



NewsLetter

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EDITORIAL

PET SCAN – OVERUTILIZED IMAGING MODALITY!!

Many patients who have completed cancer treatment fear the cancer will strike back. This leads patients and doctors to pursue frequent testing in the hope of detecting an early recurrence. But there is growing realization that repeated testing does not always come with health benefits. It is costly too. There are breast cancer patients who insist or self prescribe annual PET scan as follow up investigation to detect recurrence.

PET Scan is overutilized!!

Overutilization means applications of imaging procedures where circumstances indicate that they are unlikely to improve patient outcome. Some publications have suggested that as many as 20%–50% of high-tech imaging procedures fail to provide information that improves patient welfare and therefore may represent, at least in part, unnecessary imaging services. Overutilization also exposes patients to unnecessary radiation doses and increases the average dose to the population resulting from medical exposures. Overutilization is driven in part by the current payment system for health care services, in which individual imaging costs are reimbursed on a per procedure basis. With this approach, more procedures yield more revenue for both the institution and the physician referring or performing the procedures. There is little control over the number of imaging procedures done during the course of definitive treatment.

It is not uncommon to see prescriptions of PET scans after every 2 cycles of chemotherapy for response evaluation in locally advanced breast cancer, lung cancer and lymphoma etc. Terminal cancer patients with fungating growths and multiple site metastasis have been advised repeated PET scans despite the fact that proper clinical evaluation and simple imaging tests can give you all information about response of palliative CT. Prescribing doctors justify these PET scan by saying that scan adds objectivity to response assessment. According to ASCO guidelines (2013) routine PET scanning for follow up monitoring does not contribute to improved outcomes. They may also increase anxiety due to false positive findings which lead to unnecessary tests and treatment.

In patient with treated HNSCC, a single PET scan with negative finding at anytime after the conclusion of therapy has a NPV(Negative Predictive value) of 91%. With a second PET scan obtained 6 months after the scan with negative findings, the NPV rises to 98% which is sufficient to suspend radiologic surveillance in asymptomatic patients.

With increasing lawsuits, doctors tend to over investigate. This is defensive medicine!! Defensive medicine is defined as diagnostic or therapeutic measures applied principally to safeguard against possible accusations of malpractice rather than to benefit the patient. In a study in USA, 25% of high-tech imaging studies were ordered principally for defensive purposes. In India we don't have definitive date on overutilized imaging modalities.

Many physicians who request PET Scan have little knowledge about the techniques or possible alternative procedures that may yield the same or better information at reduced cost or with less risk to the patient. Some physicians also may have inadequate information about the patient and may request imaging procedures before they examine the patient thoroughly or check to see if imaging results that would obviate the procedures are already available. Referring physicians often are unaware of or choose to ignore practice guidelines that are available to help them request the best imaging procedures for specific patients. Moreover there are no widely accepted protocols or guidelines for the use of PET scan in the surveillance of various cancers leading to potential misapplication or overuse of this technique.

Patients sometimes demand PET Scan because they have read or heard about them, or because they have discovered information about them in the electronic media, including the Internet. They may have received imaging services in the past and believe they should receive them again for the same or new symptoms. Many patients incur little financial liability for imaging services. Many patients have little understanding of the actual benefits of PET Scan, their financial costs, and the radiation doses accompanying PET. PET Scan is increasingly being marketed directly to the public, often with encouragement to individuals to "self-present" to imaging facilities. People go to imaging centre demanding PET Scan for trivial problems. Another example of such studies is the use of PET CT to identify persons who have early-stage cancer. Education of patients and the public is the best means to counteract this source of overutilization of imaging services. Imaging studies are often duplicated when efforts to identify previous examinations are inadequate or unproductive. Duplicate studies contribute to the overutilization of further imaging.

Let us stop this epidemic of PET overutilization!!!

- (1) A national strategy should be developed to address overutilization and increase accountability in radiology and the other health care professions for the appropriate utilization of PET scan.
- (2) A radiology order-entry system should track the ordering history of each referring physician. Scorecard of each doctor practicing in any institution should be prepared and presented to him for utility and futility of PET Scan. Physicians overutilizing PET Scan should be encouraged to review and possibly change his or her ordering preferences. This could substantially reduce overutilization of various imaging studies.
- (3) The guidelines should be well publicized, easily and quickly accessible, and used as they are intended, with deviation from them allowed if deemed necessary in the judgment of the patient's physician.
- (4) We endorse the importance of educating clinicians, and consumers of medical care about the dangers of excessive testing and to set expectations that minimize patient dissatisfaction.



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FUNCTIONAL LIVER VOLUMETRY BY ^{99m}Tc-Mebrofenin HEPATOBILIARY SCINTIGRAPHY BEFORE MAJOR LIVER RESECTION: A NEW BENCHMARK

Introduction : Liver resection or transplantation is the only curative way for patients with primary or secondary liver malignancies. The extent of liver resection majorly relies upon estimated future remnant liver function (FRL-F) which may be compromised in pre-existing liver disease and /or prior chemotherapy. Insufficient FRL-F will increase the risk of post hepatectomy liver failure (PHLF) which is a challenge to treat. Various direct and indirect methods have been developed over the years for estimation of FRL-F. Blood test and clinical status based scores are first in the series of indirect methods for prediction of surgical outcome and assuming liver function. Morphological test based on computed tomography (CT) or magnetic resonance imaging (MRI) volumetry has been the most frequently used preoperative method for future remnant liver volume (FRL-V) calculation and prediction of risk of PHLF. However, these tests assume homogeneous liver function and volume is equal to function which is indeed an exception rather than the rule. Dynamic tests based on Indocyanine green (ICG) clearance and ¹³C-Methacetin breath test (LiMax) estimates global liver function. These functional tests however unable to calculate regional liver function and also assumes homogeneous liver function. Therefore, there is an urge for a test which can calculate global and regional liver function directly and predicts risk of PHLF better.

Hepatobiliary scintigraphy : Hepatobiliary scintigraphy (HBS) is a routine Nuclear Medicine (NM) procedure which exploits its tracer functional capabilities with modern day's Gamma cameras for direct calculation of global and regional liver function. ^{99m}Tc-GSA (99m technetium-galactosyl human serum albumin) and ^{99m}Tc-Mebrofenin have been used so far successfully for this purpose.

^{99m}Tc-GSA scintigraphy : GSA binds to asialoglycoprotein receptor presents only on mammalian hepatocytes on sinusoidal surface. After binding, it undergo receptor mediated endocytosis and lysosomal degradation. Hence, it remains within the hepatocytes and not get excreted into the bile. Due to different receptor mediated uptake in to the hepatocytes, high level of bilirubin will not be interfering GSA uptake [19]. Due to liver is the only site of uptake and not get excreted, 99mTc-GSA produces high quality images for FRL-F calculation. However, availability of GSA is limited to Japan only.

^{99m}Tc-Mebrofenin scintigraphy : Mebrofenin is a type of iminodiacetic acid (IDA). IDA radiopharmaceuticals were originally synthesized for cardiac imaging due to structural similarity with lidocaine molecule. In view of good hepatic extraction and clearance, soon the potential of these IDA radiopharmaceuticals for hepatic imaging was realised. Food and drug administration (FDA) has approved three IDA radiopharmaceuticals for clinical use. These are ^{99m}Tc-lidofenin (HIDA), ^{99m}Tc-disofenin (DISIDA) and ^{99m}Tc-mebrofenin (BrIDA) in their chronological order of approval. Out of these, ^{99m}Tc-Mebrofenin has the highest hepatic extraction, fastest blood clearance and lowest renal excretion. After injection, IDA binds to protein mainly albumin which minimized its renal excretion. Organic anion transporter polypeptide (OATP) located on basolateral membrane of hepatocytes are involved in IDA transport into the hepatocytes. OATP 1B1 and 1B, are able to transport ^{99m}Tc-mebrofenin into the hepatocytes. Thereafter, ^{99m}Tc labelled IDA follow the bilirubin pathway within hepatocyte without undergoing any metabolism or conjugation. IDA radiopharmaceuticals are excreted in to the bile canaliculi by multidrug resistance protein 2 (MDRP2) transporters similar to ICG. Due to same receptor uptake mechanism of IDA and bilirubin, there will be substrate competition in hyperbilirubinemia state. Mebrofenin has the strongest resistance to displacement by high bilirubin and can produce diagnostic image quality with bilirubin level of 20-30 mg/dl. Scanning protocol for ^{99m}Tc-Mebrofenin scintigraphy for hepatic extraction fraction estimation is simple and can easily be reproduced in any NM centre.

Clinical use of ^{99m}Tc-mebrofenin HBS in preoperative estimation of FRL-F and risk assessment for PHLF before major liver resection :

Various clinical studies in last two decades have shown a notable impact of ^{99m}Tc-Mebrofenin HBS in preoperative workup before major liver resection. Ekman et al. (1992) first described the method for measuring hepatocytes function by IDA clearance rate. Erdogan et al. reported the first clinical study on assessment of liver function in 54 patients with ^{99m}Tc-Mebrofenin and compared it with the 15 min ICG clearance rate (ICG-C₁₅). He found a significant correlation (r = 0.81) between 99mTc-Mebrofenin blood clearance rate at 15 min (Mebro-C₁₅) and ICG-C₁₅. In a small study, Bennink et al reported that HBS was an easily reproducible technique and a strong positive association (r=0.95) between the remnant liver function determined preoperatively and the actually measured value one day postoperatively. Besides function information, HBS can also be utilised to see segmental difference, biliary clearance and post operative biliary complications which make this technique unique.

Dinant et al. investigated the role of preoperative ^{99m}Tc-Mebrofenin HBS in post-hepatectomy liver failure and compared it with CT volumetry. Preoperative FRL-F was found to be significantly low in patient suffered from post-hepatectomy liver failure and liver failure related mortality. However, CT volume of the future remnant was not significantly associated with any of the outcome parameters. On receiver-operating-characteristic (ROC) analysis, patients with uptakes above 2.5%/min/BSA had a 3% chance liver failure and uptake below 2.5%/min/BSA had a 56% chance of liver failure. On multivariate analysis, uptake was the only significant factor associated with liver failure.

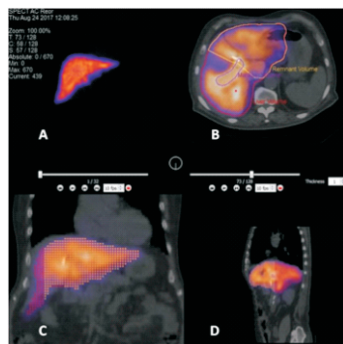
In a study of 55 high risk patients undergoing major liver resection, a cut-off value for FRL-F of 2.69%/min/m² identified patients who developed post operative liver failure with sensitivity 89%, specificity 87%, negative predictive value (NPV) 97.6% and positive predictive value (PPV) 57%. Hence, a high risk patient underwent major liver resection with FRL-F more than 2.69%/min/m² had 2.4 % risk of liver failure. Further it was found that total hepatic function by HBS was significantly lower in patient with parenchymal liver disease while non-tumor total liver volume (NTTL-V) was significantly larger in compromised liver patients. This equation suggested that form is not equal to function. In correlation of FRL-F and FRL-V, patients with normal liver showed good (r = 0.71) while patients with compromised liver showed moderate (r = 0.61) correlation. Chapelle et al. compared 88 patients future liver remnant volume (^{MRI}FLR-V) measured on MRI and effective FRL-F (eFRL-F) calculated by multiplying ^{MRI}FLR-V by TL-F by ^{99m}Tc-Mebrofenin scintigraphy. eFLRF cut off of 2.3%/min/m² was the only independent predictive factor for PHLF with sensitivity, specificity, NPV and PPV of 92%, 98%, 99%, and 92% respectively.

Clinical role of ^{99m}TcMebrofenin HBS for portal vein embolization stratification before major liver resection : Portal vein embolization (PVE) is the well accepted procedures to increase the FRL-F before major liver resection. Procedure not only reduced the chance of PHLF

but also helps in fast recovery. Cieslak et al. reported 163 patient's data underwent major liver resection with inclusion of ^{99m}Tc -mebrofenin HBS in preoperative work up with a cut-off $2.7\%/ \text{min}/\text{m}^2$ in decision making. 29/163 patients underwent (PVE) due to $\text{FRL-F} < 2.7\%/ \text{min}/\text{m}^2$ while other 134 patients underwent surgery with no PVE due to sufficient FRL-F . 8/29 patients underwent PVE due to insufficient FRL-F despite sufficient FRL-V . There was no significant difference noted in postoperative outcome in both groups. In comparison to a historical cohort ($n=55$) before implementation of HBS in preoperative work up to patient cohort ($n=134$) who underwent upfront surgery due to sufficient FRL-F with no PVE, there was significant difference seen in post operative outcome in terms of morbidity and mortality due to liver failure. Hence it was concluded that implementation of HBS in preoperative workup before major liver resection led to functional orientation to PVE decision and better post operative outcome.

FRL-F was also being investigated for hypertrophy response following PVE by Cieslak et al. Post PVE FRL-F cut-off of $2.7\%/ \text{min}/\text{m}^2$ was considered as sufficient function. On ROC analysis, 33 chemotherapy naïve patients with pre PVE FRL-F cut-off of $\geq 1.72\%/ \text{min}/\text{m}^2$ was considered safe to identify sufficient hypertrophy response 3 weeks after PVE with sensitivity of 81.3% and specificity 82.4%. 33 patients who received neo-adjuvant chemotherapy, a cut-off of $1.92\%/ \text{min}/\text{m}^2$ was able to distinguish responder from non-responder with sensitivity of 62.5% and specificity 71.4%. Overall PVE led to $1.00\%/ \text{min}/\text{m}^2$ median increase in FRL-F in 3 weeks with median increase of $0.32\%/ \text{min}/\text{m}^2$ per week. By identifying PVE non-responder, patients may be considered for associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) which has better hypertrophy response.

Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is a paramagnetic hepatobiliary specific MRI contrast agent. It is actively taken up by hepatocytes by OATP 1B_1 and 1B_3 receptor and excreted in to bile by MDRP2 similar to mebrofenin. MRI is the investigation of choices for identification and characterization of liver lesion. Due to better temporal and spatial resolution researches started using Gd-EOB MRI for assessment of FRL-F . In a recent study ($n=14$) comparing ^{99m}Tc -mebrofenin HBS and Gd-EOB-DTPA enhanced MRI for evaluation of right and left lobe liver function in post PVE patients has claimed a significant correlation. However, we need to remember that only 50 % of Gd-EOB-DTPA is taken up by normal hepatocytes and rest excreted by kidney and in hyperbilirubinemia state renal excretion will further increase and its accuracy may reduce. Routine clinical availability is another concern for Gd-EOB-DTPA enhanced MRI.



Conclusion : ^{99m}Tc -Mebrofenin HBS is a unique procedure for calculation of global and regional liver function. This takes into account the non-uniformity of liver function and underlying liver pathology. Moreover a single cut-off might fit in all for PHLF risk assessment and PVE stratification.

Figure 1: ^{99m}Tc -Mebrofenin SPECT-CT functional volumetry. Image B is showing volume of interest (VOI) for liver and remnant functional volume. VOI on right hepatic duct is showing average liver activity now.

Dr. Manoj Gupta, Consultant - Nuclear Medicine
Dr. P. S. Choudhury, Director - Nuclear Medicine

Case Vignette

Rajiv Gandhi Cancer Institute & Research Centre, Niti Bagh

THE ROLE OF SYMPATHETIC NERVE BLOCKS IN BREAST CANCER RELATED LYPHHEDEMA TREATMENT

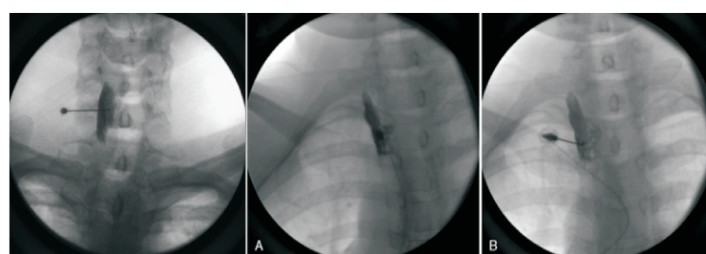


Pre Nerve Block Post Nerve Block

The following is a case of Lymphedema of the Right Upper Limb in a 59 year old breast cancer survivor. During the course of her treatment, she developed swelling of the right upper limb associated with pain [VAS 6/10], redness and hardness of the skin, tightness, unusual sensations and restricted range of motion. She was evaluated in the Department of Pain Management at Rajiv Gandhi Cancer Institute, Niti Bagh and counseled for Total Sympathectomy of the right upper limb. She was also prescribed conservative treatment in the form of exercises, massage, sequential compression stockings and limb elevation. After informed consent, patient was administered right sided Stellate ganglion block at C6-C7 level [1% Lignocaine + 20 mg Depot Methylprednisolone: 1.5 cc at each level] and T2-T3 sympathetic block [1% Lignocaine + 20 mg Depot Methylprednisolone: 5 cc at each level] under fluoroscopic guidance and local anaesthesia. Patient had complete pain relief [VAS 0/10] along with reduction in swelling on diagnostic block after which Radiofrequency ablation was done.

Sympatho-afferent coupling regulates the lymphatic flow; therefore sympathectomy of the upper limb relaxes the veins, thereby reducing the post-capillary resistance, hence releasing the accumulated interstitial fluid into the venous system. This theory has been proven by increased lymphatic flow on Lymphoscintigraphy in previous studies.

We propose Sympathetic blocks to be a viable and minimally invasive option in Breast cancer related Lymphedema to halt the progression from mild to moderate/severe lymphedema, particularly in subjects who respond poorly to conservative management.



Stellate ganglion and T2-T3 sympathetic nerve block

Dr. Sunny Malik
 Consultant - Interventional Pain Management

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CANCER CASE CAPSULE COMPETITION



RGCIRC's DNB team presented a case of aggressive blood cancer in which cutting edge modern technology targeted therapy was used in elderly man who presented with advanced blood cancer in serious condition. The team including Dr. Sneha Bothra from Medical Oncology and Dr. Venkata Pradeep Babu K from Medical Oncology, Dr. Sravya from Radiation Oncology, Dr. Taruna Goel from Nuclear Medicine and Dr. Divya from Pathology from RGCIRC under the mentorship of Dr. Dinesh Bhurani, Director – Hematology & BMT and Dr. Rayaz Ahmed, Sr. Consultant - Hematology & BMT, contested against AIIMS team and won the prize in hematology and overall championship at the C4 case capsule event. Dr. Vineet Talwar, Director – Medical Oncology concluded by encouraging the students to participate in various conferences across India and abroad.

CME - IMA KANPUR

RGCIRC organized a CME in association with IMA Kanpur on Sunday, 31st March 2019 at Lofty Hall, Ganges Club, Arya Nagar, Kanpur. Dr. Mudit Agarwal, Sr. Consultant – Head & Neck Surgical Oncology delivered a lecture on Advances in Head & Neck Surgical Oncology and Dr. Abhishek Bansal, Consultant – Interventional Radiology spoke on Interventional Radiology – Treatment Paradigms to Help Your Patients in the said CME.



CME – IMA LUDHIANA



RGCIRC organized a CME in association with IMA Ludhiana on Friday, 5th April 2019 at IMA Bhawan, Ludhiana, Punjab. Dr. Vineet Talwar, Director – Medical Oncology delivered a lecture on Early Detection and Diagnosis in Cancer and Dr. Manish Pruthi, Consultant – Musculoskeletal Oncology spoke on Bone and Soft Tissue Tumors – Impact on Society in the said CME.

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