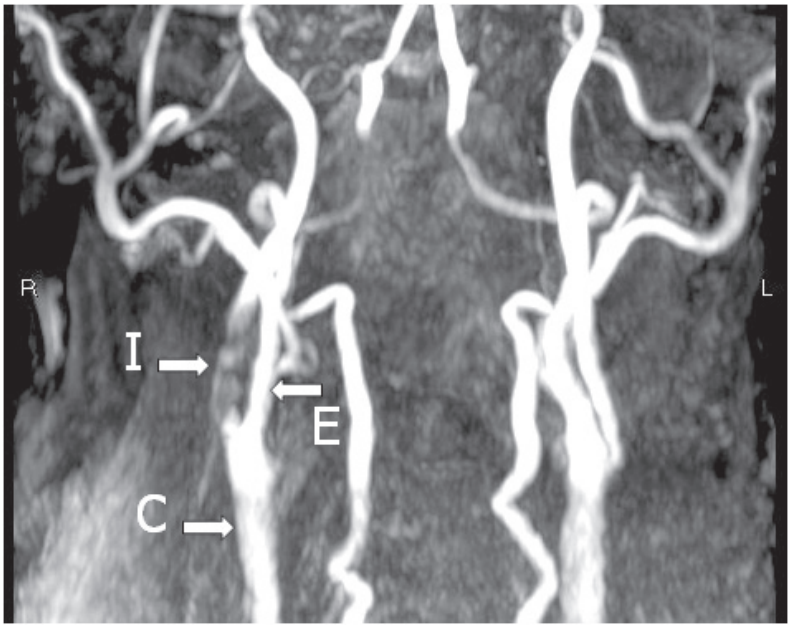

Figure 1: *The 3D, Time of Flight (TOF) extracranial MRA: Severe stenosis of the right internal carotid artery (I). E = external carotid artery, C = Common Carotid Artery*

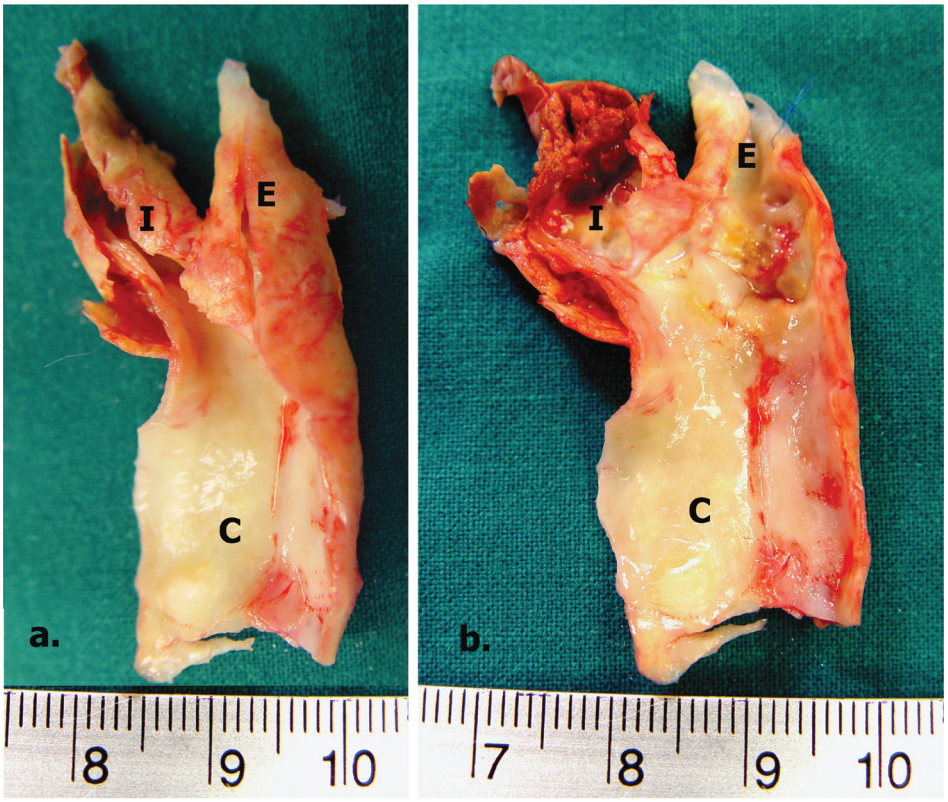

Figure 2: *Carotid Endarterectomy Specimens (a) unopened right internal carotid artery (b) opened right internal carotid artery, demonstrated severe stenosis and unstable plaque. I = Internal carotid artery, E = External carotid artery, C = Common Carotid artery*

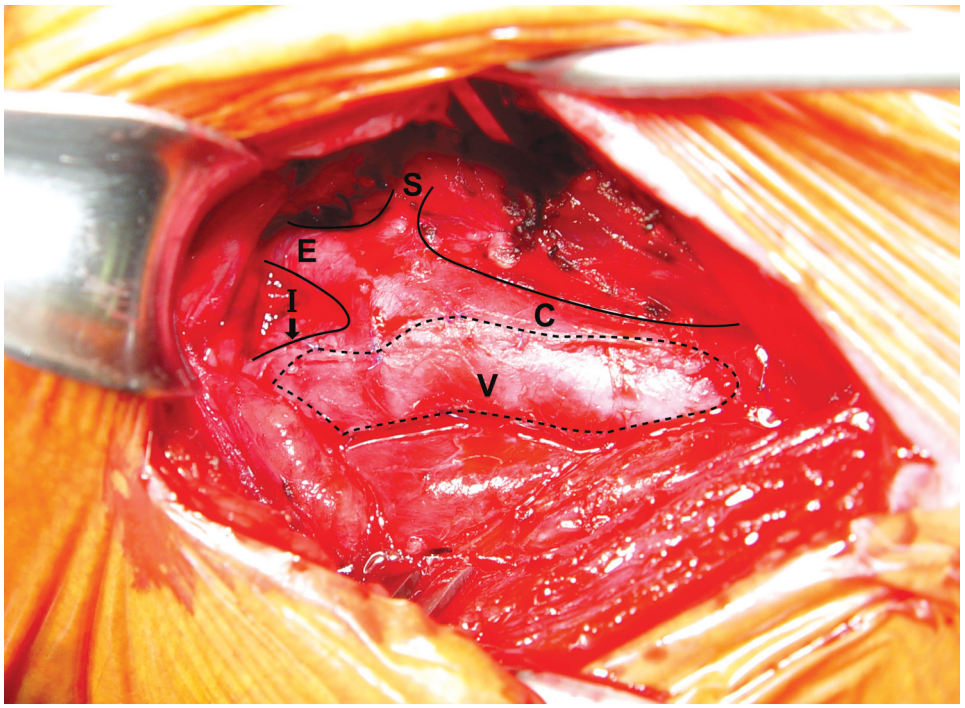

Figure 3: *Carotid Endarterectomy with vein patch: the vein patch extended from the right internal carotid artery (I) to the right common carotid artery (C). E = External carotid artery. S = Superior thyroid artery*

4. Clinicians should consider patient variables in CE decision making. Women with 50 to 69% symptomatic stenosis did not show clear benefit in previous trials. In addition, patients with hemispheric transient ischemic attack (TIA)/stroke had greater benefit from CE than patients with retinal ischemic events (**Level C**). Clinicians should also consider several radiologic factors in decision making about CE. For example, contralateral occlusion erases the small benefit of CE in asymptomatic patients whereas in sympto atic patients, it is associated with increased operative risk but persistent benefit (**Level C**). CE for patients with angiographic near-occlusion in symptomatic patients is associated with a trend toward benefit at 2 years but not associated with a clear long-term benefit (**Level C**). Patients operated on within 2 weeks of their last TIA or mild stroke derive greater benefit from CE (**Level C**).

5. Symptomatic and asymptomatic patients undergoing CE should be given aspirin (81 or 325 mg/day) prior to surgery and for at least 3 months following surgery to reduce the combined endpoint of stroke, myocardial infarction, and death (**Level A**). Although data are not available, it is recommended that aspirin (81 or 325 mg/day) be continued indefinitely provided that contraindications are absent. Aspirin at 650 or 1300 mg/day is less effective in the perioperative period.

6. At this time the available data are insufficient to declare either CE before or simultaneous with coronary artery bypass graft (CABG) as superior in patients with concomitant carotid and coronary artery occlusive disease (**Level U**).

7. For patients with severe stenosis and a recent TIA or nondisabling stroke, CE should be performed without delay, preferably within 2 weeks of the patient's last symptomatic event **(Level C).** There is insufficient evidence to support or refute the performance of CE within 4 to 6 weeks of a recent moderate to severe stroke (**Level U**).

Conclusion

Intensive medical treatments are absolute indicated in all patients with carotid disease. CE currently remains the first choice of revascularisation therapy for an asymptomatic carotid lesion in most treament centres. For symptomatic patients, CE is much safer than CS, particularly for patients older than 70 years. CS might be considered for patients with limited access to surgery or for difficult technical surgery.

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What we have learned about Lai Tai in Thailand?

Gumpanart Veerakul, MD.[1, 2]
Lertlak Chaothawee, MD.[2, 3]
Kriengkrai Jirasirirojanakorn, MD.[1, 2]
Koonlawee Nademanee, MD.[1]
The investigators from DEBUT and SUDSPAC studies.

[1] Pacific Rim Electrophysiology Research Institute at Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[2] Bhumibol Adulyadej Hospital, Bangkok, Thailand.
[3] Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Brugada's, Lai tai, Sudden cardiac death, Ventricular fibrillation, ICD.

It was for more than a century that the mysterious sudden death, so-called "Lai Tai", had been prevalent among villagers in Northeastern (NE) Thailand. Most victims were otherwise healthy young men who died unexpectedly during sleep. Moaning and gurgling sounds had been heard before they became unresponsive and expired. In some families, similar deaths had been occurred to male siblings, for over four generations, which was suggestive of genetic preponderance. It was still a local myth that these unexplained deaths were caused by a widow ghost came to take the mens' soul at night. Several years ago, Lai Tai received media attention after a cluster of deaths of Thai workers in Singapore. Despite extensive autopsies by local authorities, the cause of death remained unidentified. So far, Lai Tai had affected our nation in many ways, from the smallest unit where wives and children had lost their husbands, fathers and the heads of family, up to the national level, that lost the significant incomes from the death of workers.

In 1992, Lai Tai was brought to our attention by Professor Sumalee Nimmanit and colleagues who were studying the prevalence of kidney stones in people of the NE region. In 1994 we had an opportunity to examine the first victim of Lai Tai who had suffered sudden death from ventricular fibrillation. After that, serial investigations under the direction of Professor K.Nademanee were conducted at Bhumibol Adulyadej Hospital and other centers such as Siriraj, Ramathibodi, Central Chest, Chulalongkorn and Khon Kaen. The findings are summarized below.

1. Arrhythmogenic marker, similar to Brugada's syndrome (BrS)

Examination of a group of Lai Tai survivors in 1994 showed 90% of them to have typical ECG marker; abnormal repolarization in precordial lead (V1-3)[1-3] resembling Brugada's pattern (reported by Pedro & Joseph Brugada in 1992.[4] This marker became normalized from time to time[5] and could be enhanced by placing precordial ECG leads (V1-3) in higher position (in the 2nd and 3rd intercostal space)[6] or by giving medication that blocks sodium ion channels.[7, 8]

2. Mechanism of sudden death is spontaneous ventricular fibrillation

In the pilot study, ICDs were implanted in 10 Lai Tai survivors and revealed the cause of death was spontaneous ventricular fibrillation (VF) that sometimes could be self-terminated1.[9] Abnormal autonomic tone as displayed in our study might play a significant role in the night attack of VF in these patients.[10]

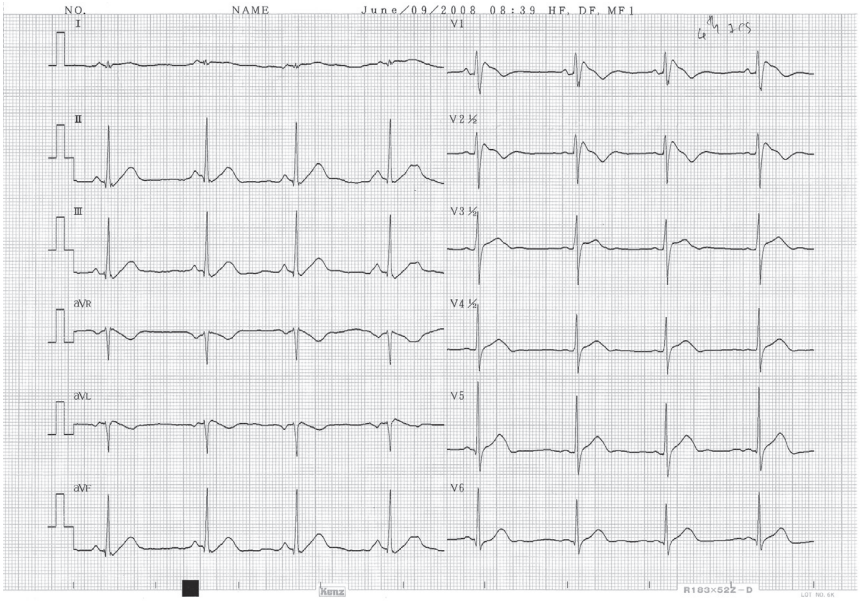

Figure 1: *Typical ECG marker (coving type of ST segment elevation) in V1-2 found in SUDS or Brugada's patients.*

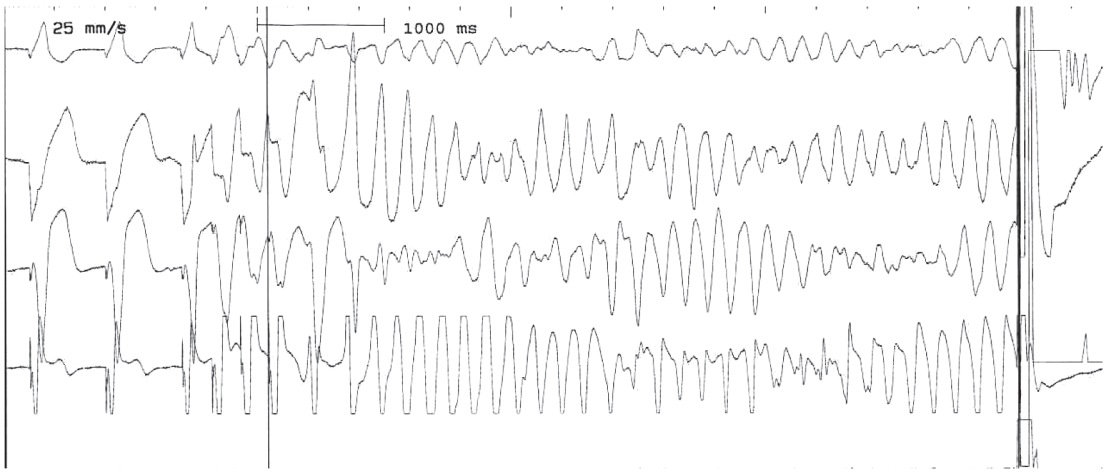

Figure 2: *Inducible sustained VF in EP laboratory of one SUDS survivor required cardioversion.*

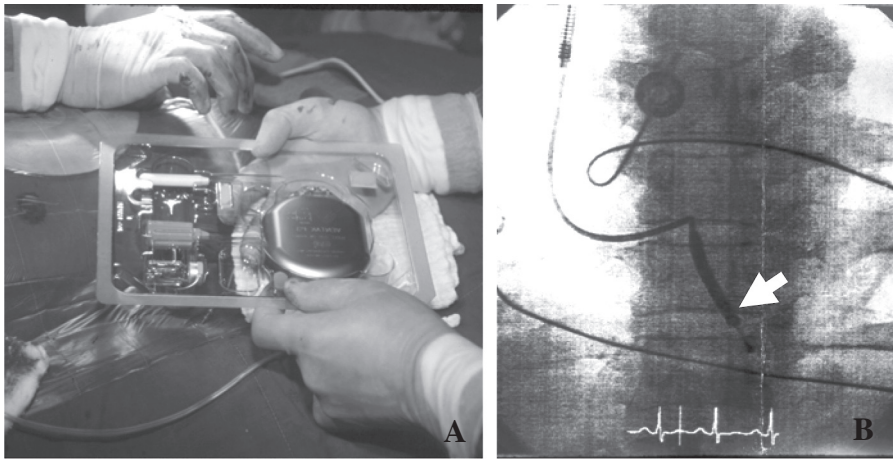

Figure 3: *ICD device (A) and lead in right ventricle (B) see arrow.*

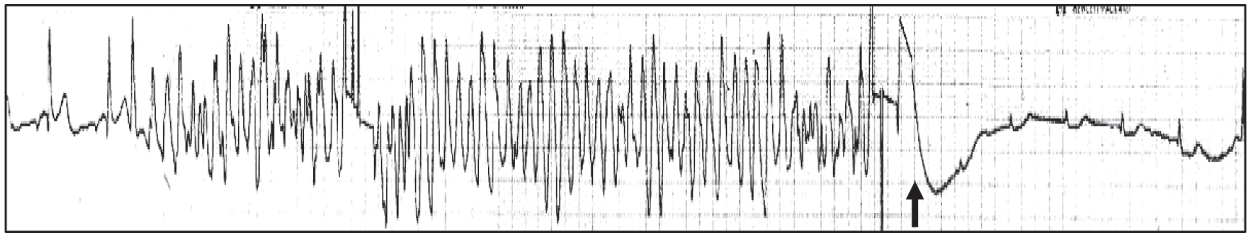

Figure 4: *Sustained VF was terminated by ICD shock in one Lai Tai survior*

3. ICD saved lives and was more effective than β-blocker

The first randomized study (DEBUT) compared using implantable cardioverter-defibrilator (ICD) and β-blockers in Lai Tai survivors. The trial was however, prematurely terminated after an interim analysis by the Safety Monitoring Board, owing to the overwhelming benefit of ICD over the drug (mortality in ICD 0% vs. β-blocker 14%, p=0.004).[11] This trial was the first randomization comparison between device (ICD) and drug in normal structural heart victims and showed no mortality in ICD arm.

4. Genetic discovery of SCN5A mutation

The genetic collaboration work with J. Towbin and colleagues in Texas revealed the mutation of gene encoding sodium ion channel in one third of Lai tai and Pokkuri (sudden unexplained death in Japanese) family members.[12] This mutation resulted in decreased or non-functioning of sodium ion channel that could explain the typical ECG changes in RV epicardium.[13] Currently, there are at least nine genes found to be associated with this syndrome.

5. ICD may not helpful in asymptomatic BrS.

While it is clear that symptomatic BrS/SUDS patients need ICD treatment, controversy exists as to what to do with the asymptomatic cases with the Brugada ECG pattern. We have launched the SUDSPAC trial which is a randomized trial comparing prophylactic ICD implantation and no ICD treatment in asymptomatic BrS/SUDS patients. After five years follow up, we concluded that ICD offered no benefit since the mortality of asymptomatic BS was quite low and did not reach statistical significance (ICD 0%, no ICD 2.3%, p=0.5).[14]

6. Arrhythmogenic substrate and epicardial ablation

Implantation of ICD is the only proven effective treatment for Lai Tai survivors, however, some patients still require anti-arrhythmic medication to reduce VF events. Despite medication, frequent ICD shocks from recurrent VF still occurred in some cases. Fortunately, in our recent study, with the advent of new mapping technology, we discovered that BrS/SUDS patients have VF substrate at the anterior aspect of the right ventricular outflow tract (RVOT), which manifests as low voltage-fragmented late potentials exclusively localized in the anterior RVOT epicardium. Radiofrequency (RF) ablations over this region not only eliminated the Brugada ECG pattern but also prevented VF episodes occurring, both spontaneously and during electrophysiologic studies. Our findings also shed light on the mechanisms of this disease; namely that the most important underlying electrophysiologic mechanism of the BrS/SUDS syndrome is delayed depolarization at the RVOT epicardium.[15]

Conclusion

How should we treat Lai Tai cases?

For the aborted sudden death cases and symptomatic patients, ICD is indicated. Reimbursement of the ICD is now available from all types of health insurance, including Social Welfare and National Health Security office. Patients should stop drinking alcohol, and check their potassium levels every 3-6 months as well as ICD interrogation. A high potassium diet is recommended if there are no other contra-indications. Cases of frequent VF should be admitted and treated with amiodarone, K, Mg should be kept within the normal range. In VF storm, quinidine or isoproterenol administration should be helpful along with K and Mg supplements. Prompt contact with the DEBUT Center, Bhumibol Adulyadej Hospital or Pacific Rim Electrophysiology Research Institute at Bangkok Hospital is highly recommended for potential RF ablation.

In asymptomatic cases, current research did not support the prophylaxis ICD since the mortality is insignificantly low. Avoid alcohol beverages, regular potassium supplement are routinely recommended. In the present of having fever, antipyretic, supportive treatment, adequate K and Mg supplement are encouraged.

Currently, ongoing research is being conducted at DEBUT Research Center, Bhumibol Adulyadej Hospital and Pacific Rim Electrophysiology Research Institute at Bangkok Hospital under the support of Duang-Tawan Foundation and Vejdusit Foundation.

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KRAS Mutation Testing in Advanced Colorectal Cancers

Shanop Shuangshoti, MD.[1, 2]

[1] N Health Biomolecularlaboratory Department, National Healthcare System, Bangkok Hospital Group, Bangkok, Thailand.
[2] Chulalongkorn GenePRO Center, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Keywords:
KRAS, Colorectal cancer, Targeted therapy, Cetuximab, Panitumumab, PCR,

KRAS is an oncogene located on the short arm of chromosome 12 (12p12.1). The gene is a member of the Ras family of small guanine nucleotide–binding proteins, first identified as a cellular homolog of a transforming gene in the Kirsten rat sarcoma virus.[1] Activating mutations in KRAS have been noted in a variety of human cancers, including carcinomas of the pancreas, lung (non-small cell lung cancer), and colorectum (Table 1). KRAS mutations are frequently found in exon 1 (codons 12 and 13) and exon 2 (codon 61).[2] Mutations in KRAS codons 12 and 13 have been associated with lack of response to EGFR-targeted therapies in patients with colorectal cancer (CRC) (Table 2).[3, 4]

In 2009, The American Society of Clinical Oncology (ASCO) issued their first provisional clinical opinion recommending that all patients with CRC who are candidates for anti-EGFR monoclonal antibody therapy should undergo testing for KRAS mutations and that patients with KRAS should not receive anti-EGFR monoclonal antibody therapy as part of their treatment.[5] Common 7 somatic mutations in KRAS codons 12 and 13 have been recommended for evaluation of KRAS gene mutation in CRC (Table 3).[3-5]

Table 1: Frequency of KRAS Mutations in Human Cancers[1]

Tumor type	Frequency (%)
Pancreas	59
Biliary tract	32
Large intestine	32
Small intestine	20
Gastrointestinal tract (site indeterminate)	19
Lung	18
Ovary	15
Thymus	15
Endometrium	14

Table 2: Impact of KRAS Mutations in Patients with Metastatic CRC Treated with EGFR

Therapy	Response Rate		Median Survival	
	Positive for KRAS Mut	Negative for KRAS Mut	Positive for KRAS Mut	Negative for KRAS Mut
Cetuximab	0/36 = 0%*	34/78 = 44%*	9 wks (PFS)	32 wks (PFS)
Panitumumab	0/84 = 0%**	21/124 =17%**	7 wks (PFS)	12 wks (PFS)

Mut = mutation, PFS = progression-free survival, wks = weeks
** Response rate includes partial and complete responders.*
*** Response rate includes only partial responders.*

Table 3: Common 7 KRAS mutations in exon 1 (codons 12 and 13) in CRC

Codon 12	nt34G>A	Gly12Ser	G12S
	nt34G>C	Gly12Arg	G12R
	nt34G>T	Gly12Cys	G12C
	nt35G>A	Gly12Asp	G12D
	nt35G>C	Gly12Ala	G12A
	nt35G>T	Gly12Val	G12V
Codon 13	nt38G>A	Gly13Asp	G13D

Table 4: Comparison of Methods Used for KRAS Mutation Testing [2, 6]

	Sensitivity,% of mutant alleles	Closed PCR system	Closed PCR system	Labor time	Turnover time*, hours
Direct (Sanger) sequencing	20	No	++	+++	5
Pyrosequencing	5-10	No	++	++	3.5
Real-Time PCR (melting-curve analysis	5-10	Yes	+	+	2.5
DxS KRAS mutation detectio kit (allele-specific real-time PCR)	1	Yes	+++++	++	2.5

KRAS Testing in the Context of Anti-EGFR Therapy for Colorectal Cancer

KRAS plays a pivotal role in the EGFR signaling network. When epidermal growth factor occupies the EGFR, it activates a signaling pathway cascade through the downstream effectors of the mitogenactivated protein kinases (MAPK) pathway. KRAS is one of the effectors (in addition to BRAF, ERK, and MAPK) which influence cellular proliferation, adhesion, angiogenesis, migration, and survival1,[6] Blocking EGFR with monoclonal antibodies (cetuximab or panitumumab) inhibits all downstream effects of the receptor. However, if the signaling pathways are activated independent of EGFR, as happens when the KRAS gene is mutated, these anti-EGFR agents become ineffective.[1, 6] Mutation of other genes in the downstream pathway such as BRAF could result in the same effect.[6]

KRAS Mutation Testing Methodologies

Detection of KRAS mutations in colorectal cancer tissue can be done by several molecular methods. Commonly used techniques can be divided in 2 main categories: DNA sequencing and real-time PCR (polymerase chain reaction).

DNA Sequencing Direct (Sanger) sequencing and pyrosequencing can be used for KRAS mutation testing. While the former has been considered a gold standard, the technique is time-consuming and the sensitivity is rather low (20% of mutant alleles required for detection) (Table 4). Pyrosequencing (Figure1) is faster than Sanger, with a lesser amount of mutant alleles required for mutation detecting.[6]

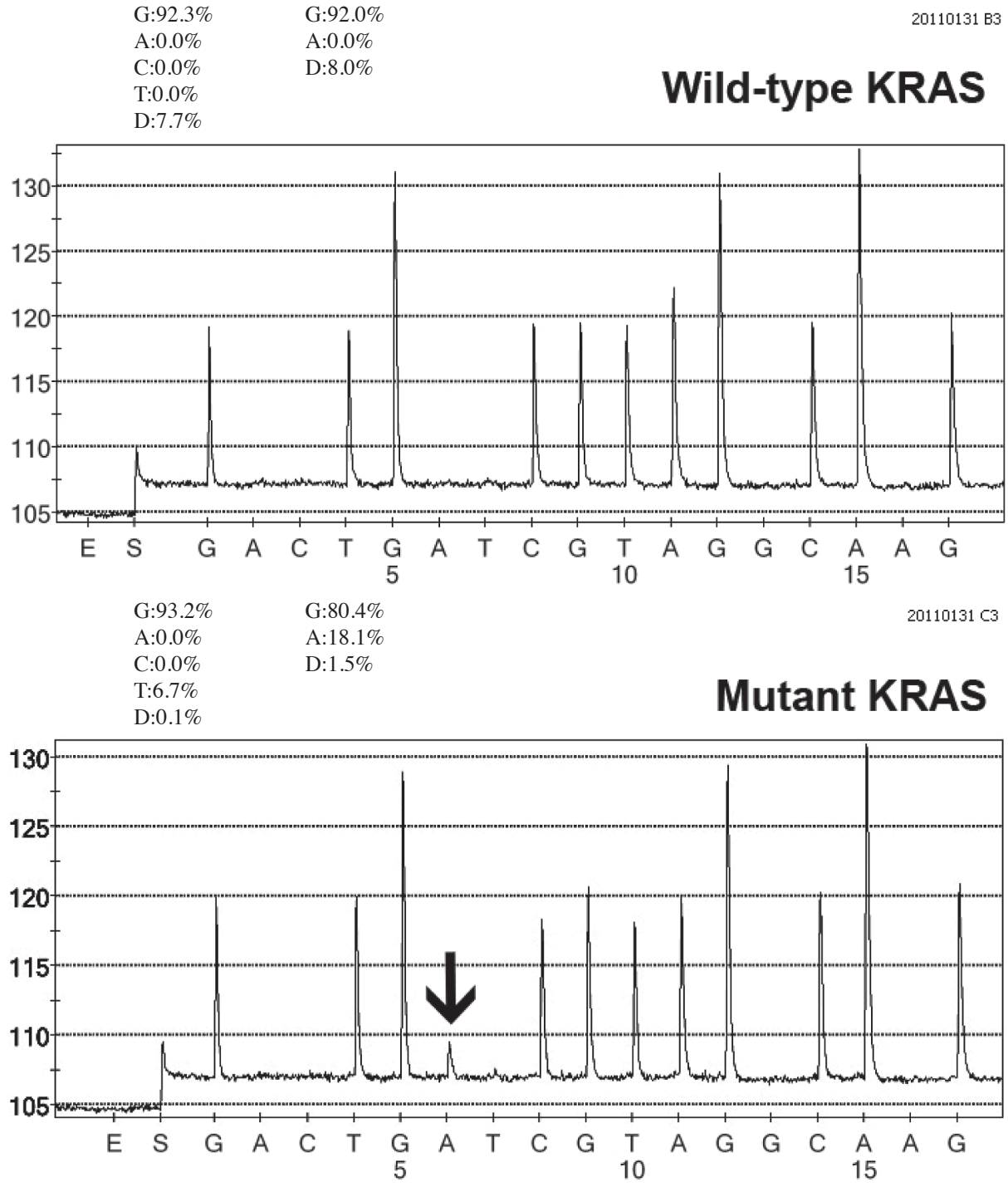
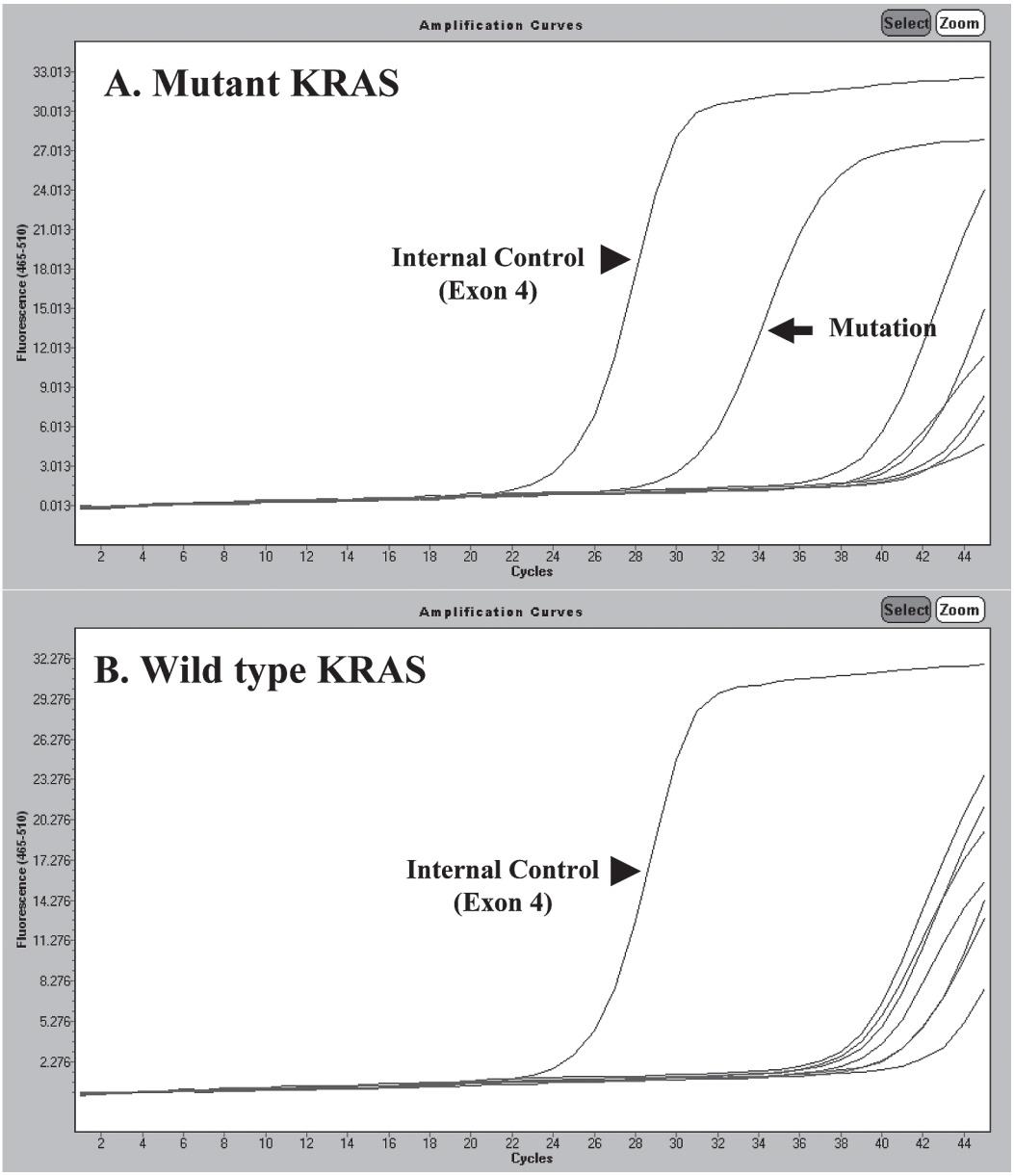


Figure 1: KRAS testing using pyrosequencing. *Pyrograms demonstrate wild-type KRAS gene (upper panel) and mutant KRAS gene (lower panel). Note a mutant "A" peak (arrow) indicating nt38 G>A (Gly13Asp, G13D) at codon 13, exon 1 of the KRAS gene. (Courtesy of Dr Chupong Ittiwut, PhD, Chulalongkorn GenePRO Center, Faculty of Medicine, Chulalongkorn University)*



C. Sample Result Table

Sample Name	Control Ct	Delta Ct	Flags / Warnings	Mutation Status
A	24.61	5.84	-	Positive 12ASP
B	25.34	-	-	Negative

Figure 2: KRAS testing using allele-specific real-time PCR (The DxS TheraScreen KRAS Mutation Kit). (A) *Positive for KRAS mutation. Note the second curve (arrow) representing the amplification of a KRAS mutation. (B) Negative for KRAS mutation. Note the curve at cycle 24 (arrowhead) served as internal control (exon 4 of the KRAS gene). (C) The DxS TheraScreen KRAS Mutation Kit analysis report using the LightCycler® Adapt Software v1.1 (Roche Diagnostics, Penzberg, Germany). (Courtesy of Dr. Alisa Junpee, PhD, Bio Molecular and Pathology Laboratory, National Healthcare Systems CO., Ltd)*

Real-Time PCR The presence of a KRAS mutation can be detected either by allele-specific real-time PCR amplification (Figure 2) or by post-PCR fluorescent melting-curve analysis. Both techniques are closed PCR system, thus reducing risk of contamination. The former is available as a commercial kit, and it is estimated to be able to detect only 1% of mutant allele.[6] However, the reagent cost is very high, and the technique requires more tissue for analysis as compared with other methods.[2, 6] The melting-curve analysis has the similar sensitivity as does the pyrosequencing, but distinguishing among mutation types can occasionally be problematic.[6]

KRAS Mutation in Colon Cancers in Thai Patients.

115 and 153 colon cancer specimens from Thai patients have been tested for KRAS mutations at Bio Molecular and Pathology Laboratory, National Healthcare Systems CO., Ltd by allele-specific real-time PCR (TheraScreen kit, DxS Ltd, Manchester, UK) and Chulalongkorn GenePRO Center (pyrosequencing), respectively (data kindly provided by Drs Chupong Ittiwut, PhD, and Alisa Junpee, PhD). 31.3% (36/115) and 37.9% (58/153) of cases were found to carry KRAS gene mutation, total mutant KRAS cases = 37.3% (94/268). Gly12Asp (G12D), Gly12Val (G12V), and Gly13Asp (G13D) are among the commonest KRAS mutation identified in both centers. The overall percentage of KRAS mutation found in our Thai patients is within the range (30-40%) previously described in the literature.[6]

Conclusion

The most challengers in oncology is that of patient selection for therapy with molecularly targeted agents. Kras are important determinants of response or resistance to anti EFGR antibodies.

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Review Article

Emergency Medicine

Somjintana Iamsanpang, MD.[1]
Anyarit Sangcharaswichai, MD.[1]

[1] Emergency services Department, Bangkok Hospital, The Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Emergency Medicine, Emergency Physician.

What is Emergency Medicine and who are the Emergency physician? These may be questions in many people's minds, not just amongst medical personnel but also patients. If we look back 5 years, Emergency Medicine was far from our thoughts and understanding. As we all can imagine, Emergency Departments (ED) in Thailand are mostly chaotic places with lots of patients and physicians who were assigned to attend ED in addition to their daily jobs, on a part-time rotating basis. Those physicians might range from inexperienced extern to boarded physician, and might include specialists from internal medicine, surgery, pediatrics, ophthalmology and otolaryngology, depending on each hospital's policy.

Most of the patients come to the Emergency Room (ER) on their own; some trauma patients are brought by unregulated volunteer ambulance services, such as Ruamkatanyu or Pohtecktung Foundation and rarely, also the Government hospital services. Most volunteers do not possess any real medical knowledge or training in basic life support; nor do they all use appropriate transportation which can provide spine immobilization or splinting. The Emergency Department has its own unique characteristic, a continuous stream of patients with conditions both acute and chronic. However, most patients feel that their condition is an emergency. Conditions may include trauma or non-trauma; there may be mass casualties. The ER needs then, specialized physicians, nurses and most importantly, a streamlined system which regulates out-of-hospital to in-hospital management.

History

In the US, Emergency medicine (EM) was born as a specialty in order to fill the time commitment required by physicians on staff to work in the EDs of the time. The first training program was established at Cincinnati General Hospital in the 1970s and in 1979, EM was voted to be a recognized medical specialty by the American Board of Medical Specialties. At the same period of time, emergency medical services were significantly improved after the publication of National Highway Traffic Safety Administration's study, "Accidental Death and Disability: The neglected Disease of Modern Society". In Thailand, Emergency Medicine was first established as a medical specialty with the permission of Medical Council in 2003. The first boarded Emergency Physicians graduated in 2007. Our Emergency Medical System also gradually evolved. We started from our well known volunteer ambulance services "Pohtecktung foundation" in 1937.[1] In 1972, medical services using radio-systems to serve the rural areas were first operated. Narenthorn, the first well organized Emergency Medical Service

(EMS) unit under authorization of Rajavithi Hospital began to serve the community in 1995.[1] Narenthorn provided a standard ambulance, dispatch center and EMT-B training program. In 2008 the Emergency Medical Institute of Thailand was first developed.[1] Currently, we have 2 dispatch and EMS centers which operate 24/7: Arawan Dispatch Center which covers the Bangkok area and Narenthorn Dispatch center which serves the other 75 Thai provinces.

What is Emergency Medicine and who is Emergency Physician?

By definition the Emergency Medicine is *"a medical specialty - a field of practice based on the knowledge and skills required for the prevention, diagnosis and management of acute and urgent aspects of illness and injury affecting patients of all age groups with a full spectrum of undifferentiated physical and behavioral disorders. It further encompasses an understanding of the development of pre-hospital and in-hospital emergency medical systems and the skills necessary for this development"*.

Emergency physicians require both a broad field of knowledge and advanced procedural skills, which often include surgical procedure, trauma resuscitation, advanced cardiac life support, conduct and interpretation of ultrasound and advanced airway management.

What is the EMS system and why it is important?

An Emergency Medical System is not just the management in the Emergency Room itself. It starts from the recognition of the emergency condition, a telephone assessment of the situation and provision of pre-hospital care through to definitive care in the hospital. A 1966 EMS White Paper stated that in 1965 there were 52,000,000 accidental injuries in the US.[2] Of these accidental injuries, 107,000 people were killed, more than 10,000,000 disabled and 400,000 permanently impaired. The paper also identified that most people did not have basic first aid training. Those who did have some basic training had little to no training for cardio pulmonary resuscitation and other life saving techniques or childbirth.

In Thailand, for the past decades the ambulance services have greatly widely varied in capability. The dispatching has been poor and communication systems in some areas of the country did not exist. There was no standard for ambulance construction. A well developed EMS has a great positive impact on patient outcomes, for both trauma patients and non trauma patients. Public education will help the people to recognize emergency condition such as stroke, cardiac arrest and the knowledge of how to provide first aid (Basic lift support (BLS)).[3-4] Well organized emergency communication systems will help people to more easily access the emergency care. Trained dispatchers and a well developed dispatch protocol will increase the accuracy in clinical assessment from the first phone call within few minutes, so the most appropriate help will be sent to the patient within the appropriate time (The most appropriate help is the nearest ambulance services with the appropriate capacity). An intelligent pre-hospital instruction algorithm provided by trained dispatchers will help by standers to offer first aid while waiting for the Emergency Medical Technicians, (EMT) especially cardiopulmonary resuscitation which will improve the patient outcomes.[5-8] According to the aforementioned White Paper, 10% of patients with cervical spine injuries were made worse by management prior to hospital arrival.[2] Well trained EMS personnel that can properly immobilize the patient and provide standard emergency care would decrease the morbidity and mortality. EMT personnel can also be trained to care for non trauma patients, for example, the first responder can provide BLS, proper immobilization or assist with baby delivery.

As we know time does matter to the outcome in many time-sensitive illnesses, such as stroke and acute MI. With a good transferal system, the patient can be sent to the right place (stroke patient to an experienced stroke unit, ACS patient to the Heart Center etc.) at the right time with the right mode of transport (ground or air-ambulance).[9-10] Emergency departments are busy, overcrowded medical units, so in order to provide the best care for the right patient at the right time, a good triage system will prioritize incoming patients and identify those patients who cannot wait to be seen.

The EMS also includes medical responses to disaster, planning for and provision of medical coverage at mass gatherings and inter-facility transfers of patients. In Thailand, Emergency Medicine is young as a medical specialty and the EMS system has just started. We continue to evolve with our strong goal, that all Thai people will be able to access the Emergency Medical System and receive the same standard of care no matter where and who they are.

BDMS-Emergency Medical Services

The emergency medical service in Bangkok Hospital has grown over the past decades. In 2000, we first established fully equipped mobile ICU and mobile CCU ambulances. Our 24/7 pre-hospital service is a multi tier system which includes ground (ALS and BLS) and air ambulance services. The ALS ambulance is staffed with an Emergency Physician, a Registered Nurse and drivers who have been trained as Emergency Medical Technicians (EMTB) or FR. In emergency situations, the patient can directly access our system by calling 1719 or through Arawan Dispatch Center. With the emergency ambulance services we have developed dispatch protocols

that guide the ambulance's in-charge nurse and the pre-hospital instructions will be provided by the ambulance doctor. The interfacility transfer system is a well organized process, with ambulance teams available round the clock, that will evaluate the patient's pre transferal condition, cooperate with the doctors at transferring facility, in order to properly prepare the patient and plan the management during transfer and at the receiving facility. The Bangkok Helicopter Services is the first medical services emergency helicopter in South East Asia. It was first established in 2005, with a fully equipped aircraft and attended by certified aviation medical doctors and nurses. We continually train our staff. Our emergency doctors and nurses must be certified with ACLS, PALS, ATLS and neonatal life support.

BDMS comprises of Bangkok Hospital Group, Sametivej Hospital Group, BNH Hospital, and Royal Angkor International Hospital and Royal Ratana Hospital in Cambodia. Together we provide unparalleled tertiary medical care in Thailand and neighboring countries. We are currently developing our Emergency Medical Services Network in order to synchronize the emergency system in our group, continually improve the process of care and to provide equally qualified emergency medical personnel (Doctors, Nurses and EMT).

There are 20 hospitals in our network, 8 hospitals located in Bangkok, 4 Hospitals in southern Thailand, 5 hospitals in the East, 1 hospital in the North-East and 2 hospitals in Cambodia. Our mission is to build up a group practice of emergency physicians, nurses and EMTs and set the standard for emergency care, including pre hospital and in hospital systems such as medical triage, dispatch protocols, standard ambulance / equipment and medical policies. We intend to set up a synchronized network, and establish support technology including full EMR and Data management system, GPS, telemedicine etc. We want to ensure continuous improvement of EMS personnel and maintain quality of care via re-certification, regular drills and monitoring of standard KPI.

With a good network system we aim to provide a simple way to access our emergency medical services and the best continuity of care for the patients. This means being a "one stop" medical service: from a single call to initial clinical evaluation, standard pre-arrival instructions, arrangements of proper modes of transportation and interfacility co-ordination, until the patient is safely transferred to the closest appropriate network hospital. Our available modes of transfer include motorance (Bangkok Hospital), hydrolance (transfer by speedboat) (Bangkok Samui Hospital), mobile CCU, mobile ICU, BLS ambulance for ground ambulance services, helicopter and fixed wing for air transportation.

We have more than 20 full time emergency physicians in our network.

Currently there are published studies that support the effectiveness of telemedicine in management of patients in rural hospitals for both trauma and non trauma patients, such as stroke and acute MI.[11-12] Recently we have established telemedicine as a part of stroke care in Bangkok Hua Hin Hospital (a primary care unit) in cooperation with the Stroke team at BMC (Stroke Center). We plan to further develop the telemedical system to cover more medical conditions such as trauma and acute coronary syndrome.

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Review Article

Mammography: From Past to Present

Nitida Mekasut, MD.[1]

[1] Imaging Center, Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Mammography, Digital Mammography, History of mammography, Breast imagng

The history of mammography can be arbitrarily subdivided into three periods: the Age of Pioneers, the Age of Technical Progress and the Modern Era.

The Age of Pioneers

In 1913, Albert Salomon, a German Surgeon (Figure 1) conducted a roentgeno-histological study on over 3,000 mastectomies comparing the macroscopic observations with microscopic pathology. The first attempts to use radiography for the diagnosis of breast cancer did not become more established until four decades later.

Figure 1: *Albert Salomon. (Courtesy of Andre Bruwer, MD, Tucson) Radiographic 1990; 10:1111-1130*

The Age of Technical Progress

In 1930, Stafford L. Warren, a radiologist at Rochester Memorial Hospital, New York reported the use of a stereoscopic technique for in vivo mammography in 199 patients who then underwent surgery.

In 1931, Walter Vogel reported a radiographic classification of benign breast lesions and how they could be differentiated from carcinoma.

In 1938, Jacob Gershon-Cohen (Figure 2) and Albert Stricker published an article describing the range of normal radiographic of the breast.

In 1950, Gershon-Cohen emphasized the importance of high contrast images obtain without screen and with collimation and compression.

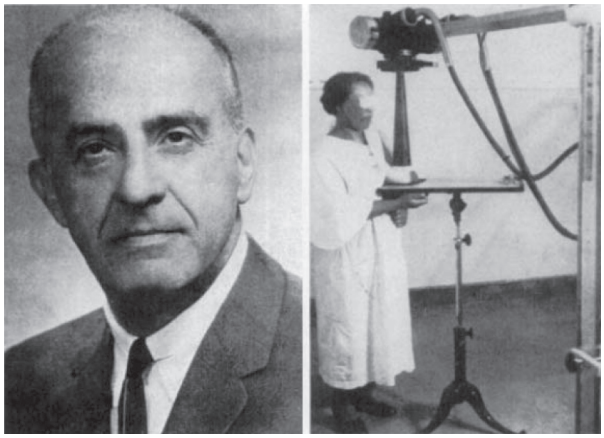


Figure 2: *Jacob Gershon-Cohen (Courtesy of Radiology) Radiographic 1990; 10: 1111-1130*

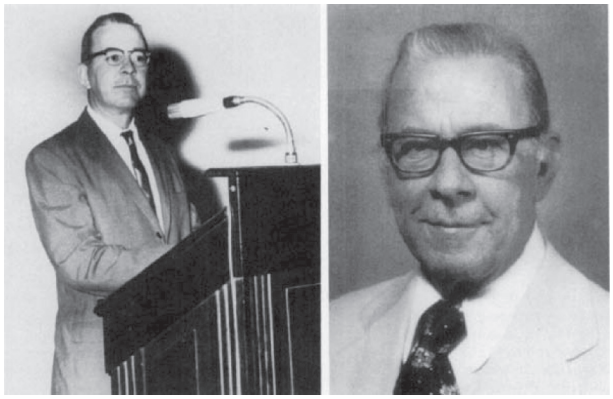


Figure 3: *Robert L. Egan, spreading the mammography gospel, in 1967 (left) and today (right). (Courtesy of Robert L., Egan, MD, Atlanta.) Radiographic 1990; 10: 1111-1130*

The Modern Era

In 1960, Robert L. Egan (Figure 3) described the high-quality images technique of mammogram. The widespread use of mammography is primarily attributable to the work of Egan.

By the 1970s, dedicated x-ray machines for mammography were established and mammography was identified as the best technique for breast cancer screening.

Although, traditional film mammography is currently the gold standard in the detection of breast cancer, yet it still has several limitations e.g. underexposure, overexposure, lost contrast and also less sensitivity in the detection of lobular cancer and ductal carcinoma in situ, resulting in additional study need and increased radiation exposure.[1]

Significant Advances Period

Digital Mammography

In the past decade, mammography is undergoing the transition to digital detector, known as full-field digital mammography (FFDM). The first FFDM system, approved by the FDA in the U.S. in 2000, demonstrated that it is at least as good as screen-film mammography at detecting breast cancer without increasing breast radiation doses, or the number of woman recalled for further investigation. Digital mammography has been shown to be superior over screen-film mammography in younger women with dense breasts. FFDM selectively optimizes the contrast in areas of dense parenchymal from stromal tissue and has improved detection of disease. Technical advances with digitally stored images allow better storage, access and retrieval data. Advances in digital systems also allow better management post-image capture to produce optimal images.

Potential Harms. The possibility of false-positive test results is similar for film and digital mammography. It is uncertain whether overdiagnosis occurs more with digital mammography than with film mammography.

Costs: Digital mammography is more expensive than film mammography.[2]

What's New in Breast Imaging?

Mammography is an effective imaging tool for detecting breast cancer at an early stage and is the only screening modality proved to reduce mortality from breast cancer. However, the overlap of tissues depicted on mammograms may create significant obstacles to the detection and diagnosis of abnormalities. Diagnostic testing initiated because of a questionable result at screening mammography frequently causes patients unnecessary anxiety and increased medial costs. Therefore, additional diagnostic exams are often required to find the right answers.

MRI breast imaging

MRI is an additional investigative tool to be used after initial mammography, to detect anatomic abnormalities, staging the local tumor and development of new blood vessels, which occur with the development of cancers. MRI is extremely sensitive and detects unexpected disease in up to 25% of patients, which obviously has implications for their treatment. It can also detect unsuspected cancer in the other breastof some patients.

The indications for and use of breast magnetic resonance (MR) imaging has increased over the past decade. Current potential indications for contrast materialenhanced breast MR imaging include (a) evaluation of the extent of known breast cancer in woman who desire breast conservation, (b) detection of contralateral breast cancer in woman with newly diagnosed breast cancer, (c) screening of women who are at high risk for developing breast cancer (e.g., those with the *BRCA1* gene), (d) assessment of responses to neoadjuvant therapy, (e) evaluation of chest wall invasion in patient with posterior carcinomas, (f) detection of breast cancer in woman with axillary metastasis and normal mammographic findings,[3] and (g) examining breasts that contain implants, examining the breasts of patients with histologically proved metastatic breast cancer with unknown primary origin.[4]

The sensitivity of MR imaging for the detection of breast cancer is very high, with 90% being the value reported in most studies.[5, 6] However, with regard to the detection of ductal carcinoma in situ (DCIS), the sensitivity of MR imaging varies between 40% and 100%.[7] The result may be false-negative in the presence of DCIS or an invasive ductal or lobular malignancy. Specificity of 37%-100% has been reported for breast MR imaging; in most studies, it has varied from 50%-70%.[5] The relative low specificity of breast MR imaging is a disadvantage, and rigorous criteria have been proposed for the interpretation of breast imaging.[8]

The specificity of breast MR imaging is improved when both morphologic and kinetic features are considered in the interpretation. In classifying breast lesions, the assessment of margin and qualitative enhancement intensity (at 2 minutes or less after contrast material injection) is the most important features currently available for breast mass characterization. The next most important feature is the qualitative assessment of the enhancement kinetic curve.

Kuhl and colleagues[9] have described three time-signal intensity curves that are important in differentiating benign from malignant lesions. The type I curve (Figure 4b) is a slow steady enhancement curve. The type II curve demonstrates plateau signal intensity (Figure 4c). The type III curve is associated with washout of signal intensity (Figure 4d) and is strong indicator of malignancy. The use of time-signal intensity curves has a sensitivity of 91% and specificity of 83%.[9]

Limitation of breast MRI

False Positive
- Overlap of benign and malignant lesion
- Incidental enhancing lesion, common in premenopausal women with dense breasts

False Negative
- Invasive lobular carcinoma
- Low grade ductal carcinoma i.e. tubular DCIS

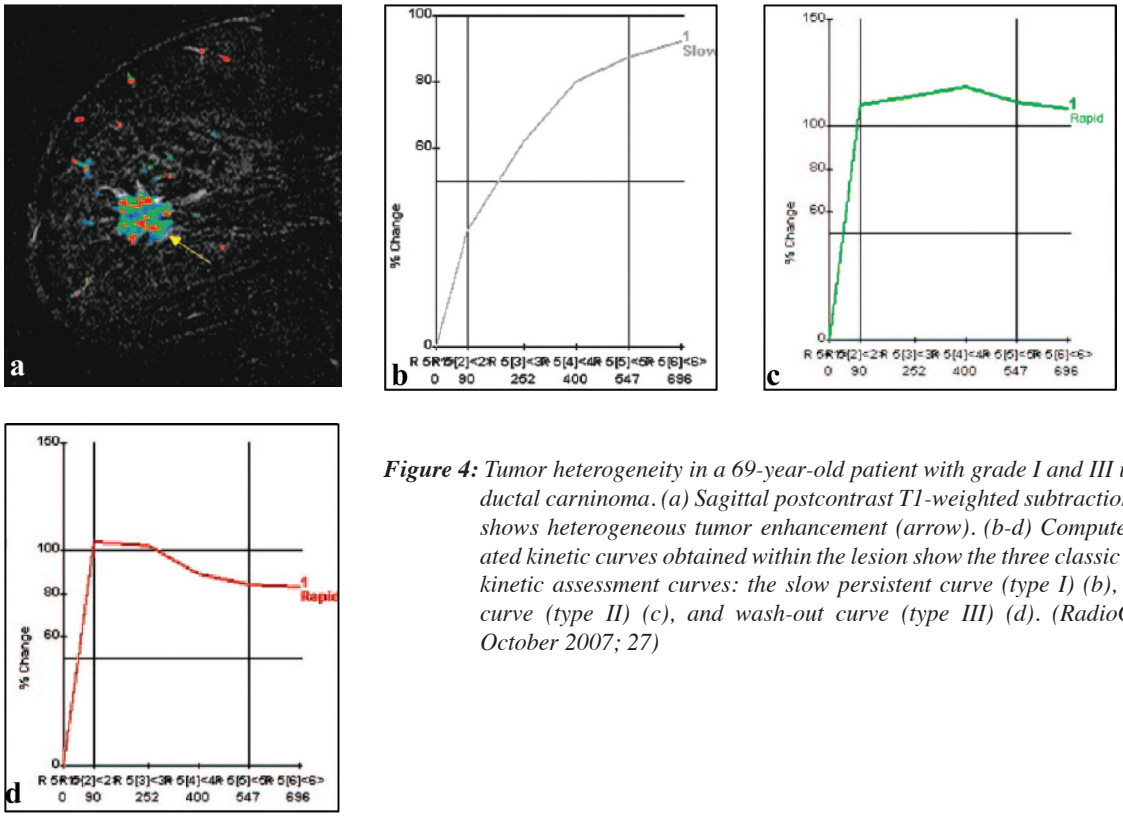


Figure 4: *Tumor heterogeneity in a 69-year-old patient with grade I and III invasive ductal carninoma. (a) Sagittal postcontrast T1-weighted subtraction image shows heterogeneous tumor enhancement (arrow). (b-d) Computergenerated kinetic curves obtained within the lesion show the three classic types of kinetic assessment curves: the slow persistent curve (type I) (b), plateau curve (type II) (c), and wash-out curve (type III) (d). (RadioGraphic October 2007; 27)*

Potential Harm: Contrast-enhanced MRI requires the injection of contrast media. Studies of MRI screening have shown that MRI yield many more falsepositive results than does mammography. MRI has potential to be overdiagnosis than mammography.

Costs: MRI is much more expensive than either film or digital mammography.

Current Practice: MRI is not currently used for screening women at average risk of breast cancer because of its being less specific than mammography screening. There is the potential, it could be be associated with higher biopsy rates and a greater degree of overdiagnosis if used in low-risk populations.

Dual Energy Contrast Enhanced Digital Mammography (DE CEDM)

The accuracy of conventional mammography is limited in dense breasts where surrounding fibroglandular tissue decreases the conspicuity of lesions and lack of intrinsic tissue contrast. Even when tumors are detected, the full extent of disease may not be clearly depicted. The growth and metastatic potential of tumor can be directly linked to angiogenesis. Tumor angiogenesis factors stimulate formation of abnormal vessels that leak and shunt blood. Therefore, imaging methods with contrast medium potentially can aid in the detection and diagnosis of cancer.[10]

In the mid-1980s, Watt et al.[12], Ackerma et al.[13], and Watt et al.[14] performed digital subtraction angiography (DSA) of the breast by using and x-ray imaging intensifier system. Benign and malignant lesions were differentiated according to the strength of enhancement.

The technique consists of high and low energy digital mammography after administration of iodinated contrast agent. DE CEDM is similar in concept to enhanced breast MRI imaging in detected new blood vessels. It can be used to detect primary breast cancer in a woman with a positive axillary lymph node and determine the extent of disease in cases of known cancer, as well as problem solving in case of mammographic findings that were not depicted in additional mammograms or US scans.

Its remains to be seen whether the sensitivity to cancer is as high for DE CEDM as it is for MRI, which has been shown to have a very high sensitivity. Both techniques make use of the same property of tumor angiogenesis, which causes cancers to take up contrast agent faster and to a greater degree than do normal tissues or benign masses, because of denser capillaries that are also abnormally "leaky". Because of its higher contrast resolution, MRI is probably more sensitive to contrast enhancement than is DE CEDM, but the degree to which that translates into higher sensitivity for cancer detection is unknown. One drawback of MRI is that its high sensitivity to contrast agent uptake causes it to be plaqued by numerous false-positive foci of enhancement. MRI also has relatively limited sensitivity to ductal carcinoma in situ (DCIS), which is depicted as microcalcifications at mammography. DE CEDM was 83% specific in this study, and the lowenergy source images showed microcalcifications, which could be used in the diagnosis of DCIS.

Findings with MRI imaging suggest that morphologic features (i.e., shape and margin) help differentiate benign from malignant enhancing areas. Because DE CEDM allows a higher spatial resolution than that with MRI, differentiation of benign from malignant morphologic features at DE CEDM should be easier. Enhancement kinetics, also used for differentiating benign from malignant lesions at MRI can be determined at DE CEDM with serial imaging. Because whole breast images can be acquired more rapidly than with most MRI sequences, kinetic formation could be determined with greater precision. Unlike MRI, however each image has a penalty of additional radiation. DE CEDM is less expensive than MRI.

The expansion of existing mammographic core biopsy or preoperative needle localization techniques to include DE CEDM would be straightforward, give the right equipment. Such procedures are difficult to perform with MRI guidance because of the geometry of a high- strength magnetic field.[10]

The results of the study of Roberta et al.[11] suggest that contrast-enhanced digital mammography potentially may be useful in the identification of lesions in the mammographically dense breast. As in MR imaging, other applications may be in the identification of the extent of disease or in the identification of an otherwise occult carcinoma that has manifested with axillary metastases. This information may aid in the diagnosis and guidance of core-needle biopsy or excision of these lesion. Furthermore, with the increasing availability of digital mammography, contrast-enhanced digital mammography will become accessible and relatively inexpensive compared with current MR imagingtechnology. These results encourage further investigation of contrast-enhanced digital mammography as a diagnostic tool for breast cancer.

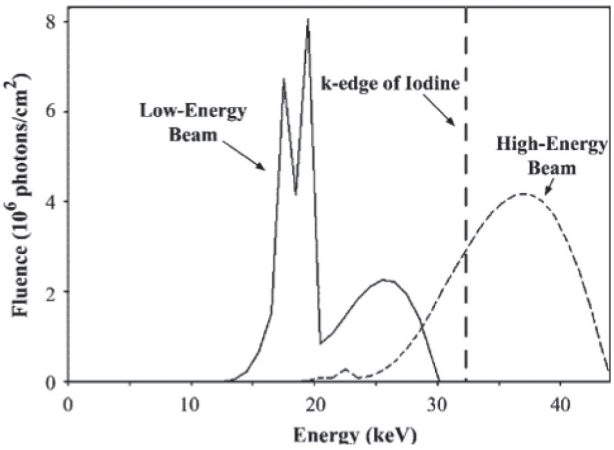


Figure 5: *X-ray spectra calculated for high and lowenergy beams. Each curve is scaled to represent exposure through a 4.5-cm-thick 50% glandular-50% fat breast. High-energy parameters include44kVp,rhodiumanode,0.025-mm-thick rhodium and 8-mm-thick aluminum filters, and 200 mAs. Low-energy parameters include 30 kVp, molybdenum anode, 0.03-mm-thick molybdenum filter, and 140 mAs. The k edge of iodine, at 33.2 keV, is marked by a dashed line. (Modeling program courtesy of General Electrical Corporate Research and Development, Niskayuna, NY.) : Radiology October 2003.*

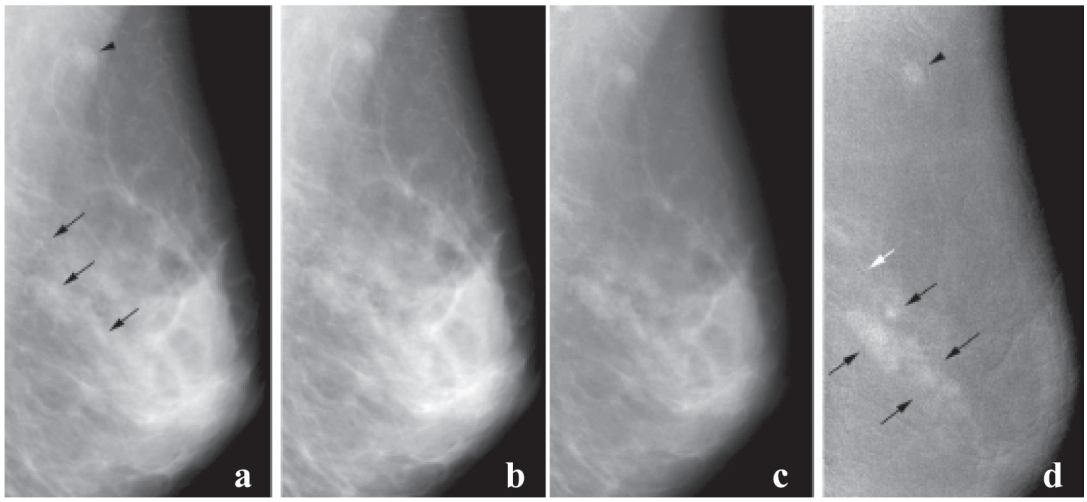


Figure 6*: Invasive ductal carcinoma and DCIS. (a) Mediolateral oblique mammogram shows grouped microcalcficationin in the breast (arrows) and in lymph node (arrowhead). Enhancement is barely perceptible on postcontrast (b.) low-energy and(c) high-energy images. (d) Subtracted dual energy enhanced DSM image shows the invasive component as enhancing lesions (black arrows), but there is no definite enhancement around grouped calcifications in the posterior breast (white arrow). The malignant lymph node (arrowhead) is also enhanced. (Radiology 2003; 229:261-268)*

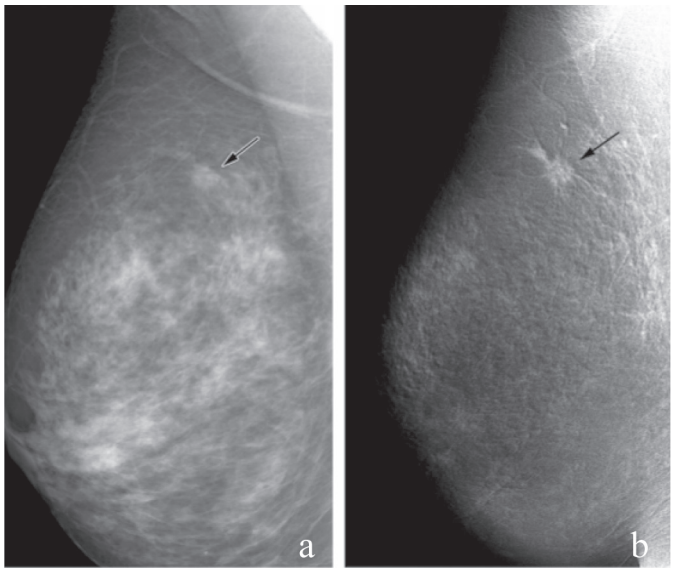


Figure 7: *Invasive ductal carcinoma (11-mm diameter). (a) Mediolateral oblique mammogram shows possible spiculated mass (arrrow). (b) Dual-energy enhanced DSM image shows the cancer as an enhancing mass with definite spiculations (arrow). (Radiology 2003; 229:261-268)*

Ultrasound Elastography

Generally, breast cancer tissue is harder than the adjacent normal breast tissue. This property serves as the basis for some examination, such as palpation, that are currently being used in the clinical assessment of breast abnormalities, as well as for elastography.

The principle of elastography is that tissue compression produces strain (displacement) within the tissue and that the strain is smaller in harder tissue than in softer tissue. Therefore, by measuring the tissue strain induced by compression, we can estimate tissue hardness, which may be useful in diagnosing breast cancer.

Clinical Impications

Ako et al.[22] findings of a significant difference between mean elasticity scores for malignant and benign lesions in patients suggests that elastography may be useful in diagnosing breast lesions in the clinical setting. To classify elasticity images, they evaluated the color pattern both in the hypoechoic lesion (i.e., the area that was hypoechoic or isoechoic relative to the subcutaneous fat [except for echogenic halo] on Bmode images) and in the surrounding breast tissue. On the basis of the overall pattern, they assigned each image an elasticity score on a five-point scale.

Ako et al.'s[22] believe that an elasticity score of 5, which shows no strain in the entire hypoechoic lesion and the surrounding are at B-mode US, indicates infiltration of cancer cells into the interstitial tissue (e.g., in scirrhous carcinoma) or into an intraductal component (e.g., in DCIS), both of which are characteristics of carcinoma.

An elasticity score of 4, which indicates no strain in the entire hypoechoic lesion, seems to be characteristic of tumors such as solid tubular carcinomas that are circumscribed and homogeneously harder than the adjacent normal breast tissue.

An elasticity score of 3 which indicates strain at the periphery of the hypoechoic lesion, was mainly found in benign lesions, including intraductal papillomas. The importance of strain at the periphery is unclear at present and requires further investigation. Ako et al.[22] recommend that all lesion with elasticity scores of 3 or higher be examined by means of aspiration cytology or needle biopsy because two (13%) of the 15 lesions with a score of 3 were malignant.

An elasticity score of 2, for which pars of the hypoechoic lesion did not show strain at B-mode US, indicate lesions that are soft yet somewhat harder than normal breast tissue. This is often characteristic of lesions such as fibroadenoma, duct papillomatosis, sclerosing adenosis or lobular hyperplasia.

An elasticity score of 1, which shows even strain in the entire hypoechoic lesion at B-mode US, indicates that lesions have almost the same compressibility as the surrounding breast tissue. In this study[22] no malignant lesions had a score of 1.

In conclusion, elastography could be complementary to conventional US, thereby making it easier to diagnose breast lesions. The skill needed to acquire adequate images is similar for conventional US and elastography; the skill needed to interpret images. Elastography is promising, and it is expected that with future improvements in the technology (e.g., the development of a pressure indicator and approaches for quantitative assessment), this imaging modality will become an invaluable tool for the diagnosis of breast disease in the clinical setting.[22]

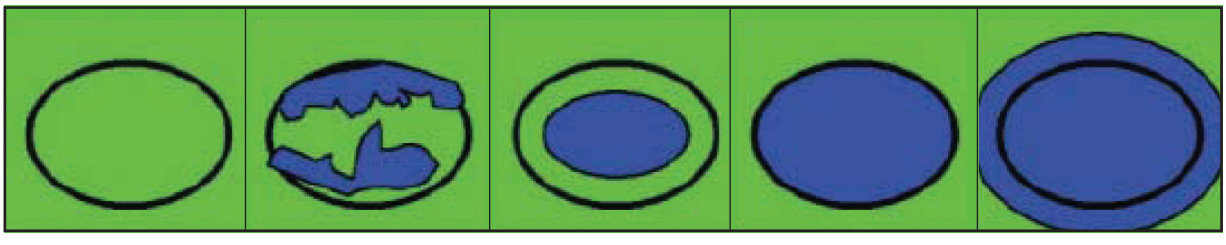


Figure 8: *Images present general appearance of lesions for elasticity scores of (a)1, (b)2, (c)3, (d)4, and (e) 5. Black circle indicates outline of hypoechoic lesion (ie, border between lesion and surrounding breast tissue) on B-mode images. (Radiology 2006;239:341-350)*

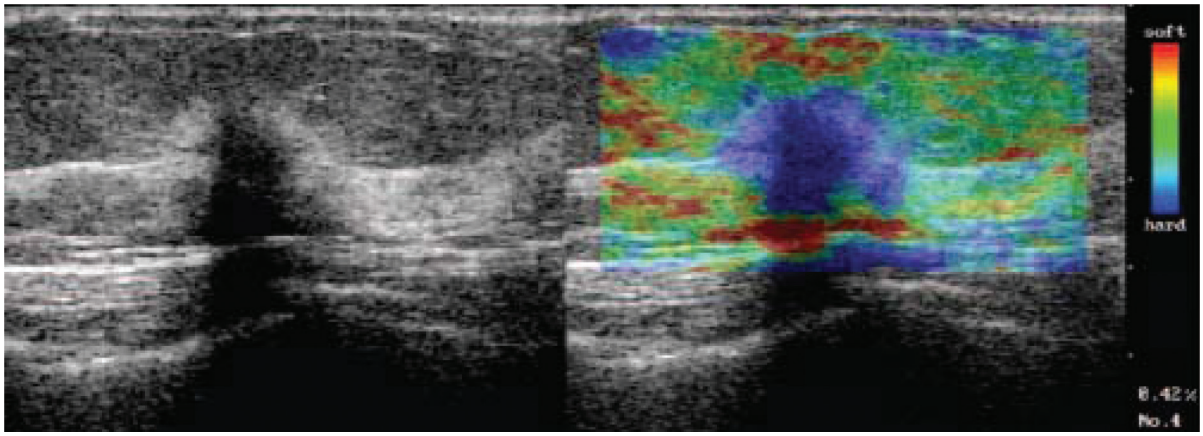


Figure 9: *Scirrhous type invasive ductal carcinoma with elasticity score of 5 in 55-year-old woman. US images were obtained in sagittal plane. Left: On conventional B-mode images, lesion was classified as BI-RADS category 5. Middle: On elasticity image, both the entire hypoechoic lesion and its surrounding area were blue. (Radiology 2006;239:341-350)*

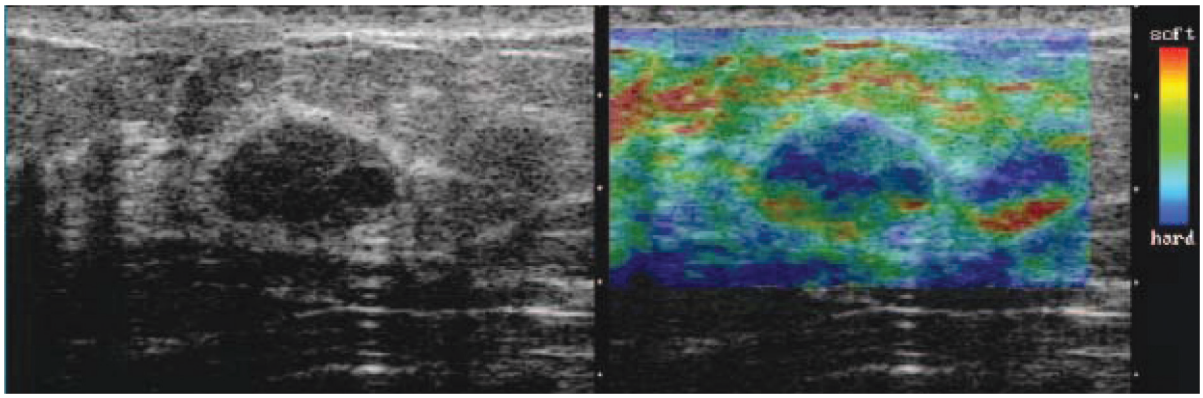


Figure 10: *Fibroadenoma with elasticity score of 2 in 39-year-old woman. US images were obtained in transverse plane. Left: On conventional B-mode image, lesion was classified as BI-RADS category 3. Right: On elasticity image, hypoechoic lesion shows mosaic pattern of green and blue. (Radiology 2006;239:341-350)*

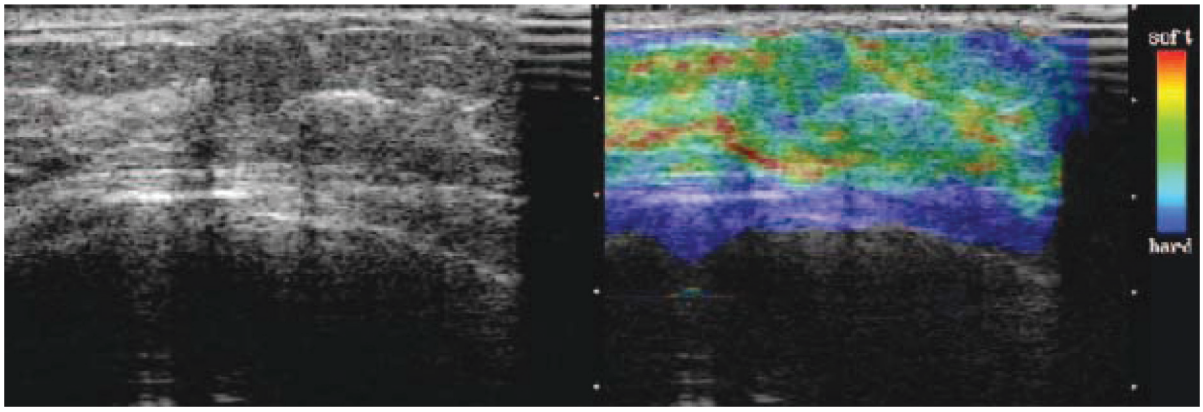


Figure 11: *Fibroadenoma with elacticity score of 1 in 51-year-old woman. US images were obtained in transverse plane. Left: On conventional B-mode image, lesion was classified as BI-RADS cathegory2. Right: On elasticity image, the entire hypoechoic lesion was evenly shaded green, as was the surrounding breast tissue. (Radiology 2006;239:341-350)*

Digital Breast Tomosynthesis (DBT)

Breast tomosynthesis is a new tool that can reduce or eliminate tissue overlap. Breast tomosynthesis technology is essentially a modification of a digital mammography unit to enable the acquisition of a threedimensional (3D) volume of thin section data. Images are reconstructed in conventional orientations by using reconstruction algorithms similar to those used in computed tomography (CT).

DBT consists of taking multiple images at multiple angles that can reduce or eliminate the tissue overlap effect that occurs so frequently with 2-D film screening mammography.

Images are reconstructed in conventional orientations by using reconstruction algorithms similar to those used in CT. DBT imaging enables 3-D breast examinations, overlapping of tissue at interpretation of projecting mammograms. DBT's potential advantages include reducing lesion localization and the selection of patients for biopsy, as well as assessing the therapeutic efficacy of chemoradiotherapy. Similar technical improvements from digital imaging supplement these performance parameters, as well.

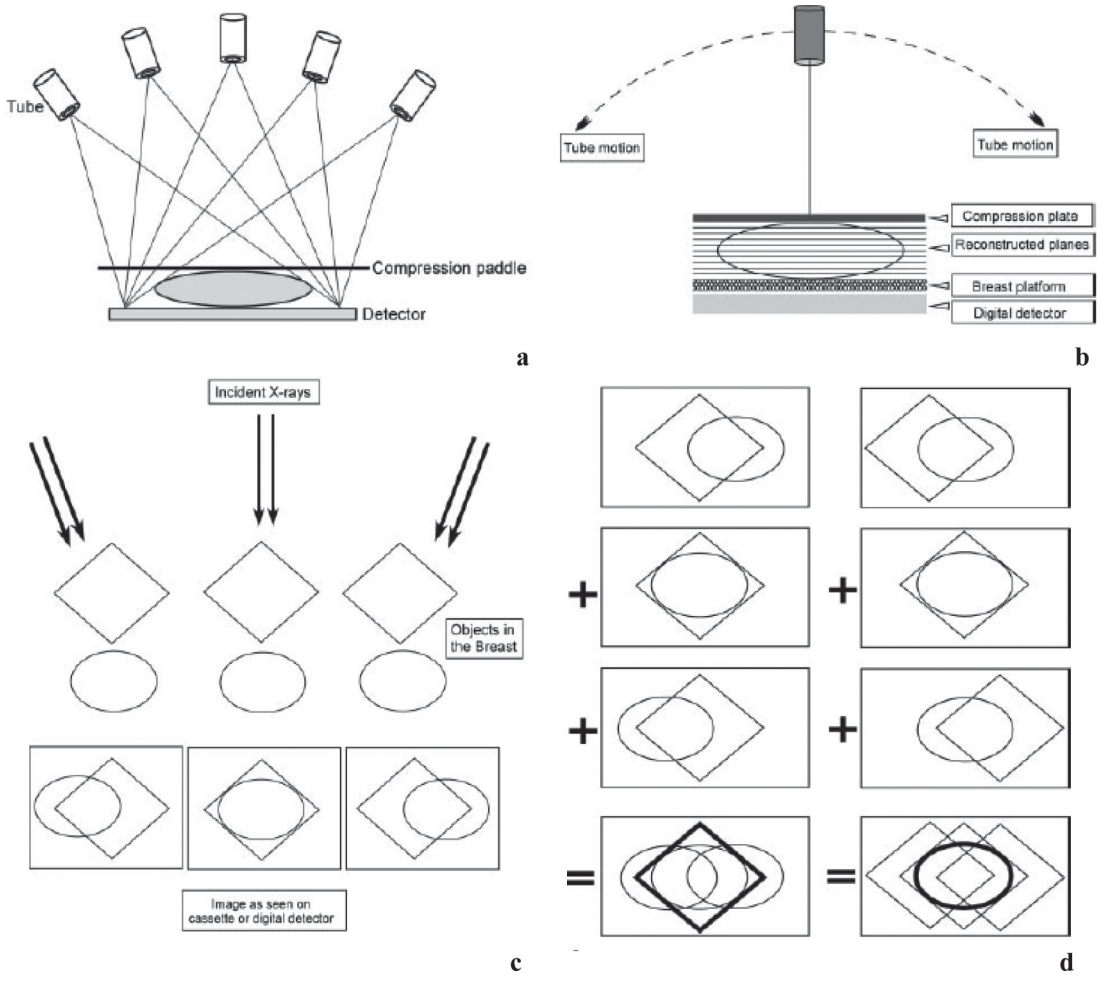


Figure 12: *Basic technologic principles of breast tomosynthesis. (a,b) Schemans shows how image data are acquired from various angles as the x-ray tube moves in an arc. Either the step-and-shoot method (a) or the continuous exposure method (b) may be used, and the detector may be moving or stationary during image acquisition. The 3D image data are subsequently reconstructed as conventional mammographic projections (cranio-caudal, mediolateral oblique and mediolateral view). (c, d) Diagrams show how different 3D image data aquired from different angles (c) are reconstructed to provide separate depiction of two overlapping structures located in different planes (d).* [15]

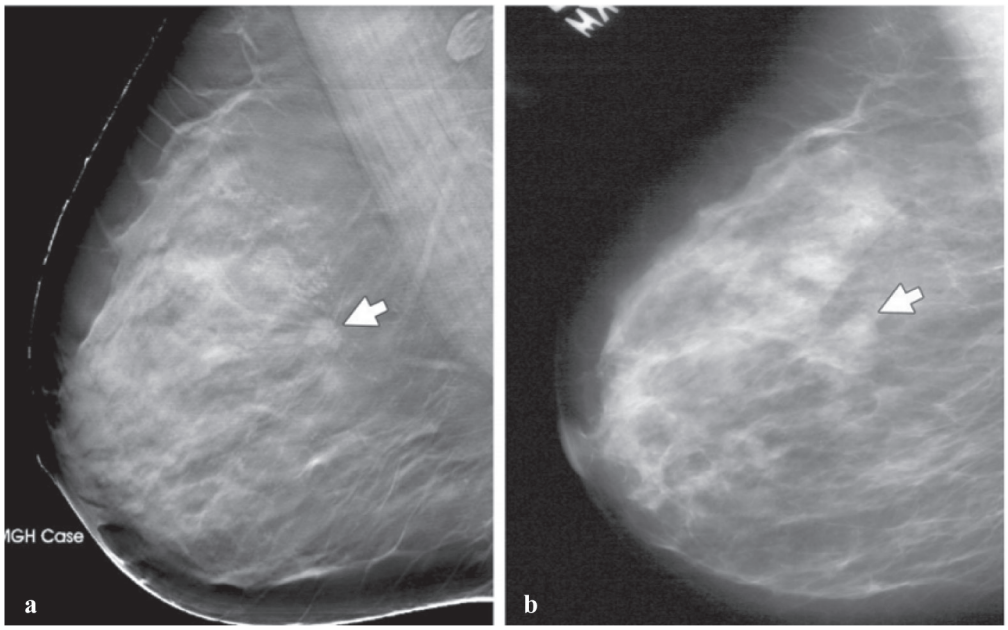


Figure 13: *Mass (arrow) depicted in the mediolateral oblique view on (a) and (b) screen-film mammograms. The spicules of the mass are much more conspicuous. (Radiology 2005; 237:1075-1080)*

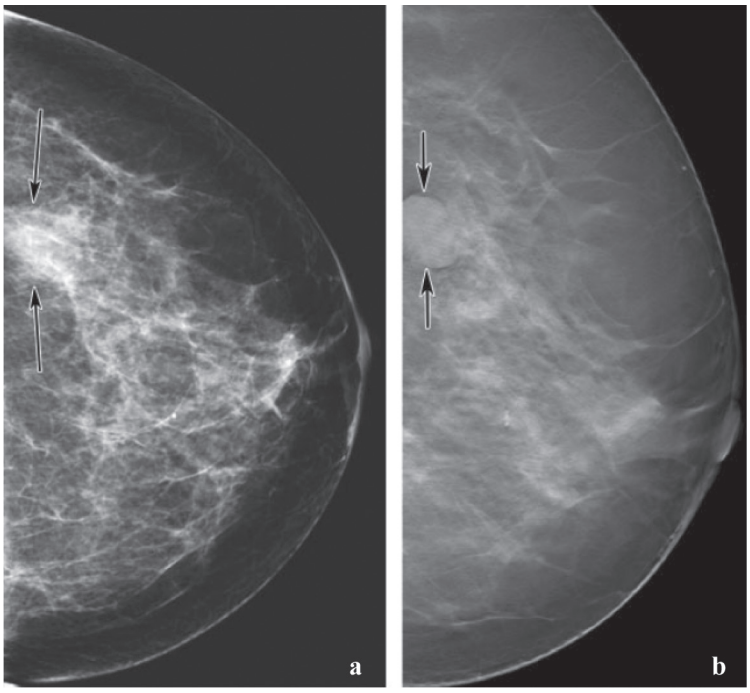


Figure 14: *Comparison of screening mammography with breast tomosynthesis in a 57-year-old woman. (a) Digital mammogram shows a mass (arrows) in the lower outer part of the left breast. The mass is not clearly visible because of surrounding dense tissue. (b) Breast tomosynthesis image provides clearer depiction of the mass (arrow), which is well circumscribed. Because its' US appearance remained stable for 2 years, the mass was considered benign. (See also Movie 1 at radiographics.rsnajnls.org/cgi/content/full/27/S231/DC1)*[15]

Contrasted-Enhanced Digital Breast Tomosynthesis (CE-DBT)

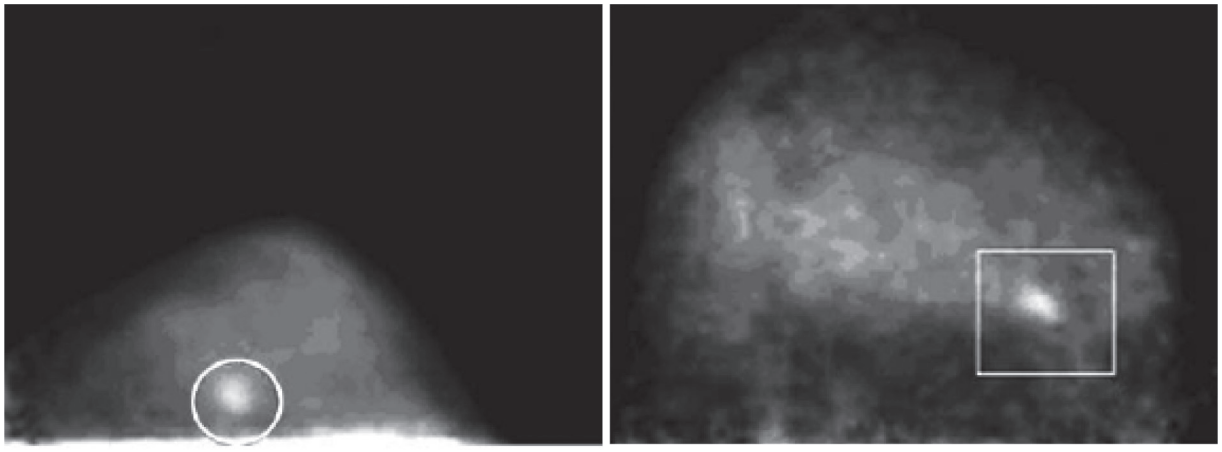
CE-DBT is a combination of the projection techniques of DBT with intravenous contrast enhancement. As tumor angiogenesis is necessary for breast cancer growth, the use of diffusion contrast enhancement utilizes the increased vessel permeability in the disorganized vessel network to better visualized the tumor function. Lesions are identified by the use of an iodinated contrast agent, which tends to pool in the tumor space. X-ray techniques using contrast agents have demonstrated the enhancement of breast cancers and increase in lesion conspicuity. This combination of contrast-enhance digital mammography and DBT into a single technique would potentially integrate the benefits of both technique, thus providing both breast cancer morphology and vascular information. These advantages of CE-DBT will be better with conventional mammography for biopsy or preoperative localization purposes. Furthermore, CE-DBT may be cheaper than breast MR and potentially be more widely available.

Positron Emission Mammography

More recently, dedicated breast positron emission mammography (PEM) units have been developed to overcome the limitation of whole-body PET and to provide a positron-emitting imaging platform capable of detection and depiction of primary breast carcinoma (Figure 11).

In general, these systems consist of two planar detectors placed opposite a gently compressed breast. The advantages of such dedicated systems include improvement geometric sensitivity, higher spatial resolution, shorter imaging time, and reduced attenuation compared with whole-body PET systems. They also have a small physical footprint, which makes their use in a breast imaging facility feasible and allows correlation of the results with those of conventional breast imaging as well as PEM-guided biopsy.

Although preliminary data demonstrate that these systems are capable of imaging smaller primary breast carcinomas than whole-body systems, their clinical utility has not been adequately demonstrated (Table 1)[18-19]. Certain limitation such as imaging posterior lesions, variable FDG uptake in small tumors, and falsepositive findings from prior biopsy have been reported, and biopsy capability needs to be further addressed[8,10-12]. Potential roles advocated for these systems included detection, problem solving, local staging, local recurrence, and assessing or predicting response of the primary tumor to chemotherapy. Dedicated breast PEM and PET are a promising technology to help overcome the limitations of whole-body imaging and may eventually provide a positron emission imaging platform capable of reliably imaging primary breast carcinoma.



a b

Figure 15: *Demonstration of small invasive breast carcinomas with FDG PEM. Images from dedicated breast PEM units show 9-mm (circle in a) and 1.3-cm (rectangle in b) invasive carcinomas. (RadioGraphics 2007; 27:S215-S229)*

Table 1: Summary of the Results of Published FDG PEM Studies

Authors and Year of Study	No. of Patients	Average Lesion Size (cm)*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Murthy et al 2000	18	NA	50	100	100	67
Levine et al 2003	14	2.0 (1.0–5.5)	86	91	86	91
Rosen et al 2005	23	2.1 (0.4–4.6)	86	33†	90	25†
Tafra et al 2005	44 + 10	2.2‡ (0.1–10.0)	88	NA	NA	45
Berg et al 2006	92	2.1‡ (0.3–10.0)	90	86	88	88
Rosen et al 2006	50	1.4 (0.8–4.0)	87	70	71	86

Note.—NA = not available, NPV = negative predictive value, PPV = positive predictive value.
*Numbers in parentheses are ranges.
†Only two of 23 were true negative, according to Breast Imaging Reporting and Data System criterion 5 only.
‡Median size, invasive lesions only.

Brest-Specific Gamma Imaging (BSGI)

BSGI is the technique of using radiotracers (^{99m}Tcsestamibi) to detect abnormal cellular metabolism, mainly of advantage in breast cancer detection. The highly advanced cancer enable optimized molecular breast imaging with a high-resolution, small field of view (FOV) detector for image acquisition used breast specific gamma camera. The devicehas a high sensitivity (96.4%).[20] The sensitivity of BSGI is comparable to MR (88%) imaging.[21]

The capability to help detect subcentimeter (defined as <1cm) cancer has been a criticism of gamma imaging of the breast. The sensitivity for subcentimeter lesion (88.9%) is higher than previously reported with scintimammography (35%-65%) and MR imaging (79.1%).[21] In Rachel et al.[20] study, five invasive cancers and three DCIS lesion measuring less than 5 mm were detected. The improved sensitivity with BSGI as compared with scintimammography results, at least in part, from the improved spatial resolution of the breast-specific gamma camera, as well as the decreased lesion-to-detector distance. The ability to detect small subcentimeter breast cancers should aid in the early detection of breast cancer, including occult foci. Additional studies with larger study populations are needed to further define the sensitivity of BSGI for both in situ and invasive subcentimeter lesions.

Rachel et al.[20] study demonstrates that BSGI has a sensitivity of 93.8% for the detection of DCIS and 97% for the detection of invasive cancers. This sensitivity is comparable to that reported in MR imaging for invasive cancers (90.9%) and better than that reported for DCIS (73%).[21] An advantage of BSGI is the greater comfort of the patient, with the patient sitting as opposed to being placed in and MR imager. Additionally, BSGI results in four to eight images as compared with several hundred images in a breast MR examination, leading to a concomitant decrease in interpretation time. The detection of occult cancers is an important goal of developing adjunct imaging modalities to mammography. In Rachel et al. study 7.2% of women with cancer were found to have additional foci of cancer that would not have been detected with more conventional imaging modalities. Given the high sensitivity of BSGI, it can be considered as a pre-surgical examination in patients with biopsy-proven cancer, to look for additional foci as well as contralateral breast cancer.

In conclusion, BSGI is a promising adjunct imaging modality with high sensitivity and moderate specificity to help detect breast cancers, including subcentimeter invasive and in situ cancers. Additional multiinstitutional studies are needed with larger study sample sizes to further evaluate BSGI.

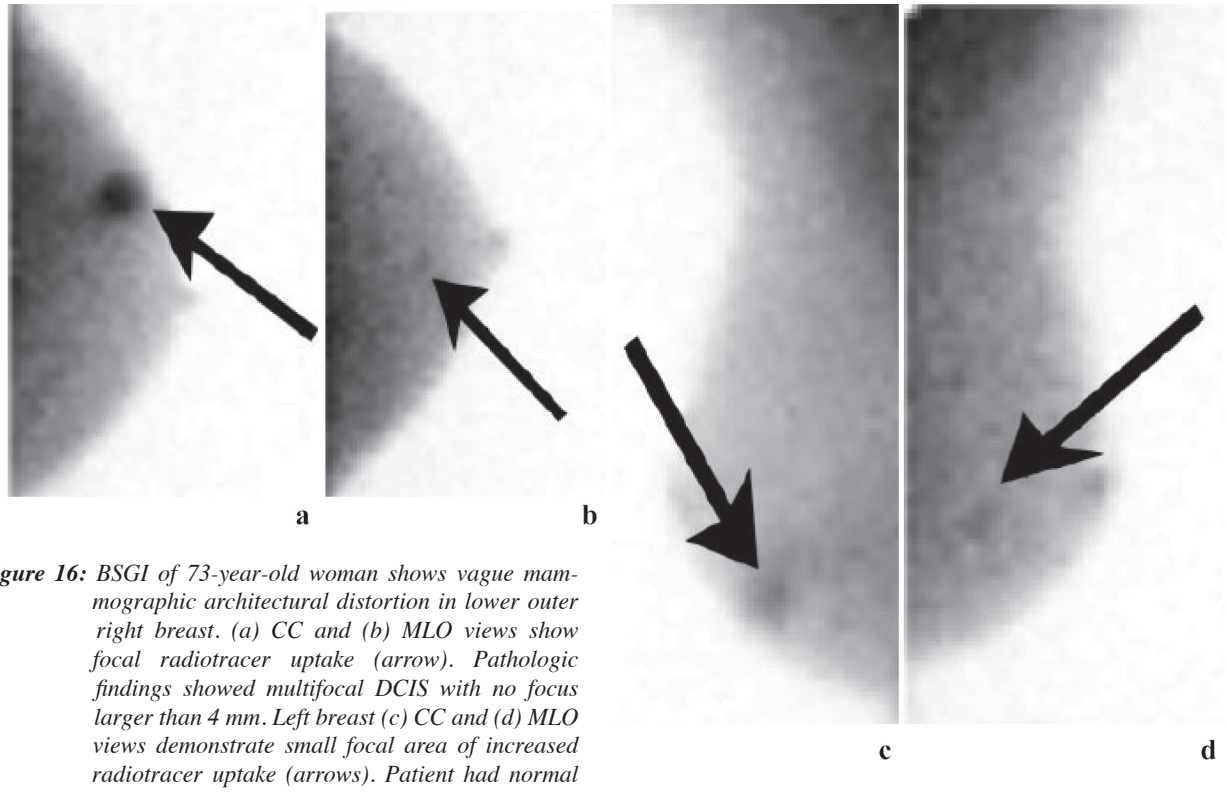


Figure 16: *BSGI of 73-year-old woman shows vague mammographic architectural distortion in lower outer right breast. (a) CC and (b) MLO views show focal radiotracer uptake (arrow). Pathologic findings showed multifocal DCIS with no focus larger than 4 mm. Left breast (c) CC and (d) MLO views demonstrate small focal area of increased radiotracer uptake (arrows). Patient had normal mammogram and initial US findings. Second-look US identified vague hypoechoic area. Surgical excisional biopsy results showed single 4-mm focus of low- grade DCIS, which was occult and unidentified prior to BSGI.*

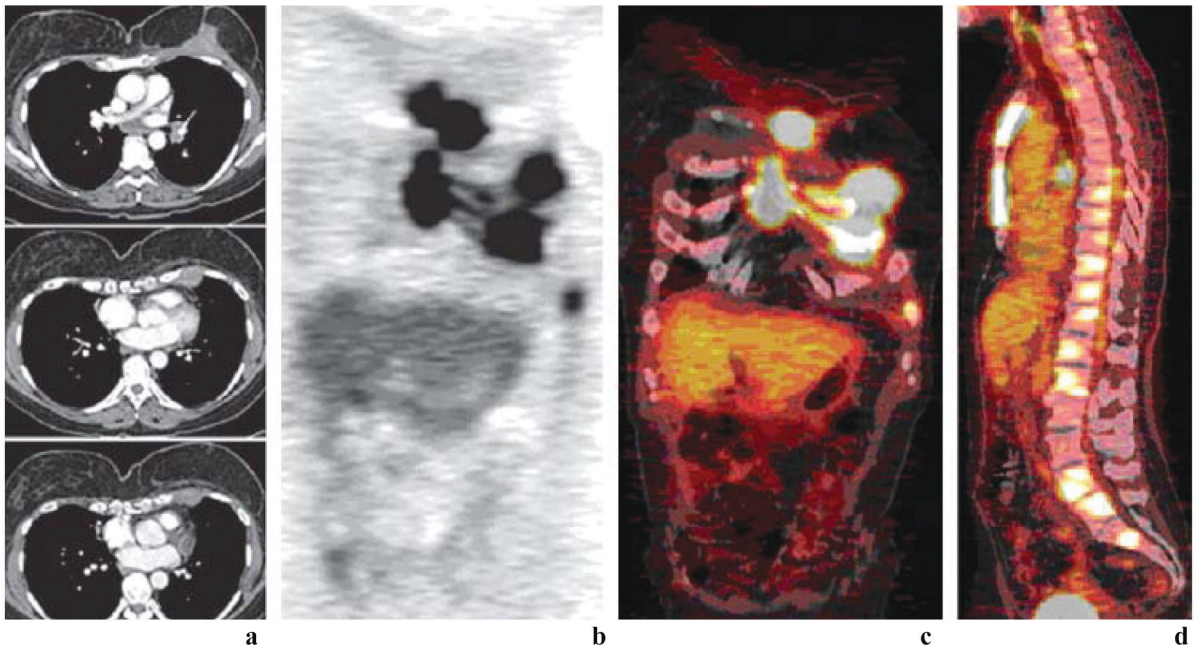


Figure 17: *Results of PET/CT in a patient suspected of having recurrent breast carcinoma. Axial contrast-enhanced CT (a), coronal PET (b), coronal fusion (c), and sagittal fusion (d) images show extensive local recurrence involving the breast, sternum, anterior chest wall, and pleura as well as hilar metastases and diffuse bone metastases. (RadioGraphic Octerber 2007 volume 27)*

FDG PET, PET/CT and Breast Cancer Imaging

Positron emission tomography (PET) and combined PET/computed tomography (CT) are increasingly used for oncologic imaging. Fluorodeoxyglucose (FDG) PET demonstrates abnormal metabolic features associated with malignancy, that often precede morphologic findings demonstrated with anatomical imaging. Combined PET/CT systems are increasingly available and currently account for almost all of the new whole body PET installations. In these systems, the CT and PET images are fused and provide combined anatomic and physiologic imaging. Typically, the CT portion is used to provided attenuation correction as well as anatomic correlation for the PET imaging component. This modality allows more precise anatomic localization of PET abnormalities and in general has been shown to improve diagnostic accuracy compared with FDG PET alone.

Further studies comparing FDG PET to sentinel lymph node biopsy support sentinel lymph node biopsy for early-stage disease and confirm the relatively low sensitivity of FDG PET for axillary nodal metastases in early-stage breast cancer. FDG PET and FDG PET/CT can improve staging and alter therapeutic options in patients suspected to have breast cancer recurrence and distant metastatic disease, primarily by demonstrating local or distant nodule involvement occult at other imaging studies.

It appears that FDG PET is complementary to bone scintigraphy, which remains the standard imaging procedure for surveying the skeleton for metastatic involvement. FDG PET can provide additional information in staging or restaging cases when results of conventional imaging are equivocal or conflicting. It also can be used in setting to evaluate the response of metastatic breast cancer to systemic therapy, since conventional imaging is often challenging in this setting.

In conclusion, FDG PET and PET/CT have been shown to be most helpful in staging recurrent or metastatic breast cancer. Emerging data support the use of FDG PET/CT in advanced axillary disease and evaluation of regional nodal spread in locally advanced breast carcinoma. FDG PET is complementary to conventional staging procedures and should not be a replacement for either bone scintigraphy or diagnostic CT. FDG PET and PET/CT have been shown to be particularly useful in the restaging of breast cancer, in evaluation of response to therapy, and as problemsolving method when results of conventional imaging are equivocal. In these situations, FDG PET often demonstrates locoregional or unsuspected distant disease that affects management. PET has demonstrated a particular capability for evaluation of chemotherapy response in both patients with locally advanced breast carcinoma and those with metastatic disease.[16]

Over the last century, the uses of mammogram for detecting breast cancer have come a long way. With the advances in imaging technology and understanding of cancer biology, earlier breast cancer detection has given direct benefits in terms of clinical outcomes. As mammography remains the standard of care for breast cancer screening, new innovations in mammography promise to advance understanding of the disease and the tumor's response to treatments, but also may integrate into existing platforms for potential ease of access and lower costs.

Summary

The innovations of mammography starting from analog mammography using on target and material in x-ray tube and then the direct and indirect conversion technique integrated to develop the full-field ditigital mammography (FFDM). This innovation shows high resolution image and becomes popular in the efficiency for PAC system which provides teleconsultation. In the mean-time, computed radiography (CR) develops a dedicated CR reader for general mammographic purposes. The CR mammography provides image comparable with FFDM. The cost of investment is lower than FFDM. The early detection for anatomic and physiologic change of early breast carcinoma are feasible. The DBT demonstrates mass accurately. It is more useful in dense breast. In the meantime US, develops a high resolution transducer which able to measure elastoplasty in mechanical and automatic shear waves. The physio-pathologic study based on neoangiogenesis and cellular metabolism as follow MRI with Gd study, CE-DSM and CE-DBT. The cellular metabolic changes are nuclear medicine for instance breast specific gamma image (BSGI). The research for early detection of early breast carcinoma is going on and nowaday, the researchers aim to detect the abnormality at molecular level.

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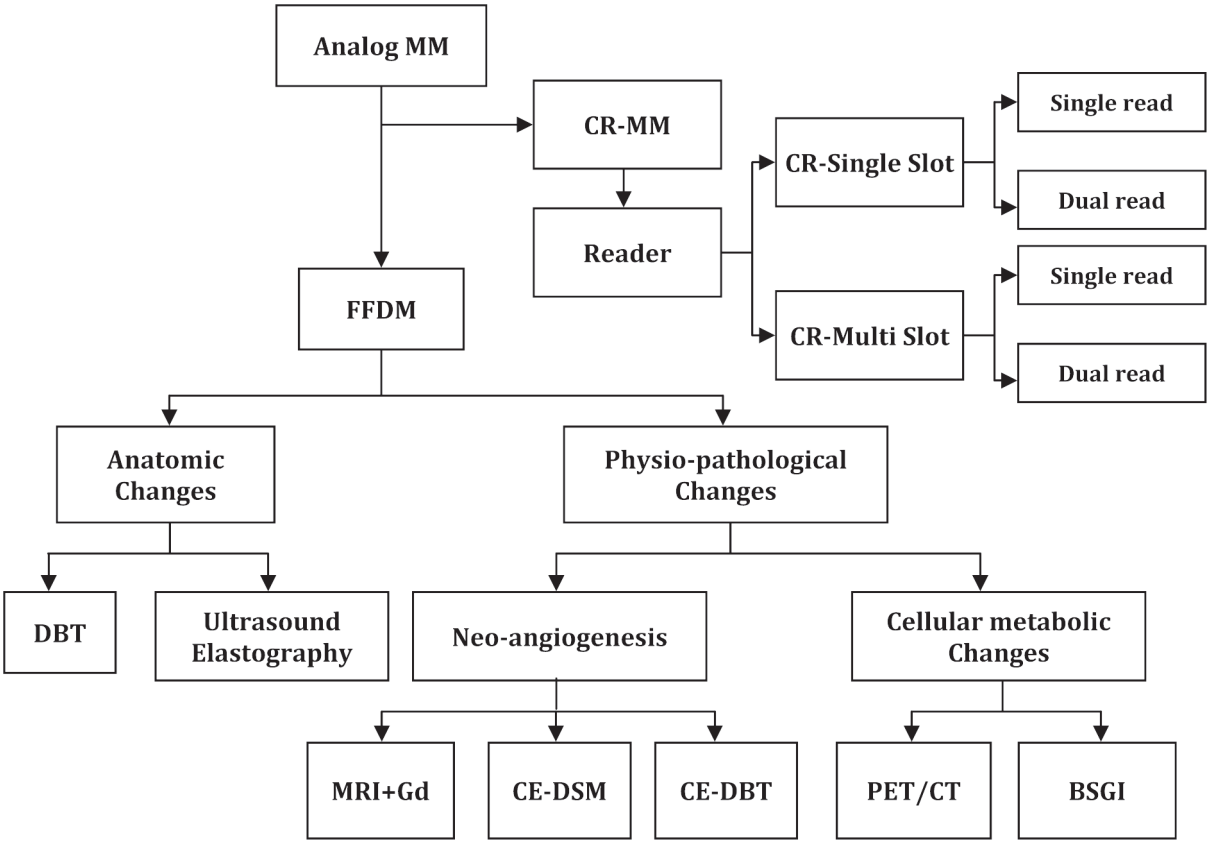

CR = Computed Radiography
Gd = Gadoliniun
MM = Mammography
DBT = Digital Breast Tom synthesis
MRI = Magnetic Resonance Imaging
BSGI = Breast-Specific Gamma Imaging
FFDM = Fill Field Digital Mammography
CE-DSM = Dual-Energy Contrast-enhanced Digital Subtraction Mammography.
CE-DBT = Dual-Energy Contrast-enhanced Digital Breast Tomosynthesis

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Review Article

Recent Advances in Neuroimaging

Orasa Chawalparit, MD.[1, 2]
Nanthasak Tisavipat, MD.[1]

[1] Neuroscience Center, Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.
[2] Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Keywords:
Brain imaging, Advanced neuroimaging

A huge leap of evolution in neuroimaging has occurred since the invention of magnetic resonance imaging (MRI). In the past, brain imaging with computed tomography (CT) could demonstrate only macro changes of the pathologic lesions. The development of MRI allows us to 'visualize' the brain not only as an organ but also at the cellular and molecular level. The developments of biomolecular nanotechnology may help diagnose underlying pathology related biomarkers, for example amyloid plaque in Alzheimer's disease (AD), or specific neurotransmitters to demonstrate brain images without the necessity for cranial vault opening.

Anatomical Imaging

The anatomical information can be revealed by using CT or conventional MRI (cMRI) which include T1W, FLAIR, T2W, GEW and MR angiography. Most CNS diseases are diagnosed by cMRI, which has higher resolution than CT. MRI also provides quantitative information such as hippocampal volumetric measurements, which can identify early cases of AD or demonstrate subtle atrophy in hippocampal sclerosis. Measurement of T2 sequence values (not visualized as subtle changes of signal intensity) were demonstrated in the hippocampal sclerosis or white matter diseases such as multiple sclerosis (MS). There are still pitfalls to watch out for if we generalize about quantitative information; standard values still need to be known for valid comparisons between patients. However, comparison of patients over different periods of time is a viable follow up treatment response.

Many pulse sequences or techniques in MRI have been proposed for demonstrating pathologic lesions. Appropriate selection of those techniques will give the highest sensitivity and accuracy for the diagnosis. For example, susceptibility weighted imaging (SWI) is very useful in identifying small microbleeds which may indicate the prescence of cerebral amyloid angiopathy. SWI is also beneficial in helping to distinguish tumors from tumifactive demyelination, deep infarction or infection. Abnormal microvascular structures in tumors with angiogenesis are clearly demonstrated by SWI. In other lesions, the transmedullary vein is seen passing through the lesions without destruction. (Figure1).

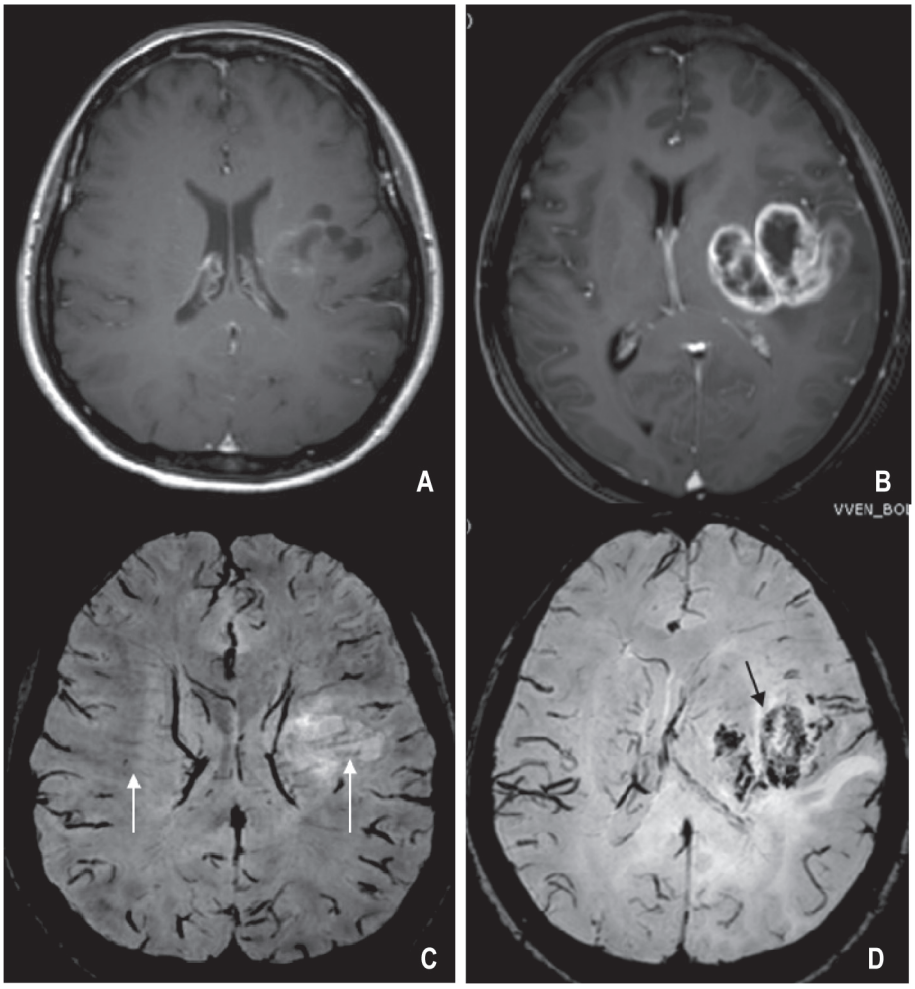


Figure 1: *(A, B) Gd-T1 W, (C, D) SWI: comparing between multiple sclerosis (A, C) and glioblastoma multiforme (B, D). There is enhancement at the periphery of both lesions. On SWI, the transmedullary vein is seen passing the MS lesion (arrows in C). In glioblastoma multiforme the normal vein was destroyed and replaced by tumor microvasculature (arrow in D).*

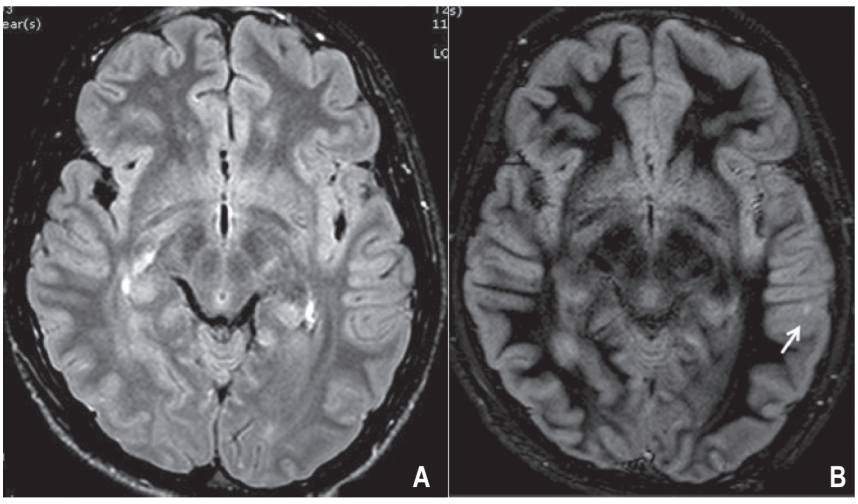


Figure 2: *Double inversion recovery (DIR) in multiple sclerosis: (A) FLAIR, (B) DIR show lesion in the gray matter of cerebral cortex on DIR (arrow in B) which is not seen on FLAIR.*

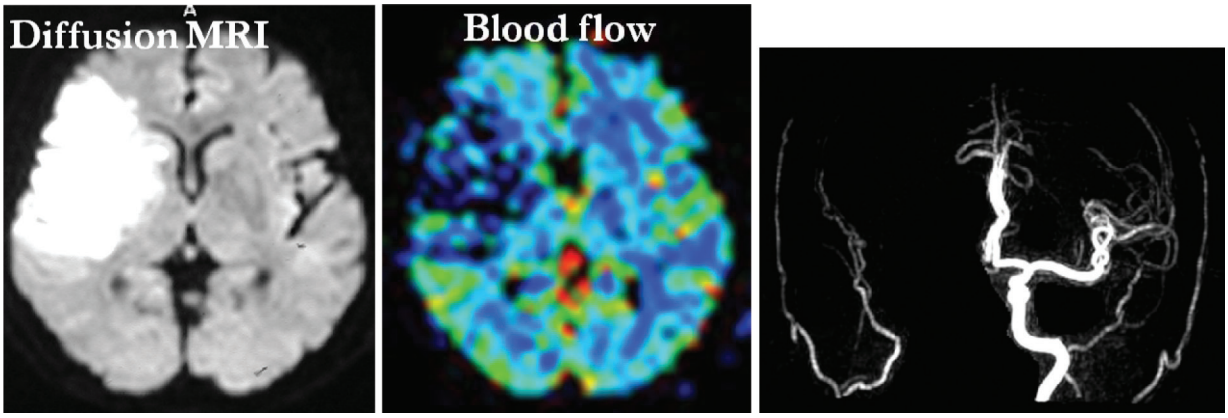


Figure 3: *Acute infarction due to occlusion of right internal carotid artery showing lesion on DWI corresponding to perfusion MRI (blood flow) or "diffusion/perfusion match". It means totally infarct without penumbra of the ischemic area and no advantage to apply thrombolytic agent.*

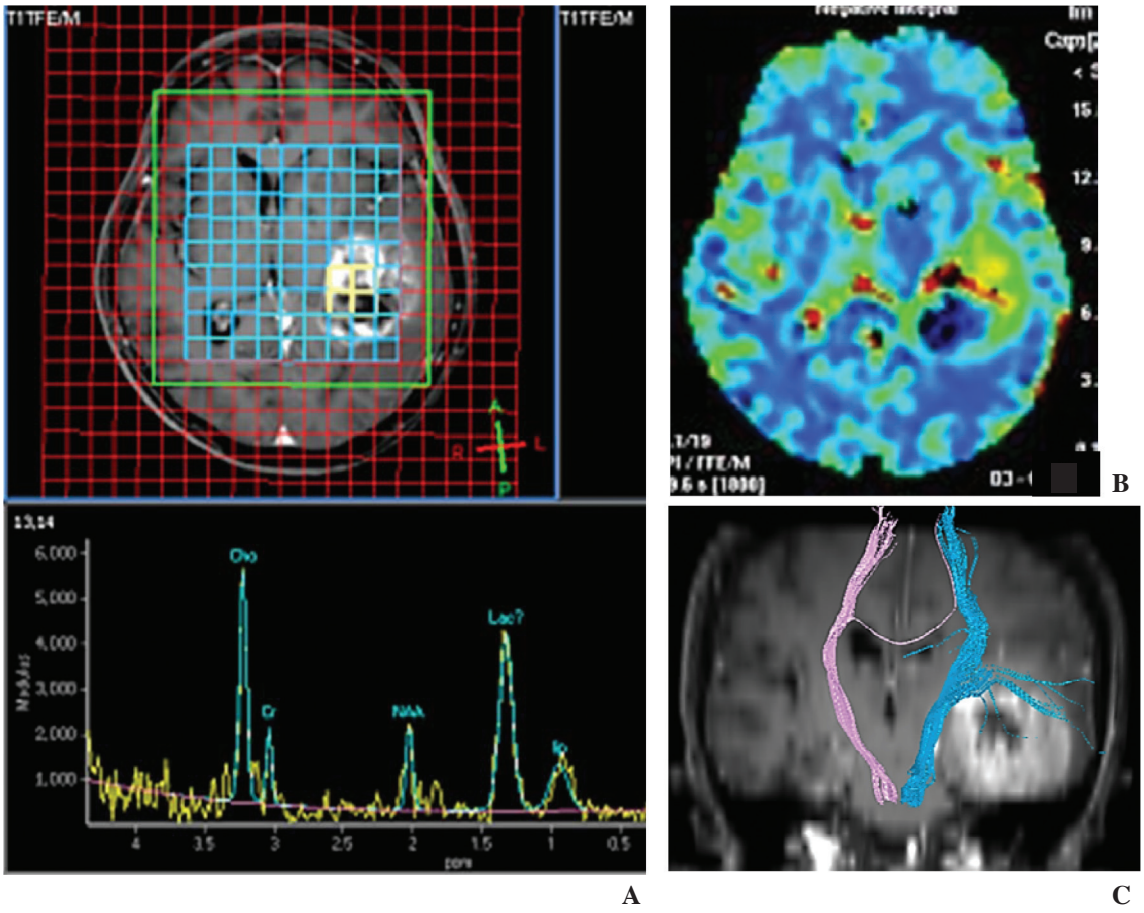


Figure 4: *Hight grade glioma (A) MRS, (B) p MRI (CBV), (C) DTI. MRS shows definitely increased Cho, Lac and Lip peaks in brain tumor. The NAA is markedly decreased. pMRI demonstrates increased blood volume at the periphery (arrow in B) and no blood supply of the central necrosis. DTI shows the relationship between the tumor and the ipsilateral corticospinal tract.*

Double inversion recovery (DIR) is an MRI technique demonstrating lesions in gray matter, especially in the cerebral cortex. This technique is useful to identify cortical lesions in MS and support the finding of cortical lesions in pathologic studies (Figure 2). DIR is also useful for demonstrating vascular wall for diagnosis of vascular dissection or identifying vulnerable plaque in atherosclerosis.

Cellular Imaging

Diffusion MRI (D-MRI) is the imaging technique of choice for making immediate decisions about treatment for acute ischemic stroke. The basic principle of D-MRI is detection of water molecule movement in the tissue. Ion-pump dysfunction of ischemic cells causes increased accumulation of water intracellularly, not equilibrate to extracellular space. Restricted diffusion of water molecules is shown as high signal on diffusion weighted imaging (DWI) or low apparent diffusion coefficient on ADC map (Figure 3).

DWI is also useful in brain tumor, MS, epilepsy and oncologic imaging both for demonstrating the pathologic lesions and measuring ADC values. D-MRI is valuable for demonstrating fiber tract in the brain by diffusion tensor imaging (DTI) technique. The technique enables neurosurgeons to plan for brain tumor surgery (Figure 4).

Molecular Imaging

Molecular imaging has been used in neuropsychiatry for a long time. CT, MRI, SPECT and PET enable us to understand the basic functions of brain biology. The protective mechanism of the blood-brain barrier (BBB) and the complexity of networks between the different areas of brain mean it is much more difficult to study brain function, compared to other organs in the body.

Molecular imaging is the technique identifying non-water molecules and their metabolism. It demonstrates brain status before disease develops. SPECT and PET are conventional molecular imaging techniques which have been in use for more than 20 years. Magnetic resonance spectroscopy (MRS) demonstrates various chemical components in the viable tissue by displaying the amplitude of substances of interest in a spectral curve. In a normal brain, N-acetyl aspartate (NAA) is a marker of viable neurons. Choline (Cho) is a marker of cell membrane metabolism which usually has low rates in normal brains. Cho is elevated during the process of cell destruction or proliferation such as occurs in brain tumors. MRS is useful to distinguish between high grade tumors and follow up treatment (Figure 4). It has been used to differentiate between recurrent tumors and post treatment necrosis. MRS is also able to show abnormalities in AD and hippocample sclerosis which cMRI cannot. Besides MRS, the new technologies using optical imaging have been able to verify progenitor cells in brain parenchyma in many research studies. In amide proton transfer imaging (APT), MRI can detect labile amide protons via the water signal. The detection of polyamide-based images is useful for following up brain tumor and ischemic disease.

In apoptosis (programmed cell death), cell shrinkage and precipitated chromatin differ from necrosis or cell autolysis. The latter processes involve cell edema and disintegration. In normal conditions, the rate of cell proliferation is balanced to apoptosis. If cell proliferation overtakes apoptosis, neoplasm develops. If the converse is true, then degeneration occurs. Annexin A5 was found attaching onto apoptotic cells. Using optical imaging, annexin A5 labeled with illuminated agent was demonstrated to identify myocardial infarct and tumor responsiveness. The annexin A5 was attached to gadolinium (Gd) or ^{99m}Tc to demonstrate tumor responses and atherosclerosis using MRI or SPECT.

Development of pharmaceutical agents for studying cells with MRI may be divided into 2 categories. One detects gene products, for example enzymes which change the chemical structure of the contrast media and leads to changes of relaxation time of the contrast. Another detects changes of transporter proteins on the cell membranes which carry the contrast media into the cytoplasm.The second category is a surrogate method of using functional MRI (fMRI) to detect the altered function of neurons after introducing some drugs such as dopamine transporter, $GABA_A$ receptors and opiate receptors.

In terms of molecular size and amount of tracer, PET and SPECT are classified as nano-molecular imaging. Besides the usual radioactive agents: ^{99m}TC, ^{125}I, ^{123}I, ^{201}Tl, ^{111}In and ^{18}F-FDG, there are other specific agents such as ^{11}C-methionine used for detecting brain tumors. ^{11}C-PIB was proved to be useful in identifying Alzheimers and other neurodegenerative diseases. ^{18}F-DOPA was used in studies of Parkinson disease and schizophrenia.

Brain Perfusion Imaging

The technology of multidetector CT and related software development have enabled calculation of perfusion of blood into the organ of interest. Computed tomography perfusion (CTP) is a recent imaging modality for studying brain circulation and perfusion.

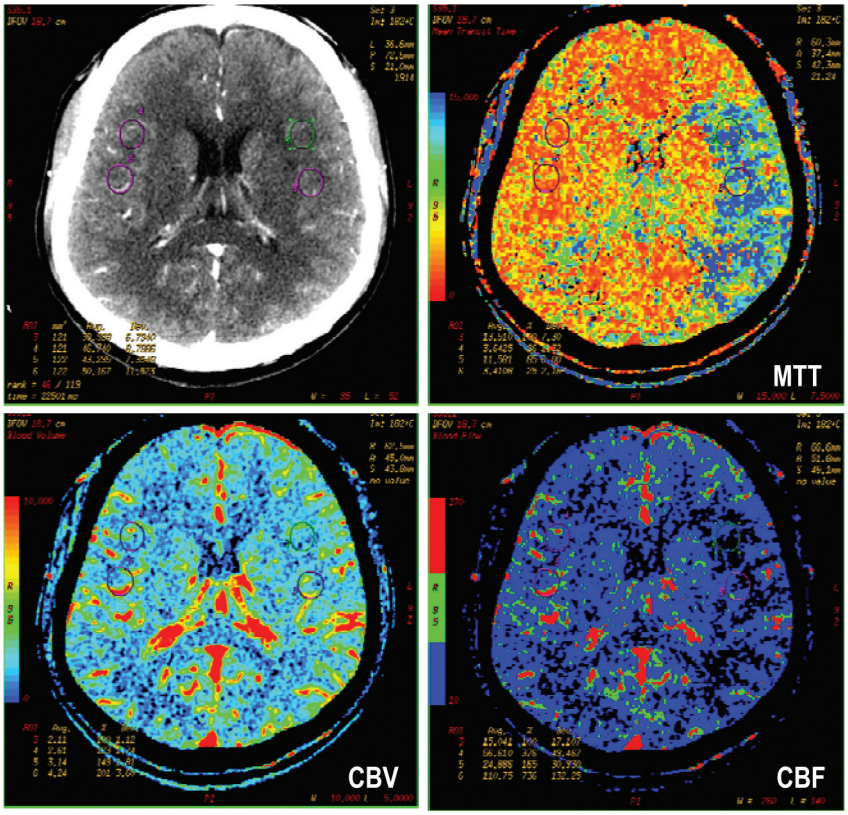


Figure 5: *CT perfusion of a patient presented with sudden right sided weakness. There is no detectable abnormality on CECT. The color map of MTT and CBF show the ischemia in left brain (left MCA territory). The CBV does not show definite abnormality.*

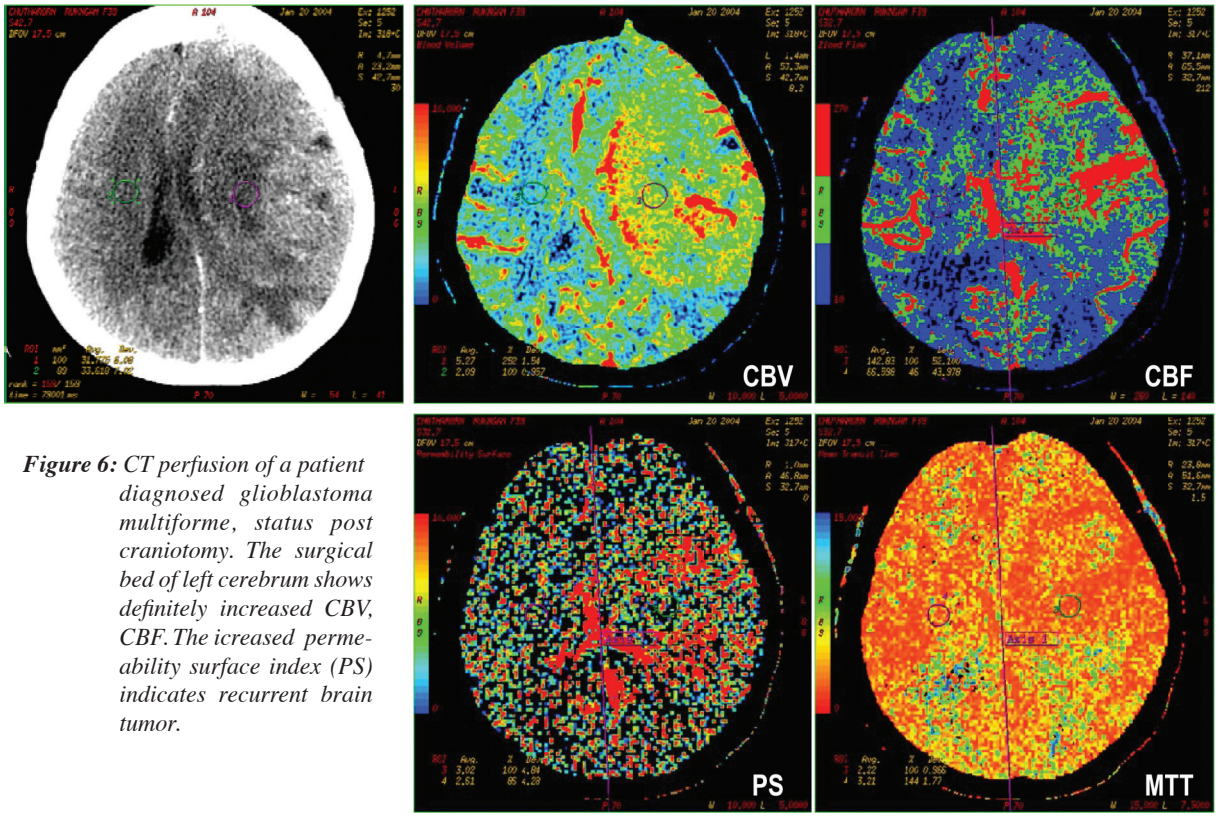
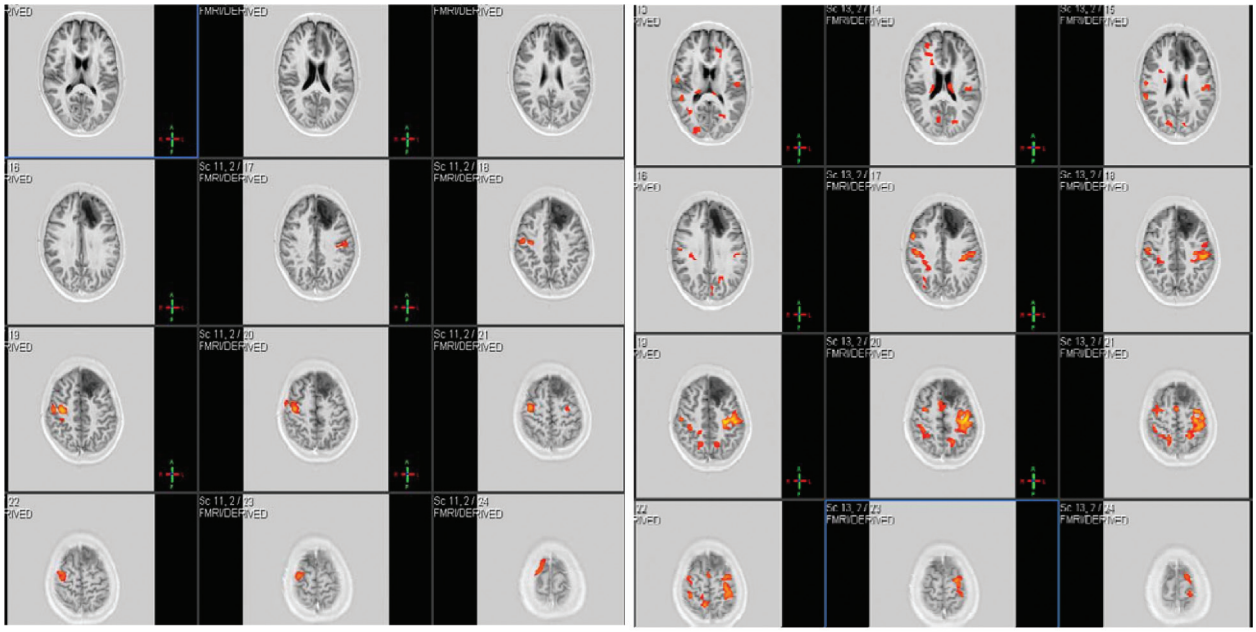


Figure 6: *CT perfusion of a patient diagnosed glioblastoma multiforme, status post craniotomy. The surgical bed of left cerebrum shows definitely increased CBV, CBF. The icreased permeability surface index (PS) indicates recurrent brain tumor.*



A B

Figure 7: *Functional MRI shows areas of stimulated brain during left hand movement (A), and right hand movement (B). There is a brain tumor in the left frontal lobe.*

Due to the increased speed of scan, changes of tissue attenuation during injection of contrast media can be detected and calculated into cerebral blood flow, blood volume and mean transit time. Some stroke centers have introduced CTP for acute stroke triage to thrombolytic therapy. It is reported to be able to reduce the number of cases with high risk of hemorrhagic complications and also treat more patients by extending golden time window from 3-4-5 hours to 6-9 hours for transarterial approach and mechanical thrombolectomy. CTP is also useful in determining cerebrovascular reserve in chronic stenosis of the internal carotid artery in order to plan for prophylactic bypass graft, thrombolectomy or stent placement (Figure 5).

CTP has been reported as useful in distinguishing brain tumors from brain abscesses, high grade or metastasis from low grade tumor, and recurrent tumor from post treatment change (Figure 6). The disadvantages of early generation CTP include limited brain coverage (2-4 cm. in 16 or 64 slices MDCT) and radiation doses. These drawbacks make MRI seem more favorable.

Perfusion MRI (pMRI) is a technique studying brain perfusion. It has been accepted as a standard imaging tool, together with DWI to identify penumbra area for intraarterial r-TPA (Figure 3). The principle of pMRI is similar to CTP but detects changes in signals during passage of Gd into the brain. The uses of Perfusion MRI are similar to CTP above. Studying permeability status of vasculature by measuring Ktrans proved to be more accurate than MRS in detecting recurrent brain tumor.

There are other MRI techniques for the study of cerebral perfusion which do not inject contrast media, namely arterial spin labeling (ASL) and blood-oxygen level dependent (BOLD). These techniques are based on observing changes of signal of intrinsic paramagnetic substances in the blood passing into the tissue.

Functional MRI (fMRI)

BOLD is more widely used to demonstrate activated neurons. The principle of the technique is detecting changes of signal during changes of cerebral blood flow and oxygen consumption of the activated neurons. It has been reported in studying brain function in AD, psychiatric disorders and planning surgery for temporal lobe epilepsy or brain tumor (Figure7).

Studies using fMRI in comatose patients reported different brain responses to environment in individual cases. Coleman M, et al reported different levels of response to sounds in a group of vegetative patients. Owen A, et al. reported a case of a patient at the vegetative stage due to traumatic brain injury and found activated brain area during which the patient was told to imagine walking in her own house or playing tennis. The patient recovered from comatose status months later. These studies may be helpful for prognosis assessment.

Another study with fMRI in soldiers with post-traumatic stress syndrome found excess areas of brain activation when the soldiers were shown violent pictures. This study may lead to more research into better treatment for this condition.

Conclusion

Inventions and applications of new technologies in brain imaging are ongoing. Combinations of these advanced techniques or parallel imaging are increasingly used, so as to compensate for the shortcomings of individual techniques. The more we know about our brains, the less we need have nightmares about untreatable diseases.

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Review Article

Treatment options for lumbar spinal stenosis in the elderly - an evidence based approach to a staged stepwise surgical treatment

Phudhiphorn Thienprasit, MD., Ph.D[1]

[1] Bangkok Spine Academy. Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Spinal stenosis treatment, Spinal decomression, Spinal surgery, O-Arm

Spinal stenosis is found frequently in the elderly, especially after the age of 55. The condition has become increasingly symp tomatic of longer life expectancy and a more active life style in the senior age group. Symptoms can range from an occasional, spontaneously reversible backache and claudication to full blown severe walking difficulties. More severe presentations of this condition frequently lead to a more rapid advancement of other existing co-morbidities such as Diabetes Mellitus and Ischemic Heart Diseases, which require the ability to regularly exercise in order to maintain good control over the condition.

Some of the reversible symptoms of spinal stenosis can be addressed by a structured life style change and regular prescribed exercise program, frequently supplemented with occasional use of patient compatible anti-inflammatory medication. More severe presentations however need to be fully evaluated for possible surgical treatment. The primary aim of surgery is to alleviate the nerve root (s) compression producing the symptoms. The secondary aim is to correct or stabilize any instability that may have contributed to the development of the stenosis or could possibly aggravate the stenosis in the future along with producing additional symptoms on its own.

Procedure has been found to provide the needed decompression and still allow a full interbody stabilization.

Historical background

The correlation between the presence of lower lumbar spinal stenosis and claudication symptoms in the affected nerve roots has long been well established. Documentation of the stenotic part of the lower lumbar spinal canal was originally done with the use of myelography and cadaver study. With the development of the Computerized Tomography (CT Scan) and later the use of Magnetic Resonance Imaging (MRI Scan) the pathology could be fully evaluated and understood without any invasive procedure. As a result, since the 1960's, a standard wide multi-level decompression though bilateral laminectomies and partial facet resections became the accepted standard of surgical treatment. By the mid 1970's it became apparent that there are surgical consequences to such an extensive approach.

Mostly in women patients, and predominantly at the L4-5 interspace the incidence of post operative progressive instability can be as high as 35%. This can lead to a recurrence of the stenosis, now a result of misalignment and other symptoms related to the instability.

The deeper understanding of lumbar spine stability, the availability of limited exposure surgical techniques through the use of microscopes in surgery and the development of muscle splitting instruments along with a more conscious philosophy of preserving the natural stabilizing structure as much as possible, led to a reconsideration of the surgical choices in the treatment of lumbar spinal stenosis. In several settings these resulted in a structured surgical treatment plan that directly addressed the patients' main symptom and reduced the associated undesirable surgical consequences.

Literature Review

For patient without instability as defined by a lack of any misalignment and no excessive motions on dynamic spine films, it has been well established that the incidence of postoperative instability is between 8-13%.[5, 17, 18] Less than half of this instability has been found to contribute to adverse decompression has a direct relationship to the possibility of instability.[5, 8] As a result, Sonntag and Marciano, Grob, Kristof and Shenkin recommend no prophylactic fusion in any cases with less than a Grande I Spondylolisthesis. With the use of more limited decompression techniques, the incidence of postdecompressive instability is further reduced. In addition, microsurgical and minima exposure techniques, some using a muscle splitting incision appear to reduce the problem of surgically induced instability further while delivering the expected improvement from the nerve root decompression.[12, 13, 17, 19] In 1995, Aryanpur and Ducker pioneered the concept of limited unilateral decompression that proved to be very useful in relieving the stenotic symptoms bilaterally.

In the presence of less instability (usually defined as less than a Grade II Spondylolisthesis) associated with limited back pain on motion, many authors have presented evidence indicating that concurrent prophylactic fusions of any type may not be indicated. [2, 10, 13, 18] Conversely, there are some reports of the benefit of pedicle screws immobilization in reducing motion related back pain after decompressive surgery: unfortunately, this does not directly correlate to the existence of solid bony fusion. There are fewer questions regarding the value of concurrent fusion at the time of decompression in cases where the presence of presurgical instability is well established .[2, 3, 12, 18] The type of fusion and the approach have evolved technically to the present stage where minimally invasive exposure and interbody implant placement are simpler and safer. [7, 8, 19] Here again, the less invasive.

Discussion

In the author's personal experience, careful evaluation of the inherent instability associated with degenerative spinal stenosis allows for a structured surgical treatment plan. In the presence of minimal preexisting instability associated with predominantly unilateral radiculopathy, a limited unilateral laminotomy over the involved segment (s) will result in a significant relief of the main presenting symptoms, while reducing the risk of surgically induced additional instability to a minimum. The use of microsurgical techniques and a conscious attention to preserving as much facet stability as possible will result in a functional lumbar spine. Staging the laminotomy decompressions by performing the decompression on the more symptomatic side first to be followed with the less symptomatic side several weeks later, sharply reduces the incidence of additional instability. In certain settings it became clear that unilateral microdecompression can significantly relieve bilateral symptoms and eliminate the need for additional opposite side surgery. The need for additional opposite side surgery in the author's experience range is about 10%, in other words 90% of the patients can do very well with a simple unilateral decompression using minimally invasive techniques with the known benefit of a much reduced risk and shortened recovery.

This staged surgical treatment requires a full detailed disclosure to the patient, at the beginning of consideration of surgical treatment. Somes patient are not willing to accept the possibility of additional surgery and may not instead for a more extensive bilateral decompression and even possibly a prophylactic fusion/ instrumentation as the definitive surgery, despite the additional scope, risks, expense and a longer recovery period. For patients with some instability, a full assessment of the origin of the stenosis is necessary. Stenosis which is the result of a collapsed slightly displaced disc space involving one or two segments can now be corrected with a direct realignment and restoration of the sagittal dimension of the nerve root foramen, by a stand alone direct anterior interbody fusion with a secured femoral ring equivalent implant that provides both the stability and the spacing restoration. This technique has the advantage of preserving the posterior elements necessary for stability and allows for additional percutaneous placement of additional instruments if felt to be necessary. This recently developed technique does require additional surgical skills and specially designed implants, as well as incurring increased expense related to new technology. For severely unstable spine with stenosis, the traditional approach of wide, multi-level decompressions

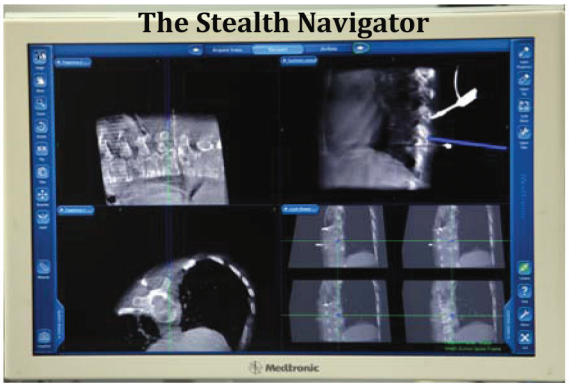
supplemented by fusion and instrumentation remains accepted. In this setting, again the advent of minimally invasive techniques, specially designed implants and dedicated surgical instruments allowed the surgeon to choose appropriate approaches. Transforaminal Lumbar Interbody Fusion through a unilateral exposure and contralateral percutaneous instrumentations is becoming more accepted. Once surgeons training and appropriate skill levels become widespread, the benefits of the new techniques will be routine. These newly developed procedures and the use of real time imaging (O-Arm intraoperative CT) and navigation (Stealth Spine Navigation) have greatly increased the level of safety.

Conclusion

Spinal stenosis is especially common in the elderly. The purposes of surgical intervention are to alleviate the nerve root compression and correct any instability. The inherent instability associated with degenerative spinal stenosis should be evaluated carefully prior to surgical treatment. Despite the improvements in the results of surgery for spinal stenosis, one can never overlook the fact that symptomatic improvement is never complete and can be short lived.

Many factors are involved in the deterioration of the result, not the least of which is the patients' own general aging process and the natural progression of the spinal stenosis and intervertebral joints degeneration with time. The possibility of additional surgery at a later date always exists

Spine surgeons therefore should rethink the traditional approach to the treatment of spinal stenosis, the concept of prophylactic fusion may not be as applicable as before, and the choice and extent of the surgical procedure should be selected based upon current updated data, with the patients' full participation after detailed discussion. The inherent increased risks with more extensive surgery can be avoided and reserved for cases where the need can be well defined. The primary objective in treating spinal stenosis by surgery remains the relief of enough symptoms to allow the patient to lead a reasonably active life while using up the least amount of time and resources to reach that point, and incurring the least possible treatment risks along the way.



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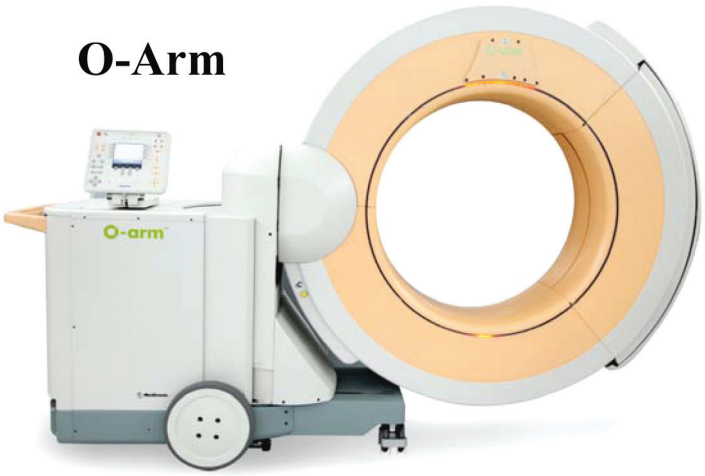

Pharmaco-invasive Therapy for STEMI;
The Most Suitable STEMI Reperfusion Therapy for Transferred Patients in Thailand

Pradub Sukhum, MD.[1]

[1] Division of Cardiovascular Medicine, Bangkok Heart Hospital, Bangkok Hospital Group, Bangkok,Thailand.

Keywords:
Pharmacoinvasive, STEMI, Primary PCI, Tranfer Primary PCI

Acute Coronary Syndrome (ACS) is the consequence of atherosclerotic plaque disruption with thrombus formation and significantly increasing different degrees of coronary artery occlusion. Using clinical features, electrocardiogram and cardiac biomarker (troponin), ACS can be divided into

1. Unstable angina
2. Non ST Elevation Myocardial Infarction (NSTMI)
3. STEMI. Diagnosis of STEMI needs ST elevation on ECG.

Figure 1 summarizes ACS pathophysiology, and clinical features. Note that STEMI is the only condition that the infarcted artery is usually completely occluded (acutely)

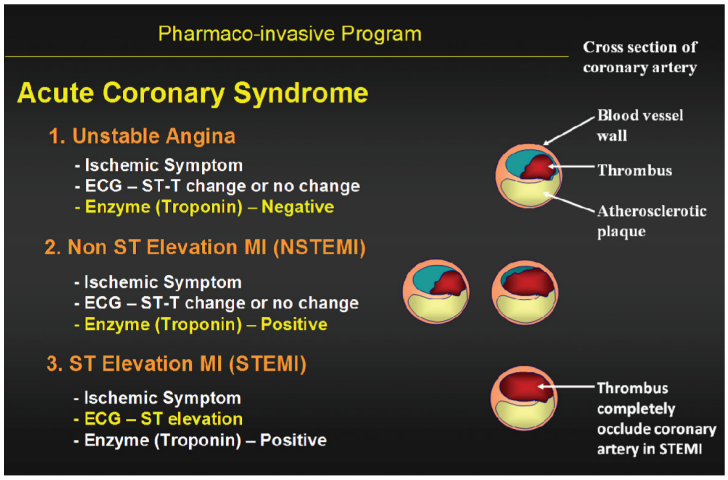

Figure 1: *ACS, Pathophysiology, Clinical Features*

The management goal of STEMI is to reperfuse the infarct occluded coronary artery **as soon as possible**, to reduce myocardial cell death as much as possible.

There are two reperfusion strategies for STEMI.

1. Thrombolysis with thrombolytic agents.

The advantage of thrombolysis is its ready availability in most hospitals that have full emergency services and that it can be administered in a short period of time. The disadvantages of thrombolysis are lower initial successful rate and higher re-occlusion rate, when compared with PCI.

Table 1: Lists the various PCI terminologies and their definition, timing and effectiveness.

Reperfusion Strategies for STEMI

Reperfusion Strategy	Definition of the Strategy	Timing	Availability/ Effectiveness
Pharmacological Reperfusion (Thrombolytic Therapy) **1986**	(Fibrin specific agents is about twice as effective as Streptokinase (when evaluate TIMI III flow at 90 minutes)	"Door to needle" time should be <30 minutes	**Available in every hospital but effectiveness is less than PCI**
Primary PCI (Hospitals that can perform PCI are limited in every country) **1990s**	Coronary angioplasty / stenting without prior administration of thrombolytic agents or GP IIb/IIIa antagonists.	"Door to Balloon" time 1. <90 minutes (for direct arrival/admission to PCI hospital) 2. <120 minutes (for transferred admission from non PCI hospital)	**Primary PCI is superior to Thrombolytic therapy when performed at appropriate (recommended) time frame**
Various Type of Pharmaco-invasive Therapy			
Facilitated PCI	A pharmacologic reperfusion treatment is given prior to planned (immediate/ early) PCI. The decision to perform PCI is already made before pharmacological reperfusion treatment is initiated	The pharmacological reperfusion treatment is given due to the expected time delay for PCI from various reasons such as transferred admission patient from non PCI hospital	**Several studies failed to show major benefit and currently this strategy is not recommended**
Rescued PCI	PCI in case of failed Thrombolytic / fibrinolytic therapy	Suspecting failed PCI are patients who continue to have chest pain; who has hemodynamic and electrical instability; whose ST elevation resolution less than 50%	**If PCI is offered to most of STEMI either by Primary PCI or Pharmaco-invasive therapy then the term Rescued PCI is not useful (ACC/AHA Guidelines 2009)**
Transferred Primary PCI **2003**	Primary PCI in patient transfer from non PCI hospital to PCI hospital	"Door" of non PCI hospital to "Balloon" of PCI hospital should be <120 minutes	**Difficult to achieve the recommended time.**
Pharmaco-invasive Strategy (that this paper refers to) **2009-2010**	Thrombolytic therapy (with fibrin specific fibrinolytic agents) followed by PCI with in recommended time frame	ESC STEMI Management Guideline, 2009 recommending time from Fibrinolytic to PCI is 3-24 hours (when use fibrin specific fibrinolytic agents)	**Appears most appropriate strategy for transferred patient from non PCI hospitals**

Other terminologies include: *Urgent PCI; Adjunctive or Early Elective PCI; Late PCI*

2. Percutaneous Coronary Intervention (PCI).

PCI is only available in a small number of all hospitals in any country (about 25% in US). It has high successful reperfusion rate but this technique requires a longer period of time to deliver, particularly if the patient has to be transferred from non PCI capable hospital.

Early on, thrombolysis and primary PCI strategies were considered separately and appeared to compete with each other. They both have advantages and disadvantages points as aforementioned. In the past 25 years, there has been extensive research to find out which single or combination of strategies works the best and for what situation.

Table 2. Thrombolytic Agents. Note that streptokinase is only half as effective as those fibrin specific products when look at TIMI 3 flow (normal coronary artery blood flow) by coronary angiogram at 90 minutes following thrombolytic administration.

Thrombolytic Agents				
	Streptokinase	**Alteplase (r-tPA)**	**Reteplase**	**Tenecplase (TNKase)**
Fibrin selective	**-**	**+++**	**++**	**++++**
Half Life	**30 min**	**5 min**	**15 min**	**18 min**
Dose (Bolus / Drip)	**D**	**B & D**	**Bx2**	**Bx1**
Adjunctive Heparin	**No**	**Yes**	**Yes**	**Yes**
Possible Allergy	**Yes**	**No**	**No**	**No**
TIMI 2/3 Flow in 90 min.	**60%**	**80%**	**80%**	**80%**
TIMI 3 Flow in 90 min.	**32%**	**50-60%**	**60%**	**60%**
Cost	**+**	**+++**	**+++**	**+++**

Evolution of reperfusion therapy for STEMI

Evolution of reperfusion therapy for STEMI can be summarized into 4 periods. Any one of these strategies are still being utilized depending on the situations. It is expected that the practice guidelines will change further for this dynamic condition. Pre hospital thrombolysis is not included in this article.

1. Thrombolytic therapy (1986).

Streptokinase was the thrombolytic agent most used in reperfusion therapy for STEMI early on. It has since been replaced by fibrin specific products which are more effective (Table 2). The current popular agent is Tenectaplase (TNK), a fibrin specific thrombolytic agent which is easy to administer. Because of its lower cost, despite lower efficacy, streptokinase is still being used in countries with less financial resources, including Thailand.

Thrombotytic therapy is more effective if it can be given within 3 hours after the onset of symptoms such as chest pain. We have not yet been able to shorten up the time from chest pain onset to the time of first medical contact (FMC). We should be able to control the time from FMC to the time of delivering the thrombolytic agent which was recommended to be <30 minutes. The so call **"Door to Needle" time is <30 minutes.**

2. Primary PCI (1990s).

Primary Percutaneous Coronary Intervention therapy has been performed since early-mid 1990s. Primary PCI is the therapy to open the infarct occluded coronary artery with angioplasty and stent placement without preceding thrombolytic therapy (See Table 1. for various PCI terminologies and their definition, timing and effectiveness)

Recommended median time for Primary PCI is < 90 minutes from FMC to infarct coronary artery open. The so-called "Door to Balloon" time is < 90 minutes. Primary PCI has better results than thrombolysis when both approaches are performed with in the recommended time frame. Early data has been collected exclusively from **direct arrival/admission** patients.

3. Transferred Primary PCI (2003)

Refers to Primary PCI therapy in which the patient transfers from first hospital to PCI capable hospital. Recommended median time for transferred primary PCI is < 120 minutes from FMC (of the first hospital) to infarct coronary artery open (of the PCI hospital). This recommended time is hard to achieve even in developed countries (Figure 2 for US) with better transport systems available. However there were more than 30 % of the

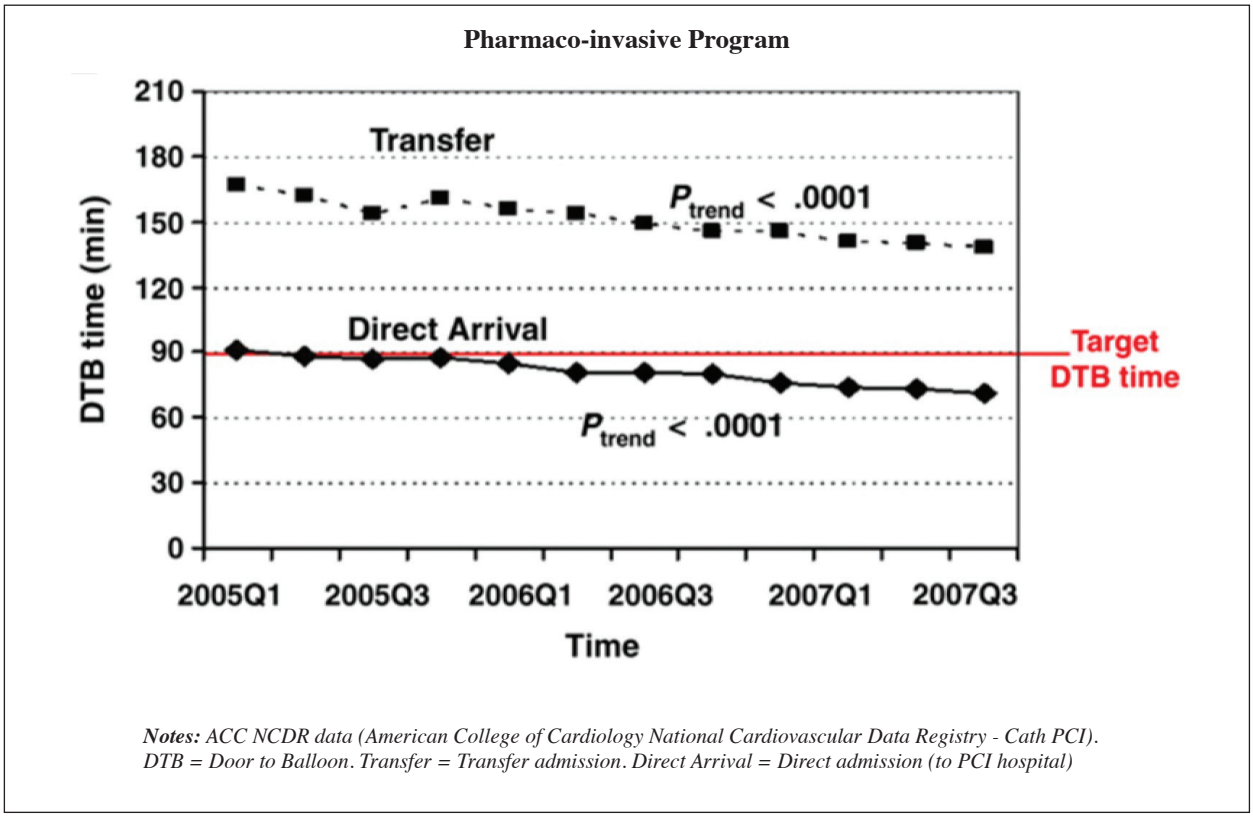

Figure 2: *Graph shows US median Door to Balloon time is now about 70-80 minutes for "Direct arrival/admission patients".However median time for Door (First medical contact of the first hospital) to Balloon (PCI hospital) for transferred patients is still over 140 minutes.*

patients that could achieve this timeline (NCDR 2005-2006) suggesting that not only is the shorter distance between the two hospitals important but also the development and execution of the proper protocol is necessary to help the achievement of this goal.

Transferred Primary PCI is not suitable (or not possible) in the locations or countries with slow transportation time (for whatever any reason).

4. ***Pharmaco-invasive approach (2009-2010).***

To off-set the time delays in transferred patients the researcher has combined the quickness and ready availability of thrombolytic (pharmaco) therapy and the delayed but complete reperfusion of PCI (invasive). There have been few approaches with different terminologies, timing between the two strategies, and different clinical set up (Table 1).

Facilitated PCI failed the test likely due to a too short period from thrombolysis to PCI. Immediate PCI after fibrinolytic therapy causes significant increase in mortality, nonfatal reinfarction, urgent target lesion revascularization and stroke and a trend toward a higher rate of major bleeding.

The pharmaco-invasive therapy in this paper in particular, refers to the technique whereby there is a time elapse of 3-24 hours between thrombolysis (pharmaco) and PCI (invasive) when using fibrin specific thrombolytic agents. This approach has been endorsed by the most recent guidelines of both ESC and ACC/AHA. Whether or not there should be a greater time delay (>3 hours) when using streptokinase is not yet known.

The pharmaco-invasive strategy appears most suitable for Thailand or similar countrie or similar situations. There should be sufficient time for transferring the patient (does not have to be within 3 hours or more) and sufficient time to perform PCI with in 24 hours. Door to needle of the first hospital (PCI non capable) should remain the same (<30 minutes).

Recommendations for Pharmaco-invasive therapy as follows:

1. Extensive education to medical and hospital personel involved in taking care of these patients.
2. Develop patient pathway and flow protocol (Examples are in Appendix)
3. Speed of the process during thrombolysis therapy is important.
4. ECG should be done with in 10 minutes after FMC (First Medical Contact).
5. Thrombolytic agent should be administered with in 30 minutes after FMC.
6. Transfer the patient
7. PCI to be performed in 3-24 hours after thrombo-lytic administered (ESC).
8. Detailed data collection and analysis (performance measurement) for further program improvement is necessary.

Example of some protocols are available in the Appendix

Protocol for Pharmaco-invasive therapy for STEMI Management. Bangkok Hua Hin Hospital (BHN) (Transferring Protocol)

Brief

1. Diagnosis (ECG should be done in <10 minutes)
2. Scan and Email ECG to BHT
3. Call BHT CCU2.
   (May call again in few minutes to confirm with BHT CCU2)
4. BHN receives call back from BHT cardiologist (In <10 minutes)
5. Administration of the thrombolytic agent at BHN
   (should be within 30 minutes from "Door" or "FMC" (First Medical Contact)
6. Arrange for transferring
7. Preparing the patient
8. Lab
9. Fill in the "Transfer Information" sheet and send it with the patient (or Fax)
   (There is a more detailed form specific to each hospital)

Bangkok Hua Hin Hospital (BHN)

Patient name

Date: _____

Pharmaco-Invasive Program
Transfer Information

Timing

Onset of Symptoms: _____ Entering ER: _____

ECG: _____ Sending ECG: _____

BHT Call back: _____

Thrombolysis: _____ Agent: _____

Leaving ER: _____ Transported by: _____

Reason of Delay Thrombolytic Therapy: _____

Clinical Data

AGE _____ DOB _____ Gender _____

Vital signs

Temp: _____ BP: _____ Pulse: _____ Rhythm: _____

Patient condition ☐ Stable / ☐ Unstable / ☐ CHF

History ☐ CAD / ☐ Previous MI / ☐ Previous CABG
☐ Previous CPI / ☐ Cardiomyopathy./ ☐ CHF./ ☐ Prosthetic valve.
☐ Bleeding./ ☐ Renal Failure. / ☐ CVA. / ☐ COPD. / ☐ Dye allergy

Additional Information

_____
_____
_____
_____

Signature ER MD _____ Referral MD

_____ Referral MD

PHONE	**BHT CCU2**	**02 310 3126 / 02 755 1327**
FAX	**BHT CCU2**	**02 755 1326**

Check list of record sent: (√)						
Transfer Note	ER Note	Doctor Note	All ECG	Lab	Log of Rx/Time	Others
			(May fax)			

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Drug Induced Cardio-vascular Events

Sumaiporn Groodpanta[1]
Urai Ieosriyoke[1]

[1] Department of Pharmacy, Bangkok Hospital Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Sibutamine, Rosiglitazone

Before drugs are launched on the market, studies should have already proven that these drugs are efficient in treatment of specific conditions, by trials in vivo, on experimental animals and then finally on humans.

However, premarketing clinical trials are limited and not necessarily homogenous. Limitations, such as the short period of drug administration, or emphasis only in the efficiency of the drug may have caused less attention to be paid towards patient safety or potentially undesirable side effects, such as water retention or worsening of patients' cardiovascular condition. These drugs have been popularly prescribed to many patients, especially in the premarketing period. However, sometimes, unexpected and undesirable symptoms arise, and increase in number, to the point where the drug may be disapproved by the FDA or similar agency. Some studies illustrate the undesirable side effects of drugs, whereby increased numbers of cardiovascular complications are occurring to people taking the drug. This report will collate some of the data relating to two drugs which are facing controversy in the market recently, namely Sibutramine and Rosiglitazone.

Sibutramine

Sibutramine, an anti-obesity agent, has a dual effect, inhibiting norepinephrine and serotonin reuptake. These reduce appetite and promote weight loss. Sibutramine improves insulin resistance, glucose metabolism, dyslipidemia, and inflammatory markers. Moreover, Sibutramine exerts a favorable effect on some surrogate cardiovascular endpoints, such as reduction of left ventricular hypertrophy and improvement of endothelial dysfunction. In some studies, Sibutramine has been shown to decrease uric acid level and reduce high- sensitivity C-reactive protein (hs-CRP).

A good cardiovascular safety profile was shown in controlled trials over 1-2 years as well as in several observation studies. However, since 2002, several cardiovascular adverse effects have been reported. Sibutramine Cardiovascular and Diabetes Outcome Study (SCOUT) was a randomized, double-blind, placebo-controlled, multicenter trial that was conducted from 2003 through 2009. The objective of this study was to evaluate the long-term effects of Sibutramine treatment, combined with diet and exercise on the rates of cardiovascular events and cardiovascular death among subjects who were at high cardiovascular risk.

All the subjects received Sibutramine during a 6-week, single-blind, lead- in period, then underwent random assignment in a double-blind to Sibutramine or placebo. Subjects who were enrolled in the study were classified into their appropriate cardiovascular risk groups: diabetes only (DM- only group), cardiovascular disease only (CV- only group), or both (CV-DM group). The primary outcome was the time from randomization to the first occurrence of a primary outcome event. The primary outcome events were nonfatal myocardial infarction, nonfatal stroke, cardiac arrest, and cardiovascular death.

The result showed that Sibutramine group had a 16% increased risk, relative to the placebo group (HR=1.16; 95% CI 1.03, 1.31; *p*=0.02). The individual rates of nonfatal myocardial infarction and stroke were also increased in the Sibutramine group (HR for nonfatal MI, 1.28; 95% CI, 1.04 to 1.57; *p*=0.02, HR for nonfatal stroke, 1.36; 95% CI, 1.04 to 1.77; *p*=0.03). The rates of cardiovascular death and death from any cause were not significantly different. An analysis of the three cardiovascular- risk groups showed the increases in nonfatal primary outcome events were seen in the CV- only and CV-DM groups but not in the DM-only group. The result of this and other studies study encouraged the manufacturer to voluntarily withdraw Sibutramine from the Australia, Canada and the U.S. market in October 2010.

Rosiglitazone

Rosiglitazone is an oral antidiabetic agent and a member of the group of drugs known as thiazolidinediones. Rosiglitazone specifically targets insulin resistance, which is thought to be central to the development of type 2 diabetes as well as dyslipidemia and hypertension in patients with diabetes mellitus. The first indications that of rosiglitazone increased the risk of myocardial infarction and cardiovascular death were published in 2007. The trials were divided between 3 categories. The first group included five of the studies submitted to the US FDA for the March 22, 1999. The second group included 35 studies, primarily identified from the GlaxoSmithKline clinical trial registry. And the last group included two studies from large, recently published trials, namely the Diabetes Outcome Prevention trial (ADOPT) and Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM). The results showed that the odds ratio for myocardial infarction was 1.43 (95% CI1.03, 1.98; *p*=0.03) and the odds ratio for cardiovascular death was 1.64 (95% CI0.98, 2.74; *p*=0.06). The result of this study raised questions concerning the safety of thiazolidinedione group of drugs, especially rosiglitazone.

Later rosiglitazone was evaluated for Cardiac Outcome and Regulation of Glycemia in Diabetes (RECORD which was an open-label, randomized noninferiority trial. The primary endpoint was unconventional, cardiovascular hospitalization or cardiovascular death. That study was limited by low event rates, which resulted in insufficient statistical powers of detection The majority of results were concordant with the first meta-analysis study; the rosiglitazone group demonstrated increased risk for myocardial infarction but not cardiovascular or all-cause mortality. The US FDA did not withdraw rosiglitazone from the market but it has cancelled ongoing phase clinical IV trials of Thiazolidinedione Intervention (00879970) at the present time. The phase II and phase III study indicated increased cardiovascular mortality, myocardial infarction and stroke including hospitalization for acute coronary syndrome and urgent revascularization procedures as a result of taking the drug. The US FDA ordered the manufacturer to demonstrate that the antidiabetic drugs therapy to treat type 2 diabetes will not increase cardiovascular risk. The European Union recommended that rosiglitazone be withdrawn from the EU market in September 2010.

Summary

Nowadays, we have many new drugs in the market; despite their apparent efficacy in treatment management, however, side effects have not necessarily been seriously investigated during premarketing. Serious reactions to the drug appear later on, which sometimes results in the drugs being withdrawn. Sibutramine was available for prescription since more than 10 years and has now been withdrawn in Western markets by the manufacturer; unlike the European Medicines Agency, the US FDA has not yet withdrawn Rosiglitazone from the market but the present clinical applications have shown it to increase the risk of cardiovascular events.

New antidiabetic agents need to be demonstrably free of causing patients increased risk of cardiovascular events.

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Autism and Epilepsy: Practical points that clinicians should aware of

Montri Saengpattrachai, MD.[1, 2]

[1] Bangkok Hospital Group, Bangkok, Thailand.
[2] Division of Neurology, Department of Pediatrics, Faculty of Medicine, HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakarinwirot University, Nakornnayok,Thailand.

Keywords:
Autism, ASD, Regression, Epilepsy, Seizure, Non convulsion, EEG

Typical Clinical Scenarios

Case 1: A 15-year-old high functioning autistic boy with normal IQ was found to have episode of eyes rolling upwards followed by rhythmic body shaking and was unresponsive for 2 minutes. Ten hours after symptom onset, EEG study was performed and reported as normal . One week later, during playing soccer, he had another attack with similar pattern. Physical examination was unremarkable. Second EEG study was normal. He has no history of head injury. Family history was negative for seizure disorder. No developmental regression is mentioned. *Should we prescribe antiepileptic drugs for this child?*

Case 2: A 7- year 2-month-old autistic girl with severe developmental delays who has developed 'bizarre behaviors' described as head nodding and rapid eye blinking during listening to radio over a two week period. During sleep, she sometimes wakes up in the middle of the night and makes loud noises for 10 minutes before falling asleep again. These behaviors are unusual and have never occurred before. Regular medications included risperidone, methylphenidate, and zinc supplements. *Are those 'bizarre, unusual behaviors' epilepsy or just stereotypic movements that are commonly found in autistic children?*

Case 3: A 5-year-old autistic girl with epilepsy. Her seizures (generalized tonic-clonic) are well-controlled by valproic acid. She has had regular rehabilitation and physical therapy for motor and speech delay. Overall milestones are gradually improved. One day after being rebuked by a friend at school, she stopped speaking, not making any sound. However, she is able to follow verbal instruction as usual. Parents are frightened and bring her to pediatrician for proper opinion. *Has she developed language regression? Could this symptom be a subclinical seizure or just a behavioral reaction?*

Case 4: A 10-year-old high functioning autistic boy is brought to clinic due to excessive drowsiness over two weeks. Actually his sleep duration is usually of 6-8 hours a day but has increased to 12-16 hours a day. Teachers have also reported to parents regarding his frequent falling asleep in the classroom. Normally, he is a good disciplined child and is always admired by parents, teachers and friends. Academic performance is average. He is a school tennis athlete. There is neither fever, history of head injury nor drug use during this episode. Physical examination is normal. Blood tests for CBC, electrolytes, sugar, BUN, Cr, liver function, thyroid function, and ammonia level are normal. CT scan of the brain shows negative study. *Shall we consider 'non-convulsive seizure' as the cause of excessive sleepiness in this patient?*

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Montri Saengpattrachai, MD.[1, 2]

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Outline:

1. Introduction of Autistic Spectrum Disorder (ASD)
2. Epilepsy in autism
   - 2.1 Prevalence and risk factors
   - 2.2 Types of seizures in autism
   - 2.3 Subclinical epilepsy & autistic regression
   - 2.4 EEG findings in autistic patients
3. Treatments of epilepsy in autism and autistic regression
4. Conclusion

Introduction

Autistic spectrum disorder (ASD) is the umbrella term for life-long developmental disorders of brain in childhood comprising (1) autistic disorder or classic autism, (2) pervasive developmental disorder, not otherwise specified (PDD-NOS) or atypical autism, (3) Asperger's disorder, (4) Rett's disorder, and (5) childhood disintegrative disorder.[1-2] The three core areas of malfunction of ASD are (i) impairments in social interaction, (ii) impairments in verbal and non-verbal communication and (iii) restricted, repetitive or stereotyped behaviors, interests and activities.[3] The prevalence of ASD is considered to be approximately 4 to 10 per 10,000 children from the 1980s and early 1990s, whereas recent studies have reported prevalence of 30 to 50 per 10,000 children.[4] Highlighted on autistic disorder, the prevalence for classic autism representing the narrow phenotype is 0.1 – 0.3% and 0.3 – 0.6% for the broader ASDs.[5] Clinical signs of ASD are frequently present at 3 years of age and recent prospective studies in toddlers indicate that abnormalities in social, communication and play behavior that may represent early indicators of autism can be detected as early as 14 months of age.[6]

Recent data indicate that the 'autism epidemic' is not real, and definitely not due to vaccines.[7] Autism has a strong genetic basis and this neurodevelopmental disorder is the most clearly genetically influenced of all developmental disorders, including so-called 'idiopathic autism' without known etiology or comorbidity. A number of nuclear and mitochondrial genetic linkages have been identified – proof that different genes cause autism in unrelated affected individuals. Studies suggest that polygenic influences (i.e.multiple interacting genes) together with environmental/gene interactions are responsible for individual phenotypes.[8, 9] In addition to genetic studies, recent work on the immunology of autism suggests that there are specific serum antibodies in mothers of children with autism that recognize prenatally expressed brain antigen.[10] Moreover, abnormalities of synaptic structure and brain function are at the forefront of current investigations of the brain basis of autism. The now well accepted alterations in cortical minicolumns with selective scarcity of gabaergic interneurons may be relevant to hyperexcitibility to sensory stimuli, increased seizure susceptibility, and systemic comorbidities in autism.[11-13]

Epilepsy in autism

Prevalence and risk factors

Epilepsy is defined as two unprovoked seizures of any type; therefore, febrile seizures (the most prevalent seizure of early childhood) and seizures in the course of acute trauma, infection, or metabolic illness are not classified as epilepsy. The prevalence of epilepsy among all children is estimated at 2 – 3%, compared with some 30% in autism.[14] A bimodal age distribution of seizures is reported in autism. One peak occurs in infancy before age 5 years and the other in adolescence after age 10 years.[15] The severity of cognitive impairment and the presence of cerebral palsy or other over motor deficits (Table 1) are the specific risk factors for epilepsy in children with ASD.[16]

Table 1: Cumulative probability of development of epilepsy in subgroups of children with autism as a function of age and severity of the underlying brain dysfunction[16]

Diagnostic group	Number of cases	Age		
		1 year	5 years	10 years
Autism alone	160	0.02	0.02	0.08
Autism with severe mental retardation but no cerebral palsy	56	0.07	0.16	0.27
Autism with severe mental retardation and cerebral palsy	21	0.29	0.35	0.67

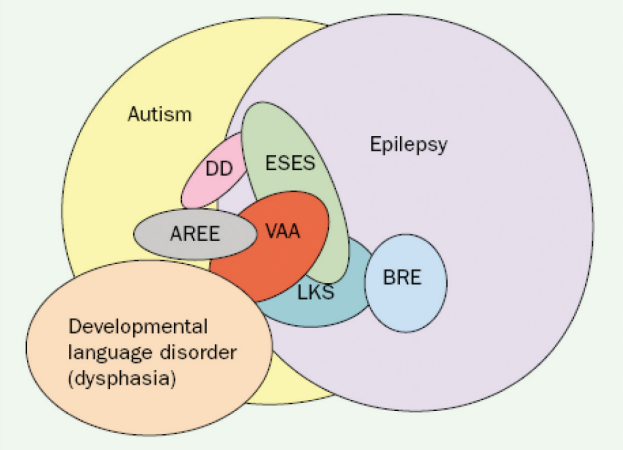

Figure 1: *Overlaps between autism with or without epilepsy and other disorders of children with or with out language regression. Although an attempt has been made to suggest the relative prevalence of each disorder by the size of its oval, the sizes of the symbols and overlaps should not be taken literally because they were constrained by the need to show the multiple overlaps clearly (e.g., developmental language disorder should be larger, ESES smaller). AREE, autistic regression with an epileptiform EEG; BRE, benign rolandic epilepsy; DD, disintegrative disorder; VAA, verbal auditory agnosia.*[14]

Types of seizures in autism

All seizure types can be associated with autism. The most prevalent seizure types found in a Swedish study were complex partial, atypical absence, myoclonic, and tonic-clonic seizures, whereas, generalized tonic-clonic and atypical absence seizures were the most common seizure type in a large American cohort.[16, 17] Overt clinical seizures do not cause difficulty in diagnosis whereas subclinical, known as subtle or nonconvulsive, seizures may present with variety of under-recognized symptoms including complex, bizarre behaviors or unexplained deterioration level of consciousness. These symptoms could be underrecognized, particularly in autistic children with moderate-to-severe developmental delay. Subclinical epilepsy in this population are often overlooked and misdiagnosed. Moreover, until recently, more studies evidence the overlaps between autism with or without epilepsy as shown in Figure 1.

Subclinical epilepsy & autistic regression

The clinical diagnosis of epilepsy in autism is complicated by the fact that subclinical complex absences may be mistaken for other childhood behaviors such as failing to respond to one's name or to participate in an activity introduced by someone else. The unusual repetitive behaviors, such as tic-like movement, common in children with autism can be difficult to distinguish clinically from seizures. For clinicians faced with an autistic child who has no clinical convulsive seizures and an abnormal electroencephalogram (EEG), to prove a link between epilepsy and autism is difficult, especially if there is history of regression and the EEG is epileptiform. Some studies suggest that epileptiform discharges on EEG without clinical seizures can cause behavioral and cognitive impairment.[18, 19]

In an open trial of valproic acid of 176 children with autism, 80 normalized on EEG and 30 more showed EEG improvement compared with the first EEG.[20] This positive outcome offers hope that treatment of these subclinical abnormalities may act to prophylactically prevent future clinical seizure development. However, there is no current consensus on whether treatment of EEG abnormalities may influence development. Commencing anticonvulsant to autistic children with abnormal EEG, particularly in autistic regression, without clinical seizures is still debated and remains unanswered.

EEG findings in autistic patients

Children with autism may have normal EEG patterns that do give leave concern to parents and physicians. Conversely, abnormal EEG finding always raises questions to physicians, regarding definite diagnosis of epilepsy, especially for autistic children who do not have clinical seizures and those with regression.

Descriptions of EEG abnormalities have included not only epileptiform discharges (e.g. spikes, spike and wave, polyspikes, sharp wave discharges) but also less clearly abnormal features, such as "diffuse theta", "low-voltage fast" and "amorphous background" which have been mentioned in many literatures. The fact is that the incidence of EEG abnormalities in nonepileptic children with autism has ranged from 6 to 83% but 46 to 59% with clinical seizures.[20, 21] The EEG abnormalities include both generalized and focal abnormalities. The epileptiform activity is usually multifocal. Epilepsy is significantly more frequent in autistic youngsters with a history of regression compared with those without regression.[22]

The relation of clinical and subclinical epilepsy to autistic behavioral and language regression is intriguing but unresolved. Clinicians should consider investigating with EEGs, particularly children with history of regression, or fluctuations in language function, or new unfavorable behaviors. Several studies suggest that prolonged overnight EEG recordings have the highest yield

Table 2: General frequency of behavioral and psychiatric side effects of AEDs[25]

AED	Behavioral side effects[a]		Psychiatric side effects[b]	
	Negative behavior	Positive behavior	Depression	Psychosis
Barbiturates (phenobarbital)	+++	-	+++	-
Benzodiazepine	+++	-	-	-
Carbamazepine	+	+++	+	-
Gabapentin	+	-	-	-
Lamotrigine	+	+++	-	+
Levetiracetam	+	+	-	+
Oxcarbamazepine	+	-	-	-
Phenytoin	+	-	-	-
Topiramate	+	+	-	+
Valproic acid	+	+++	-	-
Vigabatrin	+	-	-	+
Zonisamide	+	-	-	++

[a] Negative and positive behavior: -, rare or not reported; +, 0-20%; ++, 21-40%; +++, >40%.
[b] Psychiatric side effects: -, rare or not reported; +, 1-3%; ++, 4-10%; +++, >10%.

to assess the presence of subclinical epileptiform activity. Although there is controversy as to whether the epileptiform discharges are causally related to the language deficit or regression, the identification of such abnormalities offers possible therapeutic intervention.[23]

Treatments of epilepsy in autism and autistic regression

Medical treatment

The treatment of the seizures in autism is neither particularly difficult nor different from treatment of seizures in other children with epilepsy.[24] Seizure types, EEG findings, and related illness history will guide neurologist in choosing proper antiepileptic drug (AED). Crucial point of AED selection in autistic children is that clinician should avoid using medication that may aggravate seizure attack. Moreover, adverse effects of some AEDs causing negative behavior or psychiatric symptoms should also be considered.[25] (Table 2) There are reports that the language of limited numbers of children with autism or autistic regression has improved in response to anticonvulsants, especially valproic acid, ethosuximide (not available in Thailand), and benzodiazepines.[26] Improvements have also been reported in patients treated with corticotrophin, steroids, or immunoglobulins.[27-30]

There are several clinical reports of the use of valproic acid in children with autism with or without clinical seizures but with epileptiform discharges on the EEG.[20, 31-33] In an open trial of valproic acid, 10 of 14 individuals that completed the trial showed improvement in core symptoms and the associated affective instability, impulsivity, and aggression, and all patients with abnormal EEG or seizure history were rated as responders.[34]

Surgical treatment

Epilepsy surgery, such as surgical transection of epileptogenic foci, is mostly indicated to patients with intractable epilepsy. A few reports of children with autistic regression and clinical seizures revealed that epilepsy surgery affects positive outcomes for seizure control. Those studies hardly emphasized effectiveness of epilepsy surgery toward autistic symptom.[35-37] One study stated that both language regression and behaviors were improved by using multiple subpial transections in 12 of 18 children with autistic regression, multifocal epileptiform EEGs, and subtle seizures (e.g. staring episodes, rapid eye blinking) without overt clinical seizures[38] However, this study raises the question as to whether the use of such a potentially life-threatening intervention in autistic children who do not have intrac-

table epilepsy is either medically logical and/or ethical. In summary, more systematic studies are required for developing guidelines of surgical treatment among autistic children either with or without clinical epilepsy.

Conclusion

Epilepsy in autism is not uncommon. The prevalence of epilepsy found in autistic children is up to 10 times higher compared with general pediatric population (30% vs. 2-3%). Autism and epilepsy co-occur in some genetic disorders that follow a Mendelian pattern of inheritance. These disorders may therefore share a common neurochemical substrate that is targeted by the psychotropic mechanism of action of several antiepileptic drugs. Diagnosis of epilepsy in autism is sometimes complicated. Convulsive seizures are not difficult to diagnose and clinicians may have no doubt to start antiepileptic drugs. In contrast, non-convulsive (or subclinical) seizure is under-recognized and this condition is often an overlooked diagnosis in children with autism. Autistic children with language regression or new peculiar behaviors cause more difficulty in diagnosis of epilepsy. Moreover, subtle symptoms such as intermittent eye blinking, tic-like symptoms or fluctuation of emotion may cause parents and clinicians to doubt whether those symptoms are indeed real seizures. In such scenarios, investigating with prolonged overnight EEG recording will provide the highest yield in detecting the presence of subclinical epileptiform discharges that may be causally related to language regression or other related symptoms. Despite there being no current consensus on whether treatment of EEG abnormalities may influence development, recent positive outcomes from copious clinical studies are more promising and offer possible therapeutic intervention, such as the option to use AED or corticosteroids. Adverse effect of some AEDs that might create adverse behavior or psychiatric symptom should be avoided.

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Questions of Autism and Epilepsy

Q1. Autistic spectrum disorder (ASD) known as pervasive developmental disorder is the umbrella term for life-long developmental disorder of brain in childhood. Which one is not classified into subtype of ASD?

A. Asperger's syndrome
B. Autistic disorder (classic autism)
C. Fragile X syndrome
D. Childhood disintegrative disorder
E. Rett's syndrome

Q2. Which subtype of ASD has the highest risk of epilepsy?

A. Autistic disorder
B. Asperger's syndrome
C. Pervasive developmental disorder, not otherwise specified (atypical autism)
D. Childhood disintegrative disorder
E. Rett's syndrome

Q3. Parents of a-previously healthy 5-year-old-boy, noticed that he stopped talking for three days without loss of consciousness. There was neither history of school problem, head injury nor taking any medication. On physical examination, he was alert and able to follow verbal instruction appropriately. Otherwise were unremarkable. Investigations including CBC, electrolytes, screening for toxic substances, liver function test normal. Hearing tests and MRI study of the brain were normal. EEG study showed predominantly bilateral temporal (mainly posterior temporal) spikes or spike-wave discharges that are activated by sleep. What is the most likely diagnosis of sudden aphasia of this child?

A. Autistic regression
B. Rett's syndrome
C. Conversion disorder
D. Landau-Kleffner syndrome
E. Depression disorder of childhood

Q4. EEG study is a very useful investigation in confirmation of 'subclinical seizures' in patient who do not develop overt convulsive symptoms. Of the children described below, who should we be suspicious that they might have experienced subclinical seizures?

A. A 10-year-old high functioning autistic boy with intermittent deterioration of language skill for one month.
B. A 7-year-2-month-old autistic girl with new unusual behaviors such as head nodding and rapid eye blinking during listening to radio for two weeks.
C. A 5-year-10-month-old autistic girl with sudden waking up during the night and mumbling and walking around for 5 minutes before returning to bed. (Parents considered these symptoms as sleep walking.
D. A, B, C
E. A and C

Q5. To avoid adverse reactions affecting negative behavior and psychiatric symptoms, choosing the proper antiepileptic drugs (AED) for autistic children with epilepsy should be strongly considered. Which AED cause less unfavorable behavioral side effects and usually promote positive behaviors?

A. Midazolam (Dormicum®)
B. Valproic acid (Depakine®)
C. Topiramate (Topamax®)
D. Levetiracetam (Keppra®)
E. All of above

Answers of Autism and Epilepsy

Answer 1: C) Fragile X syndrome is a common cause of mental retardation in children. Autistic features occur in about 25% of patients with fragile X syndrome. Patients with the fragile X anomaly often show a different kind of social and communicative deficit, and, in some cases, a distinct pattern of extreme social anxiety. Classic phenotypes of children with fragile X syndrome include long, prominent mandible, large ears, macroorchidism (testicular size more than 30 ml). Other physical signs such as pectus excavatum and hyperextensibility of finger joints could also be demonstrated. Detection of repeated CGG at the 5' end of FMR1 gene at chromosome Xq27.3 by chromosome study, DNA PCR, and/or Southern blot hybridization is useful for diagnostic confirmation.

Answer 2: E) The risk of epilepsy in children with Rett's syndrome is more than 90%. Childhood disintegrative disorder is the second common subtype of ASD that the risk of epilepsy may be as high as 70%. Autistic disorder (classic autism) particularly in autistic regression is reported that the risk of epilepsy is 2 to 10 times higher than general pediatric population. The likelihood for having epilepsy in Asperger's syndrome is 5-10% in early childhood. Pervasive developmental disorder, not otherwise specified (PDD-NOS, or atypical autism) could have epilepsy and the risk of epilepsy is probably linked to the severity of the underlying brain dysfunction.

Answer 3: D) Language arrest or language regression in childhood can occur in isolation, in the setting of a more global autistic regression, or in the acquired epileptic aphasias known as Landau–Kleffner syndrome (LKS). This disorder is commonly found in boys with the ratio of 2:1. LKS typically presents with speech disturbance between the ages of 3 and 8 years in a child who has already developed age-appropriate language production. The onset can be subacute, steady, or stuttering and initially consists of a loss of understanding of spoken language. In severe instances, the child becomes entirely mute and may not respond to nonverbal sounds as well. LKS is characterized by the following: (1) seizures that are relatively easy to treat and self-limited, (2) acquired aphasia, (3) an EEG showing epileptiform discharges, usually over one or both temporal regions, and (4) no definitive brain pathology that can explain the behavioral symptoms and some degree of improvement when the epileptic condtion resolves. The key clinical features of this syndrome are loss of language in association with either epileptiform EEG activity or clinical seizures.

Answer 4: D) Diagnosis of subclinical seizures in children with autism is sometimes complicated. Clinicians should consider investigating with EEGs, particularly children with history of either language or behavior regression, or fluctuations in language function, or new unusual behaviors. Subclinical seizures should be initially excluded from sleep disorder; nocturnal frontal lobe epilepsy or temporal lobe epilepsy could be manifested by complex, repetitive behaviors during sleep that hardly distinguish from sleep disorder. Overnight EEG record provides the highest yield in detecting the presence of subclinical epileptiform discharges that may causally related to those symptoms.

Answer 5: B) Valproic acid is a broad spectrum antiepileptic drug indicating in most types of seizure. Besides epilepsy, valproic acid also has two off-label uses: (1) preventing migraine headaches, and (2) treating 'mania' part of bipolar disorder. Moreover, valproic acid could be used in patient with violent behavior and those with movement disorder e.g. Sydenham's chorea. The best-known and most-feared serious reaction is liver failure. This disorder usually occurs within he first 6 months of treatment. The risk of liver failure is much higher in children under 2 years of age, especially if they also take other seizure medicine or already have other serious disorders. Physicians seldom prescribe valproic acid for those with the highest risk. People with liver disease should not take valproic acid. Neither should anyone who has shown an allergy to valproic acid or another valproate medicine in the past.

Thalassemia: Detection, Management, Prevention & Curative Treatment

Preeda Vanichsetakul, MD.[1]

[1] Bangkok Hospital, Bangkok Hospital Group, Bangkok, Thailand.

Keywords:
Thalassemia syndrome, Genetic disease, Hemolytic anemia.

Thalassemia syndromes are inherited genetic diseases caused by mutation of alpha or beta globin genes, which result in abnormal hemoglobin synthesis. The patho-physiologic mechanisms can be divided into decreased production of particular types of hemoglobin (Thalassemias) and production of abnormal structure of hemoglobin types (Hemoglobinopathies). These lead to not only abnormal morphologic of erythrocytes (red blood cells), but also shorten life span of erythrocytes due to increased in vivo fragility and extra-vascular red cell destruction (hemolysis) along with ineffective erythropoiesis (bizarre, dysfunctional marrow production). Thalassemia gene is an autosomal inheritance, which implies that both parents of the affected child must have a silent carrier state, so called thalassemia trait or heterozygote, while they are both asymptomatic.

Thalassemias could be classified based on genotypic diagnosis into 2 groups: alpha-thalassemia and beta-thalassemia, while phenotypic diagnoses are various manifestations of hemolytic anemia from very severe to very mild. Thus, they could be categorized based on clinical degree of severities as thalassemia major, intermedia, and minor. Proper treatment and care for each patient should be determined according to clinical setting.

Detection

Thalassemias (and other abnormal hemoglobin disorders) are among the most common genetic impairments around the world. They are more prevalent in people living in South-East Asia, South Asia, Middle East, and Mediteranean regions. The affected persons have variousdegrees of anemia (low red blood cell values) and enlarged liver and spleen, depending on the type of genetic defects in red blood cells' hemoglobin production.

Sickle cell diseases are among the most common hemoglobinopathies in the world, though they are not prevalent among Southeast Asians. Many affected people are of African descent, with the majority living in Africa, the Middle East, Mediterranean regions, and North America. Children affected with the disease have not only clinical manifestation like thalassemia syndromes, but also risk of painful vasoocclusive crisis due to intermittent clumping of crescent-shaped red blood cells (sickle cells) and subsequent occlusion in small blood vessels. Circulatory blood flow would be blocked. It can cause agonizing pain, serious infections and end organ damage.

Common thalassemia diseases in Thailand (and other countries in South-East Asia) consist of:

1. Homozygous alpha-thalassemia 1 (hemoglobin Bart's hydrops fetalis). This is the most severe form of the disease. The affected fetus could result in stillbirth and its pregnant mother may have a high risk of fatal toxemia.
2. Homozygous beta-thalassemia. Children affected with this form of the disease show no abnormality at birth but become progressively anemic after six months of age or usually within the first year of life. Without appropriate care and management such as regular blood transfusions, the child will undergo growth retardation, increased liver and spleen size, and facial bony deformities known as "thalassemic facies." Most thalassemia patients are classified as thalassemia major. Only a few cases will manifest thalassemia intermedia. Without proper treatment and care, the patients will likely have a shortened life expectancy.
3. Beta-thalassemia/hemoglobin E disease. This form of the disease represents a clinical spectrum that ranges from severe chronic hemolytic anemia that needs transfusion support to mild anemia that is non-transfusion dependent. Some patients will exhibit thalassemia major, while others will manifest symptoms of thalassemia intermedia. To determine which phenotypic applies to the patient the diagnosis must be performed by clinical presentation on case by case basis.
4. Hemoglobin H disease (alpha-thalassemia 1/alpha-thalassemia 2). In this form of the disease, the child will usually have mild to moderate hemolytic anemia with an enlarged liver and spleen. This group of the disease is considered to be thalassemia intermedia. The patients generally have a baseline hemoglobin level below the normal range but over 7.0 grams per deciliter. They may not require regular blood transfusions. The main problematic issue is acute hemolysis crisis on top of chronic anemia when patients develop illness or high fever. Occasional rescuing blood transfusion may be essential at the time of crisis to avoid heart failure or hypoxic brain damage.
5. Hemoglobin H Constant Spring (alpha-thalassemia 1/hemoglobin Constant Spring). This is another variant of hemoglobin H disease but in the same category as thalassemia intermedia. The prominent physical finding is an enlarged spleen greater than commonly seen with hemoglobin H disease. The patients usually have lower baseline hemoglobin content and are slightly more transfusion dependent than when they have acute hemolytic crisis. However, they can live as well as normal people and have near normal life expectancy.
6. Homozygous hemoglobin E. This disease is usually classified as thalassemia minor because of its slight anemia without enlargement of the liver and spleen. The patients are often performing normally and have a normal life span.
7. Other less common thalassemias include AEBart's disease, EFBart's disease, homozygous hemoglobin Constant Spring (CS), etc. These usually manifest as mild to moderate hemolytic anemia. Treatment would be adjusted by clinical severities on a patient case by case basis.

People who have any type of genetic heterozygote state will be judged as carriers or in the category of thalassemia minor. They may have some abnormal red cells indices and slightly low normal hemoglobin levels, but should not have any anemia symptoms. They do not encounter hemolysis problems, and no specific treatment is needed. Meanwhile, the important role of genetic counseling will be involved when two correspond-gene carriers are going to have a baby.

Diagnosis

Patients usually present symptoms of anemia, jaundice, and enlarged liver and spleen, Erythrocytes (red blood cells) of thalassemia patients mostly reveals microscopically as hypochromia, microcytes, anisocytosis, poikilocytes, and polychromasia. In terms of abnormal red cell indices, thalassemia erythrocytes show characteristics as low MCV, low MCH, low MCHC, but high RDW. In addition, for diagnosis of hemoglobin H disease, inclusion body test could find a positive result.

In order to make a clear diagnosis of individual status, the essential laboratory blood tests for hemoglobin analysis will be performed, including hemoglobin electrophoresis or currently updated technique of automated high performance liquid chromatography (HPLC). It is advisable that suspicious, anemic children should have these special blood tests performed prior to receiving their first transfusion, or at least 3 months after last time of blood transfusion. In some cases requiring definite genotypes to be identified, blood tests for molecular assessment at particular globin genes can be conducted any times, regardless timing of blood transfusion.

Treatment & Management

In several modern tertiary-care medical centers worldwide Thalassemia Clinic is usually established to to provide advice, treatment and care for children and adults suffering from anemia due to thalassemia diseases by experienced hematology specialist. The health services and facilities will be comprehensive and accommodated for individual patients.

Guidelines for management for each severity group of thalassemias are as following

Severe beta-thalassemia diseases with a baseline hemoglobin lower than 7.0 grams per deciliter or hematocrit less than 20%, can receive the following forms of treatment:

- Allogeneic hematopoietic stem cell transplantation. This can potentially cure the disease but an appropriate HLA-matched donor is required. There are also some possible complications during and after transplant process, but most cases can be reversible or resolved.
- High or Hypertransfusion regularly together with adequate iron chelation therapy. This approach is affordable and suitable for compliant patients and parents. The patient will have normal growth and height, no facial deformity, and possibly a normal sized liver and spleen. This strategy of management is mandatory for the safety and successful outcome of patients following stem cell transplantation.
- Low transfusion, occasional and supportive as needed. Iron chelation and/or splenectomy may be indicated. This approach is suitable for poor compliant patients and parents.

Moderately severe thalassemia diseases with baseline hemoglobin about 7-9 grams per deciliter or hematocrit about 20-27%, can receive the following forms of treatment:

- High transfusion together with adequate iron chelation therapy in some selected cases.
- Low transfusion occasionally when acute hemolysis crisis occurs. Splenectomy is indicated in some cases.

Mild thalassemia diseases in which the baseline hemoglobin is over 9 grams per deciliter or hematocrit more than 27% may receive transfusions only in the event of acute hemolysis crisis. Basic treatment consists of daily oral folic acid intake.

Asymptomatic or thalassemia trait or carrier, do not require regular follow up or medication. Only genetic counseling is offered when indicated.

• Blood transfusion therapy

Regular blood transfusion program must be provided for those suffering anemia problem from severe beta-thalassemia diseases, using good-quality, safe, contamination -free, pathogens screened blood components complying with standard guidelines of universal precaution by the National Blood Centre, Thai Red Cross Society and International Blood Banks. Occasional blood transfusion regimen must also be provided for those with acute crisis of hemolytic anemia due to underlying thalassemia intermedia. Nursing staffs must be high experiences in taking good care for patients receiving blood transfusion.

• Iron chelation therapy.

Each packed-red-cell blood unit contains a certain amount of iron. When a blood transfusion is given to a patient repeatedly, the iron compound will gradually deposit in his/her body tissue. Everyone has a a limit of excreting excessive iron. In patients who receive numerous blood transfusions, an accumulated toxic iron overload will develop. This leads to vital organ damage, affecting the liver, heart, pancreas, and many endocrine glands. To combat with this problem, the patient must be treated with ironchelating medications.

Chelation therapy should begin after 12 to 15 blood transfusions or within 1 8 months of frequent transfusions. This correlates with a serum ferritin level over 1,000 nanograms per milliliter. Liver iron concentration (LIC) which is measured by liver biopsy is the best measure of total iron loading. However this invasive liver procedure may not be routinely performed because of patient's discomfort. In cases where it is performed, LIC should be more than 3,000 micrograms per gram dry weight before beginning chelation. The methods may be subcutaneous or intravenous infusion of desferioxamine, oral intake of deferiprone, or intake of modern drugs such as desferasirox, etc. Responsible hematologist will assess and determine which ones are suitable to be used in patient on case by case basis.

• Supportive treatment and care.

On progression of disease in patients who did not get appropriate and sufficient treatment, several complications can occur. Patients must be aware of potential problems, such as increased size of spleen, congestive heart failure, increased tendency of clot formation inside blood vessels, increased susceptibility to infection from certain microorganisms, growth failure, endocrine dysfunction, delayed physical and sexual maturity, etc., so they may be treated early. For those who have had trouble from adverse manifestations, a holistic approach and treatment must be provided in order to relieve or even solve the problems.

• Prevention of complications and treatment.

On progression of disease in patients who did not get appropriate and sufficient treatment, several complications can occur. Patients must be aware of potential problems, such as increased size of spleen, congestive heart failure, increased tendency of clot formation inside blood vessels, increased susceptibility to infection from certain microorganisms, growth failure, endocrine

dysfunction, delayed physical and sexual maturity, etc., so they may be treated early. For those who have had trouble from adverse manifestations, a holistic approach and treatment must be provided in order to relieve or even solve the problems.

Prevention of new birth of thalassemia baby

• Genetic counseling.

Thalassemias (and abnormal hemoglobin genes) can be inherited from symptom-free parents, if both of parents are correspond-gene carriers. Definite diagnosis is the key for relevant counseling to parents and couples at risk. Hematologists and physicians who have expertise in thalassemia issues will identify thalassemia-carrier couples at risk, and provide counseling regarding their chance of having an affected child. Based on individual genetic markers, potential parents may need to decide if they should have a baby or keep contraception until pre-natal evaluation is planned. The physician team can also coordinate with an obstetrician team for assessment of fetus-in-utero of a pregnant woman who is carrying a risk of giving birth to a severe-thalassemia baby.

The modern method to identify the fetus-in-utero before birth is so-called pre-natal diagnosis (PND). Indication for couples who require PND procedures in pregnant women are as following

1. Both are alpha-thalassemia 1 carriers.
2. Both are beta-thalassemia carriers.
3. One is beta-thalassemia carrier, while the other is a hemoglobin E carrier, or homozygous hemoglobin E.

The PND procedures can be performed under ultrasonogram as early as in the late first trimester with the chorionic villi sampling (CVS) technique by an experienced, specialized obstetrician, or it can be conducted later in the second trimester with an amniocentesis technique. In some cases, the diagnosis can be performed with cordocentesis (in utero cord blood sampling) by a specialized obstetrician. Early detection provides for a more comfortable termination of the fetus if this outcome is desired.

New technologies for in-vitro fertilization (IVF) together with pre-implantation genetic diagnosis (PGD) tests and subsequent embryo transfer to the maternal uterus have been increasingly recognized as the alternative method to achieve non-genetic-defective fetus. It may be a solution for parents to have a healthy, non-thalassemia-diseased child. In addition, if the IVF team can identify an HLA-matched, non-affected embryo, it will be beneficial for parents who have previous children with thalassemia major and needing an HLA-matched sibling's cord blood transplantation to cure the disease.

Curative treatment

• Bone Marrow Transplantation (or Hematopoietic Stem Cell Transplantation).

This modern procedure has been the only accepted method worldwide to cure beta-thalassemia diseases by means of allograft transplantation. In this procedure, the patient requires a hematopoietic stem cell donation from an HLA-matched healthy donor, possibly from a sibling or unrelated suitable volunteers. The patient's blood, as well as that of the potential donor, will be tested for typing and matching. In the case of lacking an HLA-identical sibling, the patient will be registered to search for an appropriate unrelated donor through standard volunteer donor registries and public cord blood banks. Sources of donor's stem cells may be achieved from their bone marrow, peripheral blood, or umbilical cord blood.

Due to the sophisticated scheme of patient care, high risk of complications and high expense of treatment, indications for eligible candidates for undergoing stem cell transplantation are as follows:

1. Transfusion-dependent or severe hemolytic anemic beta-thalassemia diseases.
2. Available HLA-matched, non-affected, stem cell donors. The chance of a same-parent sibling having an HLA-match with a patient is about 1 out of 4, or 25%. The chance of a volunteer unrelated donor having an HLA-match is about 1:10,000 to 1:100,000.
3. Financial status. The cost of allogeneic hematopoietic stem cell transplantation for thalassemia children varies from 700,000 to 1,500,000 Thai Baht, depending on individual body weight and sources of donor stem cells.

Estimated disease-free survival rates of patients after transplantion varies from about 75% to 92%, depending on the experience of each institute team. From the patient's perspective, the better treatment outcomes are associated with younger patients, lower number of blood transfusion units, preferred use of leuko-depleted (leukocyte-filtered) packed red cells, absence of enlarged of liver and spleen, and regular adequate iron chelation to avoid liver fibrosis and myocardium damage. In terms of donors, better outcome are related with higher degree of completely compatible HLA alleles between donors and patients (recipients), and adequacy of stem cell dose to the patient's body weight. HLA-matched sibling stem cell transplantations achieve more successful disease-free long-term survival and less post-transplant complications than HLA-mismatched, unrelated donor transplants.

Allogeneic bone marrow transplantation is the complex scheme of therapy and integration of medical sciences and technology. Bangkok Hospital Medical Center offers this well-organized comprehensive program as a

specialized, aerosol-filtration equipped, isolation units setting for particular group of patients who have full-filled indication for undergoing transplantations. The institute has experienced a considerable number of successful bone marrow and cord blood stem cell transplants for thalassemia children and young adults. The details regarding this curative therapy will be informed, discussed, and explained by relevant bone marrow transplant physicians on patient case by case basis.

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Questions of Thalassemia

Q1. We are a Thai married couple who plan to have a baby soon. What should we do in order to make certain that our baby will not have thalassemia disease?

Q2. We are a married couple. Our hemoglobin typing results both showed normal types but the counseling clinicians requested us further for molecular genetic analysis of alpha-globin genes. Why is it needed to do so?

Q3. Our one-year-old child was recently diagnoses with beta-thalassemia disease. She has marked anemia and an enlarged spleen. How can we help her? Is there a cure?

Q4. Our 14-year-old son has been diagnosed with hemoglobin H disease since he was 4 years old. He had high fever and received a blood transfusion twice last month. He had never received any transfusion before. He has a slightly palpable spleen. Does he need bone marrow transplantation?

Q5. I just learned that I have a hemoglobin E trait from a blood checkup. What I need to do? Do I need to take oral folic acid?

Answers of Thalassemia

Answer 1: Even though you both are healthy, with no anemia symptom, you should have your blood checked for hemoglobin electrophoresis, also known as hemoglobin typing test. If you both are the correspond-gene carrier which can lead to some severe types of thalassemia, the chance that your baby will have the disease is about 25%. In this case, the counseling clinicians will advise you to perform genetic testing of your offspring during its either pre-natal or pre-implantation period. If just only one of you has the carrier gene, there will be no chance of your offspring having the disease.

Answer 2: Since alpha-thalassemia-1 genes are quite common among south-east Asian people but the defects are usually presented as normal types by hemoglobin electrophoresis test, some couples at risk may miss the opportunity to prevent their baby from being affected by homozygous alpha-thalassemia-1 genes, which consequently may lead to fatal hemoglobin Bart's hydrop fetalis. So when the consultant clinicians discovers a low mean cellular volume or low percentage of hemoglobin A2 despite normal hemoglobin types, they will suggest that you undergo further blood testing for molecular genetic analysis of alpha-globin genes.

Answer 3: A child with beta-thalassemia can survive and grow relatively well by receiving adequate, regular blood transfusions. With this approach she will not develop anemia, facial deformities, growth retardation, and her spleen size will subside soon. That said, if she requires more than ten packed red cell transfusions, her body iron will accumulate and become overloaded and then she will need adequate, proper iron chelation treatment. If the patient is fortunate to have an available HLA-matched, non-affected, healthy sibling, then she can be an eligible candidate for undergoing allogeneic bone marrow transplantation which offers a high hope of cure from her disease.

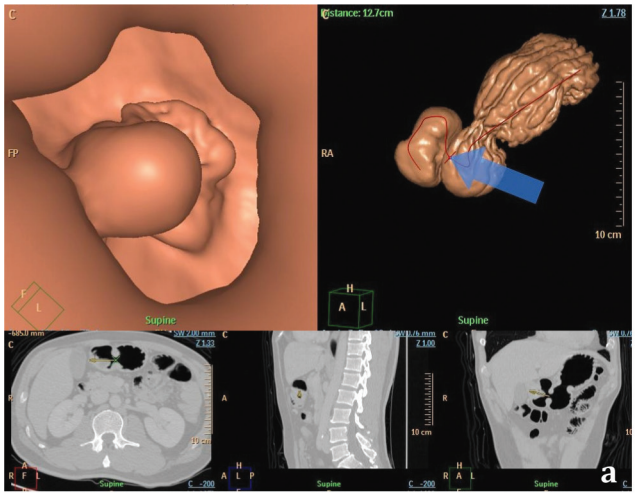
Answer 4: According to the clinical status, your son is classified as a thalassemia intermedia patient. Basically, thalassemia intermedia status does not require allogeneic bone marrow transplantation because the course of the disease is not as severe. Only some episodes of acute hemolytic anemia occur that require occasional blood transfusions. In lieu of the high risk and high cost of marrow transplantation, your son should not be considered to undergo the treatment. However, taking daily folate is recommended.

Answer 5: You should carry on as usual. You have no increased risk anemia or any destruction of your red blood cells. You will be doing fine with normal life expectancy. Folic acid tablet intake is unnecessary for any carriers of thalassemia or hemoglobinopathy state, like you. Anyhow, one essential issue is, if you have a couple, to check his/her blood for hemoglobin electrophoresis. If he/she has beta-thalassemia trait, there is a possibility of 25% that your offspring will have beta-thalassemia/hemoglobin E disease. If so you will need a consultation regarding genetic diagnosis for your baby.

Virtual Gastroscopy and Endoscopic Ultrasonic Scan (EUS)

Ratha-korn Vilaychone, MD.[1], Thawee Ratanachu-ek, MD.[1], Vijitr Boonpucknavig, MD.[2]
Wasan Poungwongkhan[3], Wanida Charoensuk [3]

[1] N Health Pathology Department, National Healthcare System, Bangkok Hospital Group, Bangkok, Thailand.
[2] Department of Pathology, NHealth Company, Bangkok Hospital Group, Bangkok, Thailand.
[3] Imaging Center, Bangkok Hospital, The Bangkok Hospital Group, Bangkok, Thailand.



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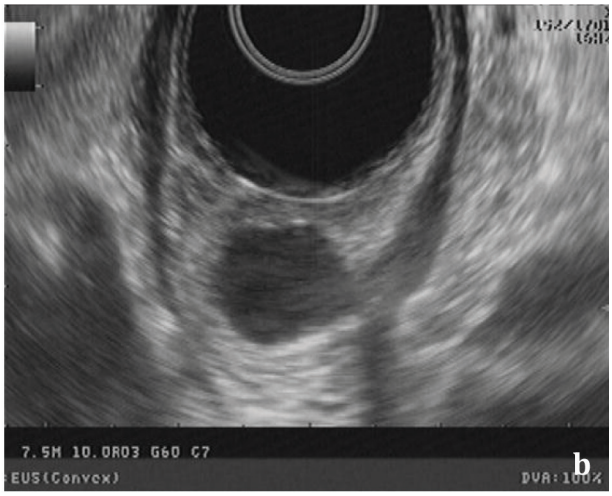

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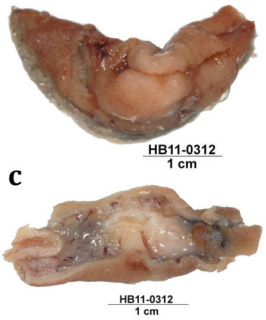
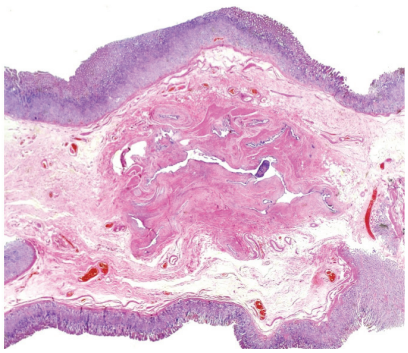
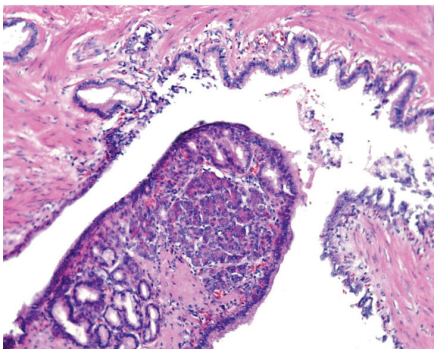


C1



C2



C3

A 51-year-old man presented with chronic diarrhea since 7-8 years. The physical examination was within normal limits. The laboratory tests were unremarkable.

Virtual gastroscopy (Figure A) revealed a submucosal mass at the antrum on greater curvature of stomach 1.4 x 8 cms. EUS (Figure B) showed heterogenic hypoechogenic lesion at 3rd and 4th layers of gastric wall. Removal of gastric mass through gastroscopy was performed. The gross examination demonstrated a small submucosal protruding nodule 1.0 cm. in diameter but, no evidence of mucosal ulceration. Serial sections showed no definite connection between the nodule and gastric mucosa, nor evidence of ulceration at the mucosa. The microscopic section (Figure C1-3) showed pancreatic tissue composed of a mixture of acinar tissue and ductal epithelial element, the endocrine element was not clearly seen.

Gastric aberrant pancreas is an unusual condition, it is only reported sporadically. The findings revealed submucosal mass without ulceration. Upper GI study and gastroscopy are well established methods, however virtual gastroscopy may well be as demonstrative as other established modalities. EUS showed heterogenic hypoechogenic mass in 3rd and 4th layers of stomach as shown on the previous literature.[1]

References

1. Matsushita M, Hajiro K, Okazaki K, Takakuwa H, Gastric aberrant pancreas: EUS analysis in comparison with the histology. *Gastrointest Endosc* 1999;49(4 Pt 1):493-497

Book Review

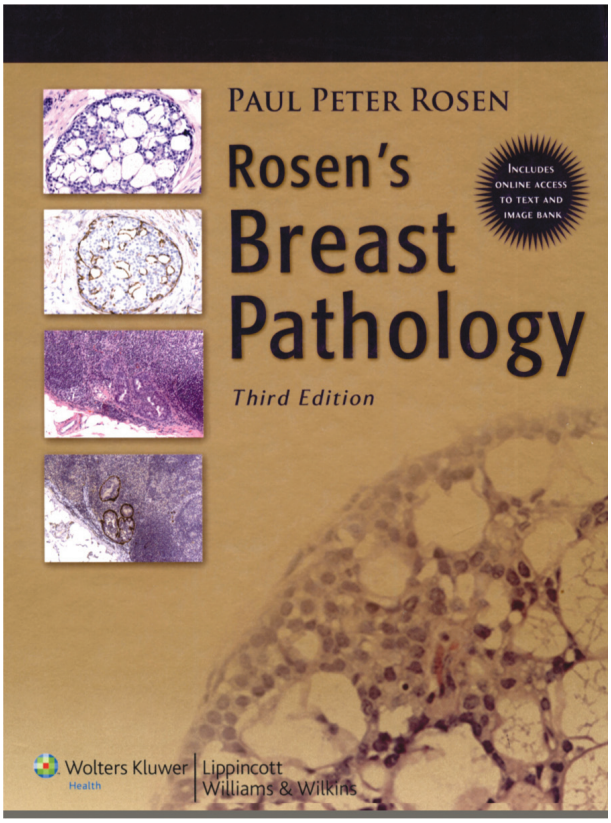
Rosen's Pathology of the Breast, 3rd Edition 2009

Paul Peter Rosen, MD. Weill Cornell Medical College New York, New York

Publisher: Lipponcott Williams & Wilkins, a Wolters Kluwer business

Reviewer: Nidhi Chongchitnant, MD.[1]

[1]N Health Pathology Department, National Healthcare System, Bangkok Hospiatl Group, Bangkok, Thailand.



This book is the product of accumulated knowledge for decades. The first edition was released in 1997 and the current third edition came out in 2009. It was intended for pathologists, but surgeons, oncologists, radiologists or any physicians who have a deep interest in this subject will benefit from it.

The book contains 44 chapters dedicated to all kinds of breast lesions with special emphasis on carcinoma. Each carcinoma has a chapter of its own. The non carcinoma and minor lesions are put together as a group, such Lymphoid Neoplasms, Cutaneous Neoplasms, Sarcomas, and Metastases to the Breast. There are also chapters on Pathology of Axillary and Intramammary Lymph Nodes, and Pathologic Examination of Breast and Lymph Node Specimens, Including Sentinel Lymph Nodes.

In the chapters of tumor; benign or malignant, the text follows a consistent pattern. Starting with an introductory paragraph then Clinical Presentation, Gross Pathology, Microscopic Pathology (including immunohistochemistry and other investigations) then Treatmentand Prognosis.

The second edition had been reviewed and rated excellent. The information was deep and accurate. So it is not easy to top it. The third edition is not a re-written edition. The basic fact about tumors is more or less the same. The authors added new findings and information on newer investigations and refined the content here and there to make it current and this is the important part. However, since data on newer investigations such as oncogenes, cytogenetics and molecular genetics are new and continue to emerge regularly. The information on these aspects will definitely change over time.

Besides the text part, there are a huge number of photomicrographs in over 1200 figures. Each contains multiple photos per figure. (The total number of photos is over 3000). They are in B&W and color. The B&W photos came from the first edition and much of the color were from the second edition. Several new color photos were added and replaced some old B&W photos. The quality of photos is fairly good but the consistency of color balance is lacking. This, however, is not the author's fault. It was the publisher who did not maintain standard of good quality color printing.

The book is heavy, weighs 3.3 kg and there is no eBook format. The internet access (www.rosenbreastpathology.com) to text and image bank is a nice feature but only a registered user who has the password can enter the site. So it is useless for everyone else. The eBook format will be a much better approach than the internet access. Anyway I doubt there will be one because a book of this type, even though very expensive, has a limited amount of production.

I would rate this book 8.5/10 (9.5 on the text part and 7.5 on the illustration; Dr. Rosen gets 10/10 for the effort and knowledge he puts into the book and the publisher gets 7 /10 for publishing it.

Memorial - Dr. Roongtam Ladpli

Dr. Roongtam ladpli was died suddenly by car accident on Sunday 17th November, 2002 at Cha-um, Prachupkirikhan, Thailand. He was 67 years old.

Dr. Roongtam was born on 28th April, 1935 in Bangkok, Thailand. His father, H.E. Phaya Ladpli Thamprakal, a nobleman, was the former judge of the Supreme Court and the Minister of the Royal Department of Justice. He lost his mother since he was young.

He attended the Faculty of Medicine at Siriraj Hospital, Mahidol University, Thailand, graduating with an MD degree with Gold Medal First Class Honors, and achieving Diplomat of Neurological Surgery in 1957. During his residency training in surgery at Siriraj Hospital, Dr. Roongtam was selected to attend a further neurosurgical training program in USA. Before returning to Thailand, Dr. Roongtam had further training in pediatric neurosurgery at the Children Memorial Hospital in Chicago and in neuropathology at the Montefiorre Hospital and Columbia University in New York. Once Dr. Roongtam returned to Bangkok, Thailand, he was appointed as lecturer and neurosurgeon in the Department of Surgery at the Faculty of Medicine, Siriraj Hospital. He taught medical students and residents in surgery and neurosurgery. With his clinical proficiency, in 1967 he was appointed as a Fellow of the American College of Surgeons (FACS). Dr. Roongtam was also fortunate to have the opportunity to do Postdoctoral research in Norway, with the support of NORAD (Norwegian Agency for International Development).

Dr. Roongtam was a person who was very successful in his career. He had fourteen royal decorations bestowed on him by His Majesty the King for his works and good deeds. He was appointed to many important and honorable positions such as being an extraordinary professor of the Faculty of Medicine, Siriraj Hospital, Mahidol University, an extraordinary professor of the Faculty of Arts, Thammasart University. He was an advisor of the Social Security Office Committee, Ministry of Labor and Social Welfare, an advisor to the Ministry of Health, and a Vice President of the National Olympic Committee of Thailand (NOCT). In all SEA Games, Asian Games, or Olympic Games events, Dr. Roongtam was regularly invited to attend joining the Thai athletic team as a sport medicine doctor. The highest honor and in his life was when he was appointed to be the Personal Royal Physician of His Majesty King Bhumibol of Thailand.

In the last 20 years of his life, Dr. Roongtam truly dedicated the majority of his time to this role, He consistently accompanied His Majesty on visits to help people

in remote rural areas as well as attending daily functions in the Royal Palaces. With sincere friendship, Dr. Prasert Prasarttong-Osoth, the President of Bangkok Dusit Medical Services Plc., sometimes heartily reminded Dr. Roongtam to allocate some portions of time to his family. Nevertheless, Dr. Roongtam insisted earnestly that dedicating his entire life in true attendance upon His Majesty the King was his highest preference

As a result of continuously supporting the H.M. King's multifarious duties by providing medical assistance to needy people in remote areas, Dr. Roongtam learnt that many people suffered from unhealthiness and disease. In the meantime, even though government hospitals were equipped with the most up to date medical technologies, their capacities were not adequate enough to support healthcare facilities and give timely services to everyone.. This was the likely inspiration for Dr. Roongtam to establish a private hospital that could provide complete healthcare services which were on a par with government hospital facilities. Consequently in 1960, the first private hospital in Thailand was proudly established under the name of Bangkok Hospital, a private hospital where advances in medicine meet with compassion. Dr. Roongtam was one of the founders and he served on the Board of Directors of Bangkok Dusit Medical Services Company Limited (BDMS) - the juristic entity's name of Bangkok Hospital development towards maximizing patient satisfaction and the enthusiastic ambition to step forward as the top model of Thai private hospitals, Dr. Roongtam desired to differentiate Bangkok Hospital from other general hospitals. He promoted Bangkok Hospital as a private hospital that was specialized in neurological diseases. In consequence, on February 1998, Bangkok Neuroscience Center was established under the leadership of Dr. Roongtam. It was a specialized center with state of the art technologies, highly experienced physicians, and well-trained medical staff. In addition, Bangkok Neuroscience Center was a pioneer in using imported Leksell Gamma Knife technology to help relieve patients who were suffering from brain diseases. At present, Bangkok Hospital has already become an internationally certified leading private hospital in Thailand.

Dr. Roongtam was responsible for granting led the greatest honor and pride to Bangkok Hospital. ***Due to Dr. Roongtam's great credibility and his consistent loyalty toward His Majesty King Bhumibol, Bangkok Hospital received the highest prestige and honor when H.M. King Bhumibol formally visited the hospital.*** 28th May 1997 was a day that would remain in all Bangkok Hospital staff memories forever. The highl respected King had arrived at Bangkok Hospital in the late evening and Dr. Roongtam had the honor to present His Majesty the Leksell Gamma Knife technology. His Majesty the King was very appreciative and was interested to learn its technical and mechanical functions. After demonstrating the Leksell Gamma Knife, Bangkok Hospital and the radiologist team were pleased to have the honor of providing MRI Spine to their beloved King. With his great intuition and genius, H.M. King had many questions regarding his MRI Spine

interpretation and human anatomy. Eventually before his departure, His Gracious Majesty granted Dr. Roongtam, Bangkok Hospital's executives, and medical staff to take the group photos.

With regard to ethics and morals, Dr. Roongtam was a role model for medical professionals. Dr. Pongsak Viddayakorn, a BDMS Board of Director and Executive Advisor, complimented Dr. Roongtam, saying that he always mindfully emphasized the patients wellbeing. *"To save a patient's life, no matter of what time it is, the hospital could call Dr. Roongtam 24 hrs. And he would come to the hospital offering treatment immediately."* reported Dr. Pongsak.

One of the many achievements of Dr. Roongtam was his successful removal of a tumor in the brain of dog. This was one of the cases in which Dr. Roongtam had closely worked together with his son, Dr. Parameth Ladpli, also a neurosurgeon. This operation was conducted successfully and smoothly in cooperation with a team of neurosurgeons, Dr. Chirochana Suchato (a radiologist), and a team of veterinarians. This case well deserved to be considered a landmark case in developing further surgical techniques in Thai veterinary medicine.

Another particularity of Dr. Roongtam was his positive attitude towards egg eating. He always encouraged Thai people to eat two eggs every day. He clarified that eggs are a low price ingredient that contains high nutritional values. The degree of cholesterol from egg was relatively low compared to its benefits. Egg also helps nourish the human brain, possibly preventing dementia and Alzheimer problems.

As to Dr. Roongtham's family life, Dr. Roongtam was married to Ms. Jeeranan Sawaittanan, who was Miss Thailand 1964 and 2nd Runner-up Miss Universe 1966. His joyful family life was completely fulfilled by the addition of his three beloved children, Dr. Atinuch Ladpli, Dr. Parameth Ladpli, and Ms. Napawan Ladpli.

The death of Dr. Roongtam was the not only very sad for his family, but was the loss of one of the best and most beloved doctors in Bangkok Hospital and the Thai medical profession. However, his name and his benefaction will certainly remain in our memory forever.