

私と超音波 — 会長講演に代えて —

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1. はじめに

この度、2010年5月29日(土)から31日(月)まで日本超音波医学会第83回学術集会を担当させて頂くことになりました。この機会に日本超音波医学会の役員及び代議員の皆様、ならびに名誉会員、功労会員の方々に「私と超音波」というタイトルでエッセイを執筆して頂きそれを出版させて頂くこととしました。大変著名な先生方の著述、エッセイが盛り込まれており楽しく拝見させて頂きました。

そもそも私がこの本を企画致したのは①類似の企画が今までなかったこと及び②現在の超音波医学会の会員には比較的著名な先生方がどのようなバックグラウンドでこれまで超音波と関わってこられたのかを知る上で大変意味のあることと考えたからであります。また一方、私にとりましては日本超音波医学会の会長を務めさせて頂くという大変大きな名誉とともに、一つの節目でもありますのでこれまでの自らの来し方を振り返り、また今後の展望をふまえて、やや長めに述べさせて頂くこととしました。例年、本学会では「会長講演」が行われてきたのが慣例ですが、私にとっては「志、未だ道半ば」ですので、「会長講演」といったおこがましいお話をする場を設定するよりは文章としてこれまでの来し方を記録するに留めさせて頂ければと考えた次第であります。

2. 大学卒業から神戸市立中央市民病院の時代

私は1978年に京都大学を卒業しました。京都大学を卒業した頃には外科医になるか消化器内科医になるか大いに悩みました。なぜ消化器を希望したかと申しますと、実は当時、柳田邦夫の「ガン回廊の朝」という本がベストセラーになっており、白壁先生などが開発した胃の二重造影法、あるいは日本で開発された胃カメラによる早期胃癌の診断などが全盛を極めており、それに憧れて内視鏡をしたいという思いから消化器を志すことにしました。

京都大学での研修は1年そこそこで2年目から当時の教授にお願いし、京都大学の関連病院としては最もアクティビティが高く最先端の病院であった神戸市立中央市民病院に行かせて頂きました。私が赴任した1979年は丁度病院の移転の前年であり、当時は新神戸の隣に古びた病院があるだけでしたが、翌年にはポートアイランドへの移転が決まっており、新病院も完成間近でした。ポートアイランドの埋め立て地に病院が移った頃には大変なエネルギー・活気が病院の中にあふれておりました。岡本道夫元京大総長が病院長に就任され、臨床研究を盛んに奨励されておりました。また循環器内科には吉川純一先生という巨星がおられ、大変活発に国内外での学会発表、論文発表が行われておりました。また消化器内科にも富田周介先生という大変立派でアクティビティの高い先生がおられました。当時心エコー室の隣に腹部エコー室があったせいもあり、私自身、研修医の頃から吉川先生の薫陶も大いに受けることができました。当時の私は前期研修医の2年目、及び後期レジデントの1～2年目くらいの間は内視鏡の習得に明け暮れましたが卒後3、4年目ぐらいから次第に肝臓病や画像診断に興味をもつようになりました。なぜならば肝細胞癌が急速に増え始めている割には当時教科書に書かれていたようなB型肝炎由来の肝癌が意外に少ないということに気がつき始め大変な興味を抱き始めたからであります。すなわちHBs抗原陰性の肝癌が大変増えてきており、また肝癌の診断も当時のコンタクトコンパウンド方式の超音波ではなかなかできず胆石がやっと診断できるというものでした。超音波で肝臓を1cmずつ丁寧にスキャンしていき、何か欠損部がありそうであれば肝シンチグラムで確認する(!)という時代でありました。当時の肝癌の診断といえば肝シンチグラムとAFPしか無く、そういった

もので肝細胞癌が疑われれば即、血管造影を行って確定診断をしていたものでした。血管造影といっても腹腔動脈造影がせいぜいであり、治療にしてもTACEやエタノール注入などはまだ登場しておらず腹腔動脈からMMCあるいはアドリアマイシンをワンショット動注して終わりという時代でありました。当時はもちろん頭部CTのみで、腹部CTは一般診療には普及しておらず、MRIなどはまだまだ存在すらしておりませんでした。1980年代に入り、電子スキャンの超音波が普及するようになり超音波によってようやく小さな肝癌が見つかるようになって参りました。リアルタイムに微小な肝癌(当時の微小肝癌は5cm以下であった)を見つけるということは大変エキサイティングなことでありました。

私の最初の超音波医学会への発表は第40回総会(1982年)(東京)で「肝癌早期診断の為のScreening法の検討」といったようなものでありました。この頃から小肝癌に対する超音波診断や血管造影などが楽しくなり、急速に肝細胞癌の診断と治療へと私の興味は傾いてゆきました。卒後8年目になる1986年に「肝細胞癌スクリーニングにおけるUSとSPECTの併用の有用性」といったタイトルでRadiologyに論文がacceptされ一般病院にずっとおり大学には戻りませんでした。京都大学から学位を頂けることになりました。

その後1987年から1989年にかけて米国のカルフォルニア大学のDavis Medical Center(Sacramento)に留学し、一時、超音波から遠ざかった時期もありました。しかしながら、この時期に暖めたアイデアが1989年帰国後US angiographyとCTAPにて結節内の血流動態をみるといった仕事につながるようになりました。UC Davisでは主として核医学とin vitroの実験の仕事をし、その研究が現在のアジアロシンチの開発につながるようになりました。これによりBerson-Yellow賞を米国核医学会から頂きました。しかしながら1989年に帰国後感じたことは私が渡米する1987年頃に大変大きな問題になっていた2cm以下の肝内の結節が良性結節か悪性の癌であるかということを鑑別するという点についてはまだまだ解決がなされていないという状況でありました。従って私共は当時、大手前病院の松田康雄先生(現在、八尾徳洲会病院副院長)が開始されたCO₂マイクロバブルを動注するといった方法をすぐに導入しました。消化器内科では血管造影を日常的に行っていたものですからまず超音波で見つかり、血管造影で濃染像がはっきりしない結節については片っ端からCO₂動注US angiography、及び門脈造影下CTと腫瘍生検を行いました。US angiography についてはRadiology誌に2本、AJRに1本、報告し、CO₂動注US angiographyによる腫瘍の血流動態からみた鑑別についての論文をレポートしレボビストが市販される10年前に肝腫瘍に対する造影エコー法の有用性を確立することができました。関連する仕事を技師の朽尾君が日本超音波医学会誌に投稿し、この論文により平成4年度に超音波医学会の菊池賞を頂きました。CO₂動注US angiographyを用いた肝癌の生物学的悪性度と血流動態の関連についてはさらに肝臓学会賞を頂きました。その後は癌化と癌の進展に伴う結節内血流動態の変化の解明、あるいは肝腫瘍診断における造影ドブラー法の有用性の確立、あるいは比較的良性の経過をたどる大型高分化型の概念の提唱をUS を用いた血流評価で行い新しい疾患概念として提唱しました。また門脈栄養結節がパワードブラの定常性流入シグナルによって診断できることも証明することができました。また肝細胞癌の流出血流についての検討や胆嚢壁からも流出血流がみられること、そしてそれが脂肪肝におけるfocal spared lesionの原因であることなども報告し、再び共同研究者の濱田君が平成10年度の日本超音波医学会菊池賞を受賞することができました。

3. 1997年に近畿大学に異動

1997年に近畿大学に異動することになりましたが当時、近畿大学にはカラードプラ装置が病院中に一台もなく、またエコー検査も内科、第一外科、第二外科、中央放射線部でバラバラに行っていましたが、1998年にはカラードプラ装置も3台に、そして各科の御協力により超音波検査は全て中央化・腹部エコー室に一体化することができました。1999年にはやっとレボビストが使えるようになりましたので肝腫瘍における静注造影剤を使ったcontrast harmonic パワードブラ法の有用性、あるいは2000年にはcoded harmonic angioを使った造影エコーの有用性なども報告することができました。また造影エコー法を治療に応用するといったことも積極的に開始致しました。1990年代後半はエタノール注入が全盛でしたが当大学ではいち早く1999年6月に造影超音波を治療支援に使いCEUSガイド下のラジオ波治療法を肝癌治療に導入しました。また胆膵疾患についても造影エコー法を応用するといった研究を始めたのも2002年の頃であります。また超音波

内視鏡を用いた生検や造影のための特殊なプローブの開発も企業との共同研究で行い、市販装置に搭載されるまでに至りました。

2006年にはGE社のLOGIQ 7を用いればraw data保存ができることを応用してpure arterial phase imagingという画期的な手法の開発を行い、肝腫瘍に対して動脈と門脈血流支配を分離評価する試みを確立することができました。また2007年1月には待望の第二世代造影剤であるソナゾイドが発売されました。このソナゾイドは低音圧によるreal time imageとともに安定したKupffer phaseが大きな特徴ですが、このKupffer phaseに注目し、Kupffer phaseでdefectを示した部位に対してre-injectionを行うことにより極めて効率的にスクリーニングやステージング、確定診断、局所再発病巣の同定・局在診断、CTで描出されるけれどもBモードで見えない結節の拾い上げ、あるいは治療支援や治療後のフォローアップなどあらゆる局面で応用できることを証明しました。この方法はDefect re-perfusion imaging法として瞬く間に日本中に広まりました。余談ですが、2007年の鹿児島での学術集会でのランチョンセミナーでこのアイデアを報告したところ、大変大きな反響がありました。従って速報でも何でも良いので早く論文に残しておくように周囲の人に勧められました。従って鹿児島から大阪への帰路のフライトの中で肝臓学会の機関誌に短報の形で論文を書きました。超音波医学会は5月18-20日でしたがこの論文は2007年5月25日投稿、6月1日採択、6月号に掲載と異例のスピード掲載となりました。後日談ですが、この論文は2007年、2008年の2年間に最も引用の多かった論文として日本肝臓学会より「学会誌High Citation賞」を頂くことになりました。現役の教授としてこのような賞を受賞するのはやや気恥ずかしい気はしましたが、それだけ多くの人が引用するに値するアイデアであったということですので内心悪い気は致しませんでした。今後、韓国、中国でもソナゾイドが発売予定とも聞いておりますが、中国や韓国に招かれる度にDefect re-perfusion法を講演しておりましたので彼らも既にSonoVueを使用しているにも関わらずソナゾイドを待ち望んでいるという状況になっております。また2009年のシドニーにおける世界超音波医学会、イタリア超音波医学会(ローマ)、2010年の国際放射線学会(ISR)(上海)、サンパウロでのブラジル放射線学会(2010年)に招待された際にも、このDefect re-perfusion法を紹介しました。どの学会においてもこの方法は大変な反響があり、特にローマではstanding ovationが出るほどの反響がありました。またWFUMBのMichel ClaudonがPresidentを務める世界超音波医学会のコントラストエコーのガイドラインにもぜひソナゾイドによるDefect re-perfusion imagingを加えたいという申し出があり、私も委員になり現在進行中であります。また2008年からは肝癌スクリーニング法をまずソナゾイドを静注しておいてvascular phaseをとらずにKupffer phaseだけで行い、defectが見つかった場合にはre-injectionで確認するという多施設共同研究を18施設でスタートさせ、現在進行中であります。もしこれで良好な結果が得られればDefect re-perfusion imagingあるいはソナゾイドKupffer phaseによるスクリーニングがBモードによるスクリーニングにとって変わる可能性があり、肝癌の診療ガイドラインも変わる可能性があると考え積極的に臨床試験を遂行しております。

4. 現在の研究内容と今後の研究の方向性

現在考えている肝胆膵、消化器疾患における超音波の方向性についてですが、まず肝癌についてはやはり3Dや4Dのますますの進歩により肝癌の確実な治療ガイド、治療支援画像となると期待されます。早期肝癌の診断に関しては残念ながらGd-EOB-MRIの肝細胞相には及ばないわけではありますが、フォローアップ、specificityにおいてはKupffer phaseの取り込み低下が優れているということは造影エコーの強みでもあります。実際この点については肝臓学会編集の「早期肝癌の診断アルゴリズム」にも加えられております。その様なことからEOB-MRIとソナゾイドとの組合せで乏血性でかつEOB-MRI肝細胞相でのみ抜ける低信号を示す結節をソナゾイド造影エコーのKupffer phaseで同定し、その血流動態の変遷を4ヶ月毎に追いかけていき、自然経過をみるという多施設共同研究も近日中にスタートさせる予定です。また現在、ナビゲーションシステムといったものも大変進歩しておりますので、これらのものを更に発展させ、4Dイメージなどにも期待をしているところであります。また分子標的薬ソラフェニブの治療効果判定にも造影エコー法が何らかの役割を果たせないかと検討中であります。また肝線維化の非侵襲的検査法としてのReal-time elastographyに関する多施設共同研究も2010年より開始しました。

5. 終わりに

私は大学を卒業後すぐに直接超音波の手ほどきを受けたのは富田周介先生であり、超音波に関して学問的あるいは学会で薫陶を受けた吉川純一先生、ならびに肝細胞癌に対するアプローチ法と論文執筆の「いろは」を教えて頂いた幕内雅敏先生に大変感謝をしております。私と超音波について語るにはこの3人の先生方を抜きにしては語ることはできません。従って特別講演にはこの吉川純一先生と幕内雅敏先生のお二人をお招きして、ご講演をして頂くことに致しました。このお二人の御講演は私にとっては大きな思い出となり、お二人の先生への恩返しとなると考えております。

以上、取り留めのないことを書かせて頂きましたが、私と超音波の関わりはこの様に肝癌に対するものが主でありましたが脾癌で北野雅之准教授、及び坂本洋城助教が日本の最先端を走っております。また私の手足となり造影超音波を積極的に遂行して頂いている前川 清技師、及び畑中絹世助教、ならびに井上達夫講師、またFibroscan、Real-time elastographyを積極的に進めて頂いている矢田典久講師、辰巳千栄医師に陳謝致します。また超音波室の技師の皆様にも多大なご助力を頂きました。またこれまで受け入れた留学生は11名(Ding Hong先生(丁 紅)(上海医科大学)、Wen YL先生(文 艶玲)(中山医科大学)、Zheng RQ先生(鄭 榮琴)(中山医科大学)、Zhou Pei(周 佩)(人民解放軍重慶病院)、Ly Sokhey先生(カンボジア)Worawan Chinamnan先生(タイ)、Kaushal Madan先生(All India Institute of Medical Science: AIIMS、インド)、Kunal Das先生(インド)、Yu Xia(北京、中国)、Md. Nadiruzzaman先生(バングラディシュ)、Lorenzo Andreana先生(ナポリ、イタリア))にもおよび、様々な意味で国際交流を行えていることにも感謝申し上げます。

また伊東紘一元超音波医学会理事長におかれましても色々のご助言を頂き、跡見元理事長には同じ消化器領域の理事として大変お世話になっております。またWFUMB、AFSUMB関係では千田理事長にも大変お世話になっております。また渡邊決先生にはAFSUMB、WFUMBの詳しい内容などについて色々ご指導を頂きました。この場をお借りいたしまして深謝申し上げます。もちろん、私を支えて頂いた他の理事、代議員の皆様および超音波医学会の会員の皆様、あるいは技師の皆様のお陰と思っております。特にAFSUMB、WFUMBでの私の活動については日本超音波医学会の理事会の強力なサポートがあり、今日に至っております。すなわち現在の私のWFUMBのPresident-elect、AFSUMBのVice-Presidentという立場は全く私の個人的な能力とは無関係であり、このJSUM理事会の単なる一代理として活動しておりますので今後とも、そのことをしっかりと頭においてJSUMの為に活動を行っていきたいと思っております。

そのようなことで日本超音波医学会に少しでも恩返しができるよう、さらに精進する所存でございますので日本超音波医学会の会員の先生方におかれましては今後とも何卒宜しくご指導、御鞭撻の程をお願い申し上げます。今回はAFSUMBのPresident(Prof. Chiang)、Immediate Past President(Prof. Choi)、Secretary(Prof. Kim)、Treasurer(Prof. Chou)を招き致しておりますし、WFUMBのPresident(Prof. Michel Claudon)、Immediate Past President(Prof. Cerri)、Secretary(Prof. David Evans)、Treasurer(Prof. Benaceraff)、およびAIUMのCouncil member(Prof. Copel)も招待致しております。日本超音波医学会の国際化も今後の課題の一つであるという思いからこのような方々を招待し、Keynote lectureならびに特別なセッション(WFUMB、AFSUMB、JSUM Joint session)を組ませていただきました。詳しくは第83回の学術集会プログラムをご参照頂ければ幸いです。

最後になりましたが第83回学術集会への御協力を感謝致しまして私の拙文を閉じたいと思います。

2010年6月
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主な所属学会

日本消化器病学会(財団評議員・指導医・専門医・国際委員会委員)、日本肝臓学会(理事・指導医・専門医・治験支援委員会委員長・倫理委員会副委員長・肝移植検討委員会委員)、日本消化器内視鏡学会(評議員・指導医・専門医)、日本超音波医学会(理事・指導医・専門医・国際交流委員会委員長)、日本内科学会(評議員・認定内科医)、日本核医学会(評議員・専門医)、日本肝癌研究会(常任幹事・追跡調査委員長・取扱規約委員長・肝癌治療効果判定基準作成委員会委員長・事務局代表)、日本肝移植研究会(世話人)、肝血流動態イメージ研究会(幹事)、日本腹部造影エコー・ドプラ診断研究会(事務局・世話人)、肝癌治療シミュレーション研究会(副代表幹事)、超音波治療研究会(常任世話人)、日本肝がん分子標的治療研究会(代表世話人・事務局代表)、日本消化器内視鏡財団(評議員)、米国肝臓学会(AASLD)(肝癌部門企画運営委員: Steering Committee hepatobiliary malignancy)、米国消化器病学会(AGA)、世界肝臓学会(IASL)、欧州肝臓学会(EASL)、米国消化器内視鏡学会(ASGE)など。

委員・資格など

- ・アジア超音波医学会(AFSUMB) Vice-president(副理事長)
- ・世界超音波医学会(WFUMB), President-Elect(次期理事長)
- ・Editor "Ultrasound in Medicine and Biology (ELSEVIER, New York)"
- ・Editorial Board "Liver International (Blackwell, UK)"
- ・Editorial Board "Hepatology International (Springer, New York)"
- ・ウイルス肝炎研究財団 日米医学協力研究会肝炎専門部会研究員
- ・米国肝臓学会(AASLD) 肝癌部門運営委員会委員(Steering Committee Member)
- ・世界肝臓学会(ILCA) 理事(Founding Board Member, Governing Board Council Member)
- ・日本肝がん臨床研究機構(JLOG) (理事長)
- ・世界保健機構(WHO) Blue Book「Classification of the Tumor」改訂委員(平成21年5月1日)
- ・International Liver Thought Leadership Study (ILCS), Council member

受賞

- ・米国核医学会Berson-Yalow Award 受賞(平成元年6月)
- ・日本対がん協会がん研究助成奨励賞 受賞(平成4年3月)
- ・日本消化器病学会奨励賞 受賞(平成4年4月)
- ・日本核医学会賞 受賞(平成5年10月)
- ・米国超音波医学会(AIUM) 学会賞受賞(平成15年6月4日)
- ・ボローニャ大学医学部医学会名誉会員賞(平成18年9月15日)
- ・フィリピン超音波医学会名誉会員(Honorary Member of PSUCMI)(平成20年3月19日)
- ・アジア太平洋消化器病学会(APDW) OKUDA Award受賞(平成20年9月13日)
- ・北米放射線学会 Certificate of Merit受賞(平成20年)
- ・インド肝臓学会Madangopalan Award受賞(平成21年3月28日)
- ・北米放射線学会 Cum Laude賞受賞(平成21年12月)(7000編の論文中上位10編に採択)
- ・日本肝臓学会「Hepatology Research High Citation賞」受賞(平成22年)

著書

- ・Contrast Harmonic Imaging in the Diagnosis and Treatment of Liver Tumors(Springer-Verlag 2003)
- ・肝腫瘍における造影ハーモニックイメージング(医学書院 2001)