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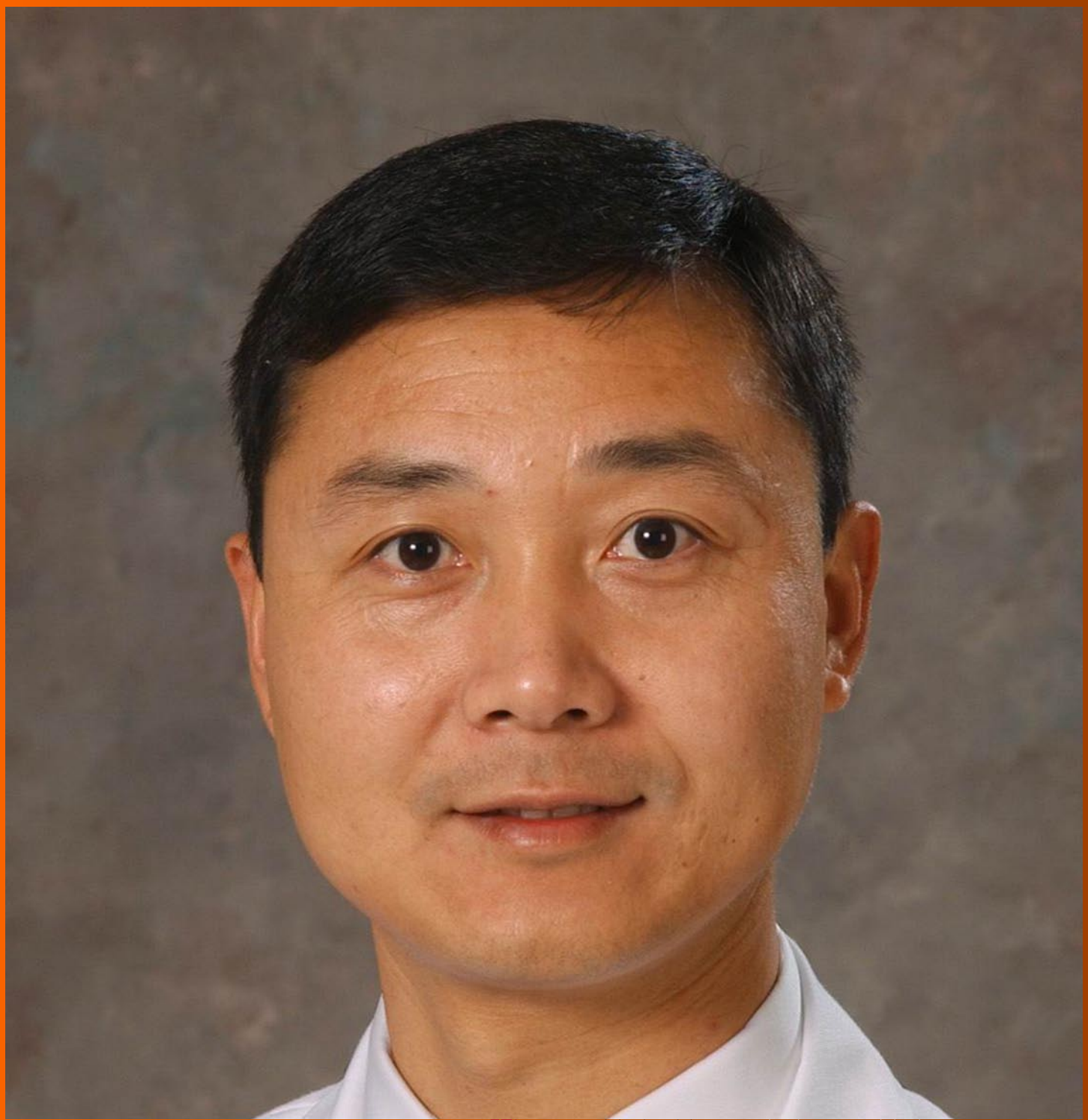

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MINIREVIEWS

Radiographic and magnetic resonances contrast agents: Essentials and tips for safe practices

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Abstract

With extended and continued expansion of medical imaging utilization in modern medical practice over last decade, radiologists as well as other faculty staff dealing with radiographic and magnetic resonances contrast media (CM) have to be well oriented with their potential hypersensitivity reactions and recognize high-risk groups liable to develop it so as to enable early recognition. Radiologists and other medical staff involved in administration and dealing with CM have to be ready to implement prompt, practical and effective management plan to deal with these scenarios should they emerge. Strategies to prevent potential contrast-induced acute and delayed renal injuries have to be routinely exercised. Paying attention to the pregnant and nursing women, pediatrics, diabetics, as well as other fragile populations is of utmost importance for patient safety during contrast administrations. Radiologists should play a pivotal role in orienting patients about necessity to use CM for their imaging studies, in case it is needed, and assure them about its safety. Moreover, they have to be oriented with the medico-legal issues related to use of CM. These will pay as improved patient safety as well as safe daily working environmentat different levels of radiology practices.

Key words: Radiographic; Magnetic resonances; Contrast; Safe practice; Medico-legal

Core tip: Radiologists have to be oriented with the potential hypersensitivity reactions of radiographic and magnetic resonances contrast media (CM) and able to recognize high-risk groups liable to develop such reactions. Effective management plans have to be ready to implement should these scenarios emerge. Strategies to prevent potential contrast-induced acute and delayed renal injuries have to be exercised. Caring for special considerations as well as other fragile populations is of utmost importance for patients' safety. Moreover, radiologists should be oriented with

the medico-legal issues related to use of CM. These will be conveyed as improved patients' safety and safe radiology practices.

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INTRODUCTION

Advances in the field of medical imaging over last decade, notably for multi-detector computed tomography (MDCT) and magnetic resonances imaging (MRI) have been associated with increased use of contrast media (CM). Likewise, the extended spectrum of therapeuticinterventional procedures in different body organs, using imaging guidancetools, has expanded the use of CM.

Although CM are generally safe, their allergy-like reactions may be mild needing just observation and patient reassurance or may rarely result in potential life threatening conditions. Thesesituations impose a day to day challenge for radiologists and allied medical staff at different levels of radiology practices. Hence, radiologists and medical personnel involved in CM administration have to be oriented to the justifications for their useand stratification of risk factors that increase the likelihood of patients to develop adverse reactions to CM. Moreover, they have to be able to recognize these adverse reactions once they show up and promptly as well as effectively deal with it for patient safety. Besides, radiology practice personnel have to familiarize themselves to the medico-legal caveats associated with their practices. They should develop their own protocols for safe practice should CM administration be required. This review aims to highlight an updated discussion about these aforementioned hot issues related to use of CM in our daily work.

CM: ESSENTIAL KNOWLEDGE

CM are pharmaceutical formulas that have been used to supplement the capabilities of various medical imaging modalities. They can be administered *via* different routes; the most widely used, and subject of the current review, is the intravenous access.

Describing the different types, classifications, uses and rout of administrations is beyond the scope of this review. However, a summary of the essential knowledge, for every radiologist, about current available CM will be underscored briefly in the next paragraphs.

Based on the differential attenuation of iodine by ionizing radiation, iodine-based contrast agents are used for contrast-enhanced radiographic and MDCT procedures[1]. Physico-chemically; iodine-based contrast agents may be grouped according to their: (1) ionicity (to ionic or nonionic CM); (2) osmolality into high osmolar CM (HOCM), low-osmolar (LOCM), or iso-osmolar (IOCM); and (3) the number of benzene rings (either monomeric or dimeric CM)[2]. Owing to the contemporary implementation of non-ionic IOCM and LOCMin clinical imaging practices worldwide with withdrawal of HOCM, our discussion on iodinated CM will focus onto the non-ionic (iso- and low-osmolar) CM.

On the other hand, gadolinium-based contrast agents (GBCAs) are used to enhance MR examinations, thanks to their ability to alter the relaxivity of infused tissues; largely[3]. However, they can provide physiologic data derived from proton density and flow within the induced field depending of the weighting of the image[4].

Likewise, GBCAs are commonly grouped according to their: (1) pharmacokinetics (either extracellular or organ specific and the extracellular GBCAs may be further sub-classified into blood-pool agents and; interstitial extra-cellular agents); (2) the chelating ligand molecular design (either; macrocyclic or linear); and (3) their ionicity (ionic or nonionic)[2].

EPIDEMIOLOGY OF CM REACTIONS

In general, CM (both iodinated and gadolinium based) are safe drugs with very low incidence of adverse reactions[5]. Hypersensitivity reactions to CM are generally sporadic and unpredictable[2,5-7]. The incidences of mild to moderate CM reactions are commoner for iodinated CM than gadolinium-based chelates[2,6,7]. Moreover, the hypersensitivity to non-ionic iodinated CM is far rare compared to their ionic correspondents[2,5,6] (Table 1). highlights the salient predisposing risk factors and populations at risk for development of acute adverse reaction to CM. Age extremes populationsare at high risk for developing mild to moderate hypersensitivity reactions to CM[8,9]. The incidence of severe sensitivity reaction doesn't differ between different CM agents including the gadolinium chelates[10,11].

An overall major determinant of patient's intolerance to CM administration is a history of a previous severe reaction to a contrast agent[8,9]. This increases the likelihood of the patient to develop a life-threatening hypersensitivity reaction by 3-6 fold[2]. Other major determinants are active generalized allergic tendencies (*e.g.*, asthma, hay fever, *etc.*) and compromised renal functions[5,10,12]. However, controlled atopies; including asthma don't preclude patients to have intravenous CM when necessary[12].

Recognizing these factors could be achieved *via* scrutinizing patient's history cautiously. Thomsen[2] proposed a simplified questionnaire to simply identify high-risk patients liable to suffer CM-induced renal complications by asking the patient seven critical

Table 1 Risk factors that predispose patients to contrast medium reactions

Patients with a prior history of allergy to CM (3-6 folds)
Patients with a prior history of allergic reactions to drugs and foods
Patients with generalized atopic tendencies (*e.g.*, asthma and hay fever)
Dehydration states
Age extremes (less than 5 yr and older than 60 yr)
Serious illness and chronic debilitating conditions, *e.g.*, CVS diseases and renal failure
Anemia
Certain co-medications, *e.g.*, β-blockers and metformin
Malignancies
Patient's anxiety due to public concerns about CM-induced reaction

CM: Contrast media; CVS: Cardiovascular.

Table 2 Co-morbidities indicating renal profile checkup prior to contrast agent administration

Age extremes	Older than 60 yr and less than 5 yr
History of relevant renal disorders	Anatomic variations: Solitary kidney and horse-shoe kidney
	Renal surgeries
	Renal endangering medications, *e.g.*, NSAIDs and chemotherapy
	Renal-induced nephropathy (prior)
	History of prior renal dialysis
	Renal malignancies
Nephropathy-associated chronic diseases	*E.g.*, uncontrolled DM, hypertension and hyperuricemia
Drugs interfering with renal excretions	Metformin

NSAIDs: Nonsteroidal antiinflammatory drugs; DM: Diabetes mellitus.

questions: Whether the patient had or has: (1) renal disease; (2) previous renal surgery; (3) proteinuria; (4) diabetes mellitus; (5) hypertension; (6) gout; and (7) recent administration of nephrotoxic drugs]. The authors thought that adding two more critical questions, which are (1) whether the patient had underwent a contrast-enhanced imaging study or not? and (2) if any, what was his/her experience with it? May expand the benefit of this questionnaire to be more global for identification of most high-risk patients are prone to develop CM induced hypersensitivity.

PATHOGENESIS OF CM HYPERSENSITIVITY

In spite of different postulations, the exact nature of CM hypersensitivity reactions is not clearly understood yet. The osmolality and chemotoxicity of a contrast agent are thought to be major determinants of its adverse reaction liability[13,14].

For immediate hypersensitivity reactions, both the Ig-G mediated mechanisms (allergy-like) and the unpredictable non-allergic (idiosyncratic) mechanisms, thought to depend on the chemotoxic effects and physico-chemical properties of the agent, are plausible. For either pathway, cell-membrane injury of basophils and mast cell with subsequent release of histamine; bradykinins; and other inflammatory mediators is the main event[14,15]. Also, activation of the clotting factor XII with subsequent activation of kinin system as well as cyclo-oxygenase and lipoxygenase inflammatory pathways and production of bradykinin, prostaglandins and leukotrienes is thought to mediate the CM induced respiratory and cardiovascular manifestations presented in moderate and severe hypersensitivity reactions[13,16].

Recent research revealed that iodine is the initiating factor in immediate and delayed sensitivity reactions to iodinated CM[17]. Consequently, hyper-osmolar contrast agent use has been largely replaced in clinical imaging practices, over last two decades, with worldwide shift towards their non-ionic counterparts (whether; iso- or low-osmolar CM) thanks to improved safety profiles of these agents[18].

Similarly, recent researches emphasized that immediate and moderate hypersensitivity reactions to GBCA may occur with high incidence in females, patients with history of allergies and previous reactions to CM[6]. Notably, severe hypersensitivity reactions to GBCA were higher for abdominal examinations rather than brain and spines[6]. Although an Ig-E mediated mechanism was suggested, the exact mechanism hasn't been elucidated. Interestingly, these hypersensitivity reactions seem to vary between various GBCA in different studies with no solid evidence whether it depends on the specific characteristics of gadolinium-based structure or not, at least for the GBCA immediate reactions[7,19,20]. On the contrary, delayed CM hypersensitivity reactions are thought to be T-cell mediated[10,14].

SERUM CREATININE SCREENING BEFORE CM EXAMINATIONS

Based on the safety profile of CM in clinical use nowadays, adequate screening questions as mentioned earlier, mitigates the need to have recent serum creatinine level done in normal average adults in most radiology practices[2,5,10,21]. However, having a laboratory renal profile for fragile patients due to senility and/or chronic debilitating disorders is highly advisable, especially in elective examination. Many patient co-morbidities require intentional lookup of the patient's renal profile (Table 2).

Renal creatinine is the widely acceptable indicator for renal function. The agreed upon simple general practices are to administer CM in patients with creatinine $\leqslant$ 1.5 mg/dL, be cautious in patients with creatinine in the range of 1.6-2.0 mg/dL, and to avoid contrast in patients with creatinine > 2.0 mg/dL[8,9].

Other groups suggested relying on estimated glomerular filtration rate (eGFR) as reliable indicators

Table 3 Common elective premedication protocols for high-risk patients to develop iodinated contrast medium hypersensitivity reactions

Elective		Emergency
Lasser protocol	**Greenberger protocol[1]**	**IV protocols (in descending order of desirability)**
Oral prednisone 50 mg at 13/7 and 1 h before contrast medium injection	Oral methylprednisolone 32 mg at 12 and 2 h before contrast medium injection +/-	Methylprednisolone sodium succinate 40 mg OR hydrocortisone sodium succinate 200 mg every 4 h till examination + diphenhydramine 50 mg *IV* - 1 h
+ (oral/IM or *IV*) diphenhydramine 50 mg just 1 h before examination	+/- (oral/IM or *IV*) diphenhydramine 50 mg just 1 h before examination	No corticosteroids at all (not preferable) Only diphenhydramine 50 mg *IV*

[1]IV hydrocortisone 200 mg may be a substitute for oral prednisone, if the patient cannot tolerate oral medication.

of renal function in adults, as it consider age, gender and ethnic variations[22,23]. eGFRs between 30 and 60 mL/min per 1.73 m^2 requires precautions to be practiced to avoid contrast induced renal injuries and needs close post-procedural monitoring of renal functions[8,9,22,23].

In emergency examinations requiring CM administration, reliance on urine dipstick check for creatinine done in the emergency room was suggested as a predict for serum creatinine along with adequate history taking[24,25]. Although no consensus exists regarding serum creatinine and CM administration time window, a renal profile done within last 30 d is an acceptable recent documentation in general[9,26]. The authors recommend shorter time-intervals for high-risk groups, however.

Concerns about volume of used iodinated CM and the usage of absolute rather than the absolute and relative creatinine levels are on the rise, more recently, to avoid systematic inaccuracies in assessment of renal function and avoid contrast-induced nephropathy[27,28].

PRE-MEDICATIONS FOR PATIENTS AT RISK

Premedication before IV contrast administration is a well-known and widely practiced protocol that aims to reduce the incidence of mild to moderate adverse reactions to iodinated CM, primarily[29,30]. However, the possibility of severe reactions occurrence albeit rare is unaffected by premedication regimens[16].

Corticosteroids are the critical component of any premedication regime. The use of antihistamine alone or as a supplement to corticosteroids is a customary practice[8,9]. The mechanism of action of both drug groups is still controversial yet they are thought to interfere with the mechanisms of antigen-antibody response and actions of the released mediators[31]. However, the sole use of antihistamines did not prove to be working alone in prevention of contrast-induced hypersensitivity reactions[32]. Two common elective premedication protocols, the Lasser[33] and the Greenberger[34] (Table 3), are widely implemented and supported by recognized bodies[8,9].

HYDRATION (EXTRACELLULAR VOLUME EXPANSION)

The osmolality of iodinated CM was postulated to cause extracellular fluid shifts, leading to cell dehydration and increased intracellular fluid viscosity, which precipitates cellular dysfunction[35].

Volume expansion appears to be an amenable effective strategy to obviatecontrast induced nephropathy (CIN). A practical hydration regime has to be initiated before and be continued for several hours after CM administration[36]. Various hydrations regimens either *via* oral and/or IV administration of crystalline solutions are available including normal and half-strength saline's, sodium bicarbonates infusion, N-acetylcysteine and statins[37]. Yet the privileges of one over another have not been effectively established; thanks to limited studies done in patients receiving IV CM for diagnostic purposes[36,37].

ADVERSE REACTIONS TO CM

CM adverse reactions are usually grouped according to their emergenceand necessity for interventioninto: (1) acute; happening during or within the 1st hour following injection; (2) late, presenting up to 1 week thereafter; and (3) very late group that surfaces weeks to months following contrast administration. However; for easy academic deliberation, we will consider it under two main categories, the (1) immediate (acute) adverse reactions; occurring up toone hour from injection; and the (2) non-immediate (delayed) reactions; occurring later on. Furthermore, for the increased awareness

Table 4 Severity scale, signs, symptoms and management options of adverse reactions to contrast media

Category of reaction	Symptoms	Treatment
Mild (self-limited without evidence of progression)	Hives, rashes and sweats	Patient reassurance usually suffices in some cases
	Nasal symptoms	Close observation till resolution of symptoms
	Nausea, vomiting	May require symptomatic treatment in some cases
	Pallor	
	Cough	
	Flushing	
	Warmth	
	Chills	
	Headache and/or Dizziness	
	Self limited anxiety	
Moderate (signs and symptoms are more pronounced)	Generalized or diffuse erythema	Requires prompt treatment
	Tachycardia/bradycardia	Requires close, careful observation for possible progression to a life-threatening event
	Bronchospasm, wheezing and/or dyspnea	
	Hypo- or hyper-tension	
	Voice hoarseness	
Severe (sign and symptoms are often life-threatening)	Laryngeal edema (severe or rapidly progressing)	Requires hospitalization and aggressive treatment by emergency teams
	Convulsions	
	Profound hypotension	
	Unresponsiveness	
	Clinically manifest arrhythmias	
	Cardiopulmonary arrest	

by renal side effects of different CM these will be sub-classified into renal and non-renal reactions.

IMMEDIATE NON-RENAL ADVERSE REACTIONS TO CM

From practical point of view we will describe it as mild, moderate and sever reactions. Table 4 shows the immediate non-renal adverse reactions and their common manifestations as well as the general guidelines that every radiologist and/or medical staff dealing with CM reactions hasto be oriented with.

In general, the majority of reactions to CM areof the mild form in form of hives and nausea[5-7] and occurs within the first minutes following CM administration while severe and potentially life-threatening reactions to intravascular CM occur within 20 min after contrast administration[5,6,11,19]. It is recommended to keep patients under observation for 20-30 min in the radiology department after contrast medium injection[8,9]. This is of special consideration for the pediatrics population who can't verbally communicate.Mild reactions may require no more than observation, patient re assurance and/or a dose of an antihistaminic. In moderate to severe adverse reactions more therapeutic interventions will be implemented.

Every radiology practice has to be equipped with a general emergency cart loaded with up to date medications and instrumentations used in dealing with CM-induced reactions[8-10]. A cooperative plane with concerned emergency teams should be put into effect in hospitals to deal with severe reactions to CM.

BREAKTHROUGH REACTION

A breakthrough reaction refers to a reaction that occurs after iodinated CM injection in patients who have already been intentionally pre-medicated to prevent CM sensitivity reaction[31]. So, they are patients who are principally labeled as being at high risk for a reaction. Severity of reaction is more or less similar to those of the initial reaction and needs likewise treatment. Practically, these patients should be advised that they are likely to be at increased risk for more severe reactions if iodinated contrast material is administered in the future. Furthermore, radiologists have to recommend other alternative safe imaging modalities to help with their diagnoses.

IMMEDIATE RENAL ADVERSE REACTIONS TO CM

Iodinated CM may cause disturbed renal functions known as contrast induced-acute kidney injury (CI-AKI), that is commonly defined as "abrupt deterioration in kidney function, manifested by an increase in serum creatinine level with or without reduced urine output"[38]. There are more specificdiagnostic criteria for diagnosing (CI-AKI) delineated by the consensus gentium of concerned major concerned bodies (Table 5)[39]. Dehydrated, debilitated and high-risk chronic illness fragile patients, especially the diabetics, are more prone to develop CI-AKI[22,40-42]. CI-AKI is likely to

Table 5 The criteria for diagnosing contrast induced-acute kidney injury

Absolute serum creatinine increase of greater than or equal to 0.3 mg/dL (> 26.4 μmol/L)
An increase in the percentage of serum creatinine of greater than or equal to 50%
Urine output reduced to less than or equal to 0.5 mL/kg per hour for at least 6 h

Table 6 European medicines agency nephrogenic systemic fibrosis-risk stratification categorization of gadolinium-based contrast agent

GBCA NSF-risk class	Scientific (generic) name
Highest risk of NSF	Gadodiamide (Omniscan®)
	Gadopentetatedimeglumine (Magnevist®)
	Gadoversetamide (Optimark®)
Intermediate risk of NSF	Gadobenatedimeglumine (Multihance®)
	Gadofosvesettrisodium (Vasovist®, Ablavar®)
	Gadoxetate disodium (Primovist®, Eovist®)
Lowest risk of NSF	Gadobutrol (Gadovist®)
	Gadoteratemeglumine (Dotarem®)
	Gadoteridol (Prohance®)

NSF: Nephrogenic systemic fibrosis; GBCA: Gadolinium-based contrast agent.

be the result of burden of coexistent morbidity rather than the CM itself. Moreover, this depends on the base line renal profile[22,42,43]. Moreover, it was noticed that CI-AKI is more likely to develop in patients undergoing intra-arterial use of contrast above the level of renal arteries more than in patients undergoing Ⅳ administration of the CM[41].

EXTRAVASATION

Extravasation refers to the escape of contrast material from the vascular lumen with infiltration of the interstitial tissue around injection site during injection. It is reported to be less than 1% and is not directly correlated with injection[44]. The physician has to promptly recognize and evaluateit to reduce the chance and severity of injury. The staff in charge of CM injections should: (1) check the adequacy of vascular access; (2) adjust injection rate; (3) council the patient to report any unpleasant sensations at the injection site; and (4) monitor the injection site during and/or following the procedure.

If extravasation commences the injection should be withheld, assessment is done. Small and limited extravasations are self limited and just need monitoring, reassurance, hot and cold foments. Large injurious extravasations may require surgical intervention[45].

DELAYED NON-RENAL ADVERSE REACTIONS TO CM

Delayed contrast hypersensitivity is defined as a reaction that occurs 1 h to 1 wk following iodinated contrast administration. They are usually limited to skin rashes and occasionally mild and self limited. Originally, these reactions were reported to be associated with the non-ionic iso-osmolar iodinated CM[8,9]. However, recent reports addressed its occurrencefollowing GBCA[11,19].

Iodine-provoked thyroid dysfunction

Iodinated CM have a free iodine content that is greatly higher than average daily human needs[46]. In general, it is contraindicated to administer iodine based CM intra-vascularly to patients at risk of thyrotoxicosis[2,9].

Iodine-provoked thyroid dysfunction is a self-limited, relatively rare entity of transient altered thyroid hormones in the blood in response to high load of free iodine following intravenous administration of iodinated CM (disrupted auto-regulation)[46,47]. Subjects with normal thyroid function are not at risk[47,48]. The problem is for patients with hyperthyroid states, *e.g.*, thyroid autonomy and graves' disease who become deprived of thyroid hormones and need treatment adjustments. Theoretically speaking; long term suppression may end with hypothyroidism[46].

Another caveat is patients planned for radio-active iodine scanning. In this population, the use of iodinated contrast agents has to be postponed after planned radioactive iodine imaging or therapy. Excess free iodine following Ⅳ administration of iodinated CM will saturate its receptors and result in sub-optimal or non-diagnostic studies and/or management of their disease[2]. A noteworthy point to mention here, is that iodinated CM used during ^{18}FDG-PET/CT do not have a dumping affect on the clinical assessment of these studies[49,50].

Reports about iodine-provoked thyroid dysfunction following non-vascular uses have emerged recently and the issue has to be monitored by radiologists[51-53].

DELAYED RENAL ADVERSE REACTIONS TO CM (NEPHROGENIC SYSTEMIC FIBROSIS)

Actually, all iodinated CM have a nephrotoxic potential yet variable potentialities exist for GBCA[10,11,19]. Table 6 shows the popular classification of commercially available GBCA by European Medicines Agency EMA[54].

Nephrogenic systemic fibrosis (NSF) is a serious progressive clinico-pathologic entity that may progress to be fatal. It has no associated imaging findings. NSF came into attention more than a decade earlier and has been described to develop in patients with compromised renal functions[55-57]. Clinically, it is a diagnosis of exclusion that can be suspected in patients showing variable skin rashes up to subcutaneous scleroderma-like plaques as well as variable systemic manifestations who received a GBCA[57,58]. However, these should be coupled with histological findings[58]. Although its pathogenesis has not been agreed upon, postulations assumed that weak stability of gadolinium chelates leads to its free dissociation in tissues and incite a fibrotic response in different body tissue. Association with linear; more than the macro-

Table 7 Strategies for safe clinical practice of contrast media to reduce risk for renal complications in patients with renal problems

Patients with SCr ≥ 2 g/dL and/or eGFR ≤ 60 mL/min per 1.73 m^2	Withhold contrast whenever possible and use alternative imaging modalities if feasible Adequate hydration
Patients with end-stage renal disease who still produce urine	Consider alternative diagnostic study if feasible Avoid use of CM whenever possible Use lowest possible dose of contrast Use intermediate to low osmolar and/or low risk GBCA followed by prompt dialysis if the patient is already undergoing dialysis
Patients with end-stage renal disease who are anuric	Can receive routine volumes of intravenous contrast material without risk for further renal damage or the need for urgent dialysis

GBCA: Gadolinium-based contrast agent; CM: Contrast media; eGFR: Estimated glomerular filtration rate.

Table 8 Practical guidelines for safe contrast media-metformin interaction

Renal function (eGFR-indexed)	Action
Patients with normal renal function (eGFR ⩾ 60 mL/min per 1.73 m^2)	No need to withhold metformin
Patients with compromised renal function (eGFR ⩾ 30 but ⩽ 60 mL/min per 1.73 m^2)	Withhold metformin for 48 h Re-institution after renal function monitoring
Patients with compromised renal function (eGFR < 30 mL/min per 1.73 m^2)	Have not to be on metformin Consult nephrologist

eGFR: Estimated glomerular filtration rate.

cyclic; formulas of GBCA is supportive for these assumptions[59,60].

POPULATIONS WITH SPECIAL CONSIDERATIONS

Patients liable to and/or actually have renal compromise

It is of utmost importance for radiologists to identify patients withrenal compromise in advance using same screening tips for identifying high risk groups, discussed in earlier section (Table 1). So radiologists can adhere to some precious strategies for safe clinical practice of CM to reduce risk for NSF (Table 7).

The use of renal protective agents such as N-acetylcysteine, sodium bicarbonate, diuretics, and theophylline is debatable and has not proven great benefits[36]. The previous recommendations of hemodialysis in patients at high risk for CM-associated complications are no longer sound and consulting a nephrologist is a wisdom practice[61].

METFORMIN

Metformin is an oral anti-hyperglycemic agent, commonly, used to treat patients with non-insulin-dependent diabetes mellitus. Metformin is excreted unchanged in the urine. However, in the presence of renal failure, either pre-existing or induced by iodinated contrast medium, metformin may potentially accumulate in sufficient amounts to cause lactic acidosis. Hence, radiologists have to cautiously approach those patients for safe practices considering the potentiality for contrast-induced renal injury with subsequent metformin use co-morbidity (Table 8)[2,8,9]. For GBCA, there is no necessity to discontinue metformin before examinations, however[9].

PREGNANT AND NURSING WOMEN

Although iodinated contrast agents and gadolinium cross the placenta in little traces reaching the fetus, no definite gene mutation or teratogenic effects have been reportedin human[62,63]. The large scientific bodies in radiology[8,9] recommend that, no contrast should be administered to the pregnant mother unless there is prudent need to intervene to save both mother and baby, based on these contrast-enhanced studies. Furthermore, post-natal assessment of neonatal thyroid function has to be carried if the administered CM was iodine-based[53,64] while this is not of clinical utility for the GBCA[8,9,63].

Small traces of iodinated contrast material or GBCA are excreted in breast milk and absorbed by the infant with no reports of fetal reactions to the best of author's knowledge. So, breast feeding abstinence following contrast studies of nursing women is not recommended[8,9,26].

PEDIATRICS

Due to limited number of studies, estimating the incidence of reactions to CM in children is difficult. Special considerations have to be weighted when dealing with infants and young children. These include: Fluid shifts in neonates, low weights, immaturity of their renal function, lower (eGFR), fragile vascular access and lack of communicability. Most CM reactions in children are mild and in the form of skin and respiratory reactions. Warming of iodinated CM before administration to children is recommended to increase their viscosity and diminish rates of contrast reaction[65,66]. Other recommendations may include, use of low-osmolality contrast agents, diminishing the volume of contrast given, avoid nephrotoxic drugs and adequate hydration of the patient[67].

GCBA reactions are rare in children and exclusively presented in children with pre-existing renal problems[68]. However, GBCAs use should be limited in children and only used when necessary[9]. Recent

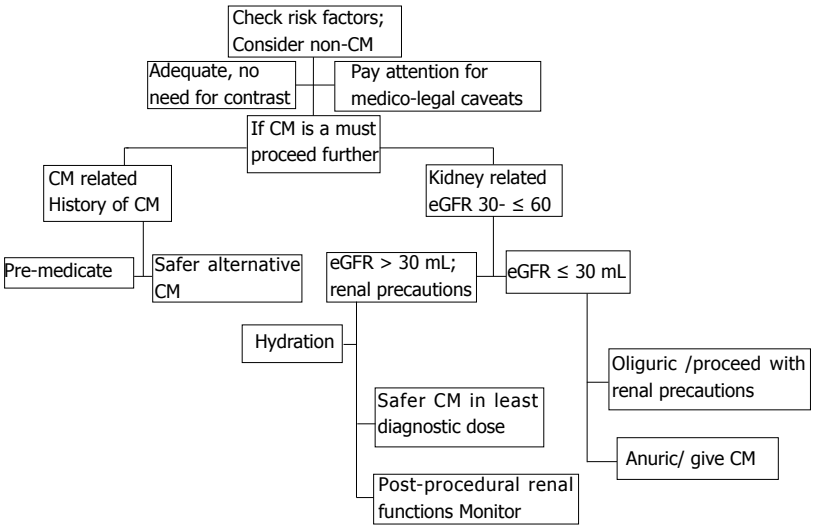

Figure 1 Procedural infographic display for safe clinical practice use of iodinated and gadolinium-based contrast agent for IV use in clinical imaging. CM: Contrast media; eGFR: Estimated glomerular filtration rate.

reports recommended the use of gadobenate dimeglumine (Multihance) in pediatrics of different ages[69].

CM: MEDICO-LEGAL CAVEATS

Informed consent is defined as "a process of a patient-physician communication that results in the patient' s authorization or agreement to undergo a specific medical intervention"[70]. The aim of informed consent is to gather relevant information that makes the procedure both safe and comfortable as possible[26].

With increased daily implementation of different clinical imaging modalities worldwide, obtaining an informed consent remains a practical caveat as it is not possible to achieveits requirements for every running contrast-enhanced imaging procedures[71]. Practically, this is compromised by patient's unfamiliarity with the invisible nature of radiation, its measurements and the probability of its stochastic effects compared to orientation with incisions and intubations for example[72]. Moreover, informed consent timing, work list scheduling and radiologists' discomfort, about discussing CM complications with their patients are added limitations for the classic informed consent process[73]. After all, the patient-radiologist relationship which is brief and episodic, especially for the outpatients basis[72,73].

Based on the aforementioned highlights and the documented evidences that CM are largely safe drugs, a ready to sign informed consent form, by the patient or his/her guardian, is a customary practice worldwide in most radiology practices[26,73]. Previous reports emphasized that adoption of adequate interactive verbal communication, along with providing multi-media approaches, *e.g*., on-site videos, leaflets, educational seminars, *etc*., explaining the benefits of CM use, the rarity of their hypersensitivity reactions, the propensity of these reactions to be mild and transient, the populations at risk for developing it, can effectively relieve the patient's apprehensions and confusions for elective diagnostic imaging as well as interventional procedures requiring the administration of CM[74-76].

The authors thought that conducting those stepsalong with pro-viding an easy to tick, short targeted questionnaire fulfills the aim of informed consent, by identifying high-risk populations to develop CM reactions, and make the process of gaining it is a time-effective and easy routine. Undoubtedly, these routine practices relieve the patient's anxiety and mitigate an important provoking element thought to be involved in developing reactions to CM[77].

Justification for the use of CM based on clinical concerns is the sole responsibility of the radiologist in charge based on regional laws, institutional and departmental policies[8,9].

Another medico-legal caveat is the off-label contrast media (OLCM) which are defined as CM that are used in otherwise originally tested, indicated and licensed purposes, *e.g*., CT and/or MR angiographic, cardiac and arthrographic procedures[73,78]. Although, these applications are proved;by recognized scientific bodies[8,9] as well as scientifically-based well conducted large population and multicenter studies[7]; to be clinically beneficial and are widely used since decades, the use of CM for these examinations remains outside legal boundaries[78,79]. This imparts medico-legal responsibility to the radiologist in charge to divulge exhaustive information to patients and get a documented informed consent from patients before proceeding into such procedures. Shortly, most scientific societies and regulatory bureaus ascertain that radiologists using CM for an off-label indication should judge his/her use based on sound scientific medical evidences and should maintain a record of the

products used and their effects[80].

Lastly, a simple applicable working safety practice hierarchical info-graph for administrating radiographic and MR CM is suggested by the authors (Figure 1).

CONCLUSION

In conclusion, radiologists as well as faculty staffs dealing with radiographic and MR CM have to be well oriented with the potential CM hypersensitivity reactions, high-risk groups liable to develop it and their early recognition. They have to be ready to implement prompt and effective management plan to deal with these reactions should they emerge. Faculty staff dealing with radiographic and MR contrast administrations have to exercise strategies to prevent potential contrast-induced acute and delayed renal injuries and pay attention to the pregnant and nursing women, pediatrics, diabetics, as well as other fragile populations for optimized patient safety. Moreover, radiologistsshould be oriented with the medico-legal issues related to use of CM and play pivotal role in patient learning and assurance about CM safety. These will pay dividends as improved patient safety as well as safe radiology practices and working environment.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical significance of prostate ^{18}F-labelled fluorodeoxyglucose uptake on positron emission tomography/computed tomography: A five-year review

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Abstract

AIM

To determine the significance and need for investigation of incidental prostatic uptake in men undergoing ^{18}F-labelled fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for other indications.

METHODS

Hospital databases were searched over a 5-year period for patients undergoing both PET/CT and prostate magnetic resonance imaging (MRI). For the initial analysis, the prostate was divided into six sectors and suspicious or malignant sectors were identified using MRI and histopathology reports respectively. Maximum and mean ^{18}F-FDG standardised uptake values were measured in each sector by an investigator blinded to the MRI and histopathology findings. Two age-matched controls were selected per case. Results were analysed using a paired t-test and one-way ANOVA. For the second analysis, PET/CT reports were searched for prostatic uptake reported incidentally and these patients were followed up.

RESULTS

Over a 5-year period, 15 patients underwent both PET/

CT and MRI and had biopsy-proven prostate cancer. Malignant prostatic sectors had a trend to higher ^{18}F-FDG uptake than benign sectors, however this was neither clinically nor statistically significant (3.13 ± 0.58 *vs* 2.86 ± 0.68, $P > 0.05$). ^{18}F-FDG uptake showed no correlation with the presence or histopathological grade of tumour. ^{18}F-FDG uptake in cases with prostate cancer was comparable to that from age-matched controls. Forty-six (1.6%) of 2846 PET/CTs over a 5-year period reported incidental prostatic uptake. Of these, 18 (0.6%) were investigated by PSA, 9 (0.3%) were referred to urology, with 3 (0.1%) undergoing MRI and/or biopsy. No cases of prostate cancer were diagnosed in patients with incidental ^{18}F-FDG uptake in our institute over a 5-year period.

CONCLUSION

^{18}F-FDG uptake overlaps significantly between malignant and benign prostatic conditions. Subsequent patient management was not affected by the reporting of incidental focal prostatic uptake in this cohort.

Key words: ^{18}F-labelled fluorodeoxyglucose; Positron emission tomography reporting; Positron emission tomography/computed tomography; Prostate cancer; Magnetic resonance imaging

Core tip: ^{18}F-labelled fluorodeoxyglucose (^{18}F-FDG) uptake overlaps significantly between malignant and benign prostatic conditions. In a cohort of nearly 3000 patients over a 5-year period, the reporting of incidental elevated prostatic ^{18}F-FDG uptake did not affect subsequent clinical management or patient outcomes.

Chetan MR, Barrett T, Gallagher FA. Clinical significance of prostate ^{18}F-labelled fluorodeoxyglucose uptake on positron emission tomography/computed tomography: A five-year review. *World J Radiol* 2017; 9(9): 350-358 Available from: URL: http://www.wjgnet.com/1949-8470/full/v9/i9/350.htm DOI: http://dx.doi.org/10.4329/wjr.v9.i9.350

INTRODUCTION

Positron emission tomography of ^{18}F-labelled fluorodeoxyglucose uptake combined with computed tomography (^{18}F-FDG PET/CT) is a mainstay of oncologic imaging. PET/CT imaging is well-tolerated and therefore has become a powerful tool for the diagnosis, staging and monitoring of many metabolically-active cancers. However, ^{18}F-FDG PET/CT imaging is not routinely used for detecting prostate cancer for both biological and technical reasons. Firstly, glucose uptake in well-differentiated prostatic adenocarcinoma is less avid than in many other cancers due to low glycolytic activity[1]. Secondly, urinary excretion of ^{18}F-FDG in the bladder and urethra can mask pathological uptake in the adjacent prostate. Thirdly, there is a large overlap in ^{18}F-FDG uptake between malignant disease, benign hyperplasia and inflammation of the prostate[1].

In men undergoing ^{18}F-FDG PET/CT for unrelated reasons, incidental prostatic uptake is found in 0.6%-2.8% of studies[1-5]. Although this is a small percentage of cases, it affects a large number of men given the growing number of PET/CT studies performed per year: 50000 annually in the UK and 2 million annually in the United States[6,7]. The significance of such incidental uptake, together with the need for further investigation, is both uncertain and controversial.

A previous meta-analysis of prostatic uptake on ^{18}F-FDG PET/CT imaging showed that PET/CT cannot reliably differentiate benign from malignant disease, although only a small percentage of these patients underwent a definitive biopsy[8]. The published positive predictive value of ^{18}F-FDG uptake for detecting prostate cancer ranges between 30% (in a low-risk population of men with bladder cancer undergoing radical prostatectomy) to 65% [in a high-risk population of men undergoing prostate magnetic resonance imaging (MRI)][9,10]. Some studies argue that the positive predictive value is increased if ^{18}F-FDG uptake shows a high SUV_{max}, the lesion is in a peripheral location and the CT demonstrates a lack of calcification[11-13]. However, these features all show considerable overlap between malignant and benign disease.

Serum prostate-specific antigen (PSA), multiparametric prostate magnetic resonance imaging (mpMRI) and prostate biopsy can be used to investigate incidental prostatic ^{18}F-FDG uptake to determine if the patient has significant prostate cancer[5,9]. However, there is no consensus on the management of patients with incidental prostatic ^{18}F-FDG uptake[9].

In order to better understand the significance of incidental prostatic ^{18}F-FDG uptake, we investigated both the correlation of prostatic ^{18}F-FDG uptake with findings from MRI and histopathology, and the impact on patient management of reporting increased ^{18}F-FDG uptake in the prostate.

MATERIALS AND METHODS

Study design and patient population

This single-institution retrospective study was approved locally, with the need for informed consent for data analysis waived. The hospital radiology database was searched to identify a total of 2846 ^{18}F-FDG PET/CT studies performed on male patients in the period January 2010 to September 2015. For the first part of the study, 23 eligible men were identified who had both a prostate MRI and an ^{18}F-FDG PET/CT study. 15 of these men had prostate adenocarcinoma on

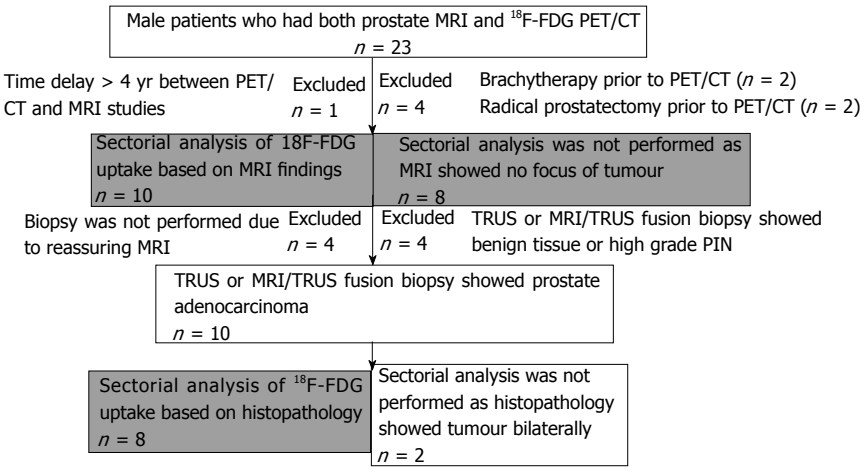

Figure 1 Flowchart showing inclusion and exclusion criteria for selection of cases for sector-based analysis.

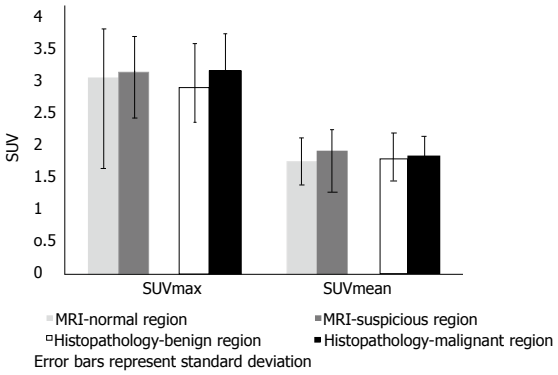

Figure 2 Sectorial analysis comparing ^{18}F-labelled fluorodeoxyglucose uptake in sectors found to be suspicious on magnetic resonance imaging or malignant on histopathology with ^{18}F-labelled fluorodeoxyglucose uptake in the remaining sectors. Mean values and standard deviations have been shown.

ultrasound-guided biopsy or MRI/ultrasound fusion biopsy. Five men were excluded (the prostate cancer was treated prior to undergoing PET/CT in 4 patients, and one patient had > 4 years between MRI and PET/CT). For the second part of the study, the ^{18}F-FDG PET/CT reports were searched to identify patients with incidentally reported focal prostatic ^{18}F-FDG uptake. Patient records were examined for details of follow-up investigations and management. Two cases were included in both the first and second parts of the study.

MRI and ^{18}F-FDG PET/CT analysis

A proprietary workstation and software (Volume Viewer, Advantage Workstation, GE Healthcare, Milwaukee, WI, United States) were used to review the ^{18}F-FDG PET/CT images. The prostate was divided into six sectors: Left and right sides at the apex, mid-zone and base of the gland. Standardised uptake values (SUV) in each sector were measured by an investigator who was blinded to the MRI and histopathological findings. A threshold of 75% of the SUV_{max} was used to calculate the SUV_{mean}[14].

MRI reports were used to identify the prostatic sectors that were suspicious for tumour. Histopathology reports were used to identify the prostatic lobe(s) in which cancer had been detected. Sectorial analysis could not be performed for patients with no tumour focus on MRI, or bilateral tumour on histopathology (Figure 1).

Age-matched controls undergoing ^{18}F-FDG PET/CT but without prostate cancer were randomly selected for each case from PET/CT studies recently undertaken in the department; two controls for each case were acquired. Age matching within 18 mo was used as the criterion, and patients with a known tumour close to the prostate were excluded.

Statistical analysis

A paired two-tailed student's *t*-test was used to compare the ^{18}F-FDG uptake within suspicious or malignant sectors, with that in the remaining prostate for each individual patient. A paired two-tailed student's *t*-test was also used to compare prostatic ^{18}F-FDG uptake in patients with that from the controls. A one-way ANOVA was used to compare prostatic ^{18}F-FDG uptake between histopathological subgroups. Statistical analyses were performed using GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, United States).

RESULTS

Eighteen patients who had both ^{18}F-FDG PET/CT and prostate MRI studies were included in the first part of the study. The median age was 72 years, median PSA was 7.30 ng/mL and median time difference between the ^{18}F-FDG PET/CT and the prostate MRI was 11.5 mo. See Table 1 for patient characteristics.

There was a trend for a higher ^{18}F-FDG uptake in prostatic sectors shown to be suspicious on MRI or

Table 1 Characteristics of patients who had both ^{18}F-labelled fluorodeoxyglucose positron emission tomography/computed tomography and prostate magnetic resonance imaging studies

Age (yr)	MRI before or after PET/CT?	18F-FDG PET/CT indication	Prostate SUVmax	Prostate MRI indication	MRI result	PSA (ng/mL)	Biopsy result
73	2 mo before	Bone metastases (prostate primary)	3.4	Negative TRUS biopsy	T2aNxMx	20.8	Gleason 4 + 5 = 9
72	11 mo after	Non-Hodgkin lymphoma	2.7	Elevated PSA, negative TRUS biopsy	T2aNxMx	8.8	Gleason 5 + 3 = 8
62	3 mo after	Cancer of unknown primary	3.9	Prostate cancer staging	T3bNxMx	37	Gleason 4 + 3 = 7
75	46 mo after	Head and neck cancer	3.4	Active surveillance	T1NxMx	2.28	Gleason 4 + 3 = 7
76	6 mo before	Gastrointestinal stromal tumour	3	Elevated PSA, negative TRUS biopsy	T2bNxMx	150	Gleason 3 + 4 = 7
79	22 mo after	Non-Hodgkin lymphoma	2.9	Elevated PSA	T2aNxMx	5.4	Gleason 3 + 4 = 7
66	30 mo after	Non-Hodgkin lymphoma	3.1	Active surveillance	T2cNxMx	4.8	Gleason 3 + 4 = 7
73	26 mo after	Oesophageal cancer	2.4	Active surveillance	T2cNxMx	7.8	Gleason 3 + 3 = 6
68	18 mo after	Cancer of unknown primary	3.9	Elevated PSA	T2aNxMx	6.1	Gleason 3 + 3 = 6
74	5 mo before	Oesophageal cancer	3.9	Elevated PSA	T1NxMx	7.3	Gleason 3 + 3 = 6
68	5 mo before	Hodgkin lymphoma	9.9	Elevated PSA, negative biopsy	No focus of tumour	4.7	High-grade PIN
65	39 mo before	Colorectal cancer	5.2	Elevated PSA, negative TRUS biopsy	No focus of tumour	8.6	High-grade PIN
76	34 mo before	Non-Hodgkin lymphoma	4.2	Elevated PSA	Suspicious foci bilaterally	15	Benign
67	4 mo before	Non-Hodgkin lymphoma	4.1	Incidental prostatic 18F-FDG uptake	Suspicious foci bilaterally	5.5	Benign
72	16 mo after	Pyrexia of unknown origin	2.7	Chronic urinary infection	Likely prostatitis	Not done	Biopsy not performed
78	1 mo after	Non-Hodgkin lymphoma	3.1	Elevated PSA	No focus of tumour	11.4	Biopsy not performed
61	12 mo after	Lung nodule	5.2	Elevated PSA, positive family history	No focus of tumour	4.5	Biopsy not performed
68	7 mo after	Colorectal cancer	8.8	Incidental prostatic ^{18}F-FDG uptake	No focus of tumour	3	Biopsy not performed

SUV: Standardised uptake value, PSA: Prostate specific antigen, TRUS: Transrectal ultrasound.

Table 2 Sectorial analysis, case-control analysis and subgroup analysis showed no significant difference in ^{18}F-labelled fluorodeoxyglucose uptake

	Mean SUVmax	Mean SUVmean
Sectorial analysis		
MRI - normal prostatic sectors	3.02	1.74
MRI - suspicious prostatic sectors	3.1	1.89
Histopathology - benign prostatic lobe	2.86	1.79
Histopathology - malignant prostatic lobe	3.13	1.82
Case-control analysis		
Age-matched controls	3.09	1.83
Cases with prostate cancer	3.26	1.81
Subgroup analysis		
Biopsy not performed	4.95	1.91
Benign disease and high-grade PIN	5.85	2.86
Low-grade prostate cancer (Gleason $\leqslant$ 3 + 4)	3.2	1.83
High-grade prostate cancer (Gleason score $\geqslant$ 4 + 3)	3.35	1.78

SUV: Standardised uptake value, PIN: Prostatic intraepithelial neoplasia.

malignant on histopathology, compared to those in the remainder of the prostate, but this was not statistically significant (Figure 2). There was no significant difference in ^{18}F-FDG uptake between cases with prostate cancer and age-matched controls undergoing PET/CT who did not have prostate cancer. Patients were classified into the following subgroups according to histopathology findings: biopsy not performed (n = 4), benign biopsy or high-grade prostatic intraepithelial neoplasia (PIN) (n = 4), low-grade prostate cancer with Gleason score $\leqslant$ 3 + 4 (n = 6), and high-grade prostate cancer with Gleason score $\geqslant$ 4 + 3 (n = 4). ^{18}F-FDG uptake was not significantly different between subgroups; we therefore found no correlation between prostatic ^{18}F-FDG uptake and the presence or grade of tumour confirmed on histopathology. Figure 3 illustrates a representative case of a 70-year-old man with high-grade prostate cancer that showed no uptake on PET/CT. See Table 2 for mean values of SUV_{max} and SUV_{mean} derived from sectorial, case-control and subgroup analysis.

For the second part of the study, 2846 male patients undergoing ^{18}F-FDG PET/CT over a 5-year period were followed-up. 46 men (1.6%) had an

Table 3 Characteristics of patients in whom elevated prostatic ^{18}F-labelled fluorodeoxyglucose uptake was investigated

Age (yr)	^{18}F-FDG PET/CT indication	Prostate SUVmax	PSA (ng/mL)	Urology referral made	Urology outcome
68	Adrenal nodule	10.4	3	Yes	MRI - no suspicious foci
77	Lung nodule	4.5	2.78	Yes	Biopsy - high-grade PIN
67	Non-Hodgkin lymphoma	4.5	5.5	Yes	MRI - suspicious foci Biopsy - benign
68	Colorectal cancer	5.9	3.04	Yes	PSA monitoring
58	Colorectal cancer	7.6	1.38	Yes	PSA monitoring
64	Non-Hodgkin lymphoma	5.4	1.84	Yes	PSA monitoring
58	Non-Hodgkin lymphoma	19.9	7.44	Yes	PSA monitoring
81	Cholangiocarcinoma	10.3	18	Yes	Lost to follow up
75	Hepatic metastases (colorectal primary)	8	-	Yes	Lost to follow up
61	Colorectal cancer	14	1.47	No - PSA normal	
55	Paraneoplastic syndrome	4.8	0.62	No - PSA normal	
61	Non-Hodgkin lymphoma	5.8	2.85	No - PSA normal	
68	Gastrointestinal stromal tumour	13.2	1.48	No - PSA normal	
71	Hepatic metastases (colorectal primary)	9.2	4.9	No - palliative care	
87	Oesophageal cancer	5.3	11.86	No - palliative care	
82	Colorectal cancer	15.4	3.85	No - palliative care	
35	Hodgkin lymphoma	11.8	3.04	No - suspected prostatitis	
71	Oesophageal cancer	7.3	4.58	No - likely urethral uptake	

SUV: Standardised uptake value; PSA: Prostate specific antigen; PIN: Prostatic intraepithelial neoplasia.

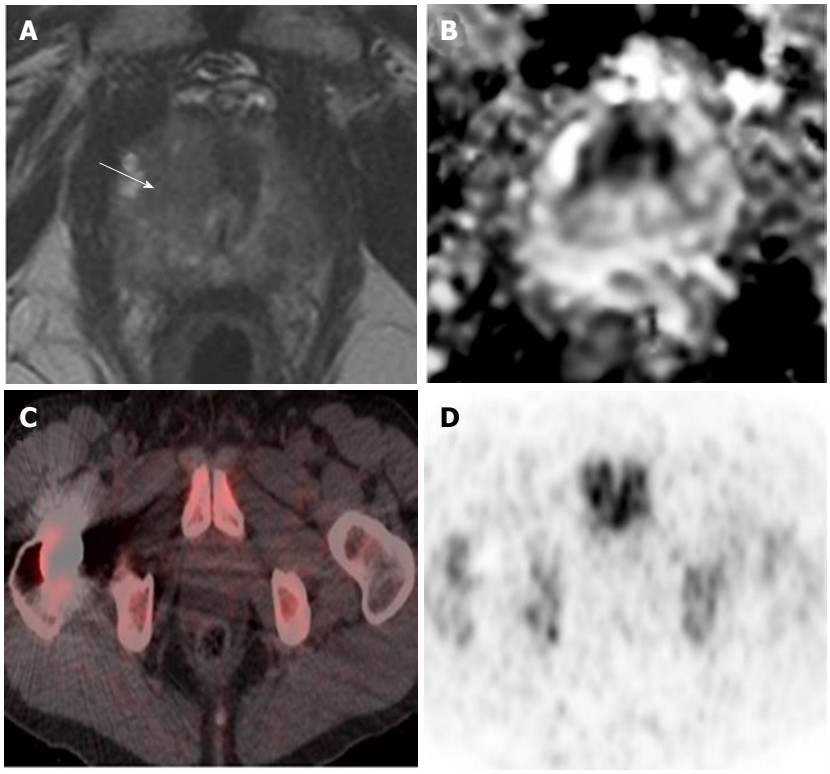

Figure 3 High-grade prostate cancer showing no increased uptake on positron emission tomography/computed tomography in a 73-year-old man. A, B: Prostate MRI performed for raised PSA (19 ng/mL) showed a high probability lesion in the right apex transition zone (arrow in A) with matching restricted diffusion on the ADC map (B). Subsequent targeted transperineal biopsy confirmed Gleason 4 + 5 disease in 40% of cores; C, D: PET/CT performed after a two-month interval and no intervening treatment showed no focal uptake in this region shown as both fused PET/CT imaging (C) and PET alone (D). PET/CT: Positron emission tomography/computed tomography; MRI: Magnetic resonance imaging; ADC: Apparent diffusion co-efficient; PSA: Prostate specific antigen.

incidental and unexplained finding of elevated prostatic ^{18}F-FDG uptake. 18 (0.6%) of these patients underwent further investigation. They had a median age of 68 years, median prostatic SUV$_{max}$ of 7.80 and median PSA of 3.04 ng/mL. See Table 3 for patient characteristics.

Of these 18 men, 9 (0.3%) were referred to urology. Two men had a prostate biopsy, which showed benign disease and high-grade PIN respectively (Figure 4). No cases of prostate cancer were diagnosed in the 5-year period. See Figure 5 for more detailed clinical outcomes.

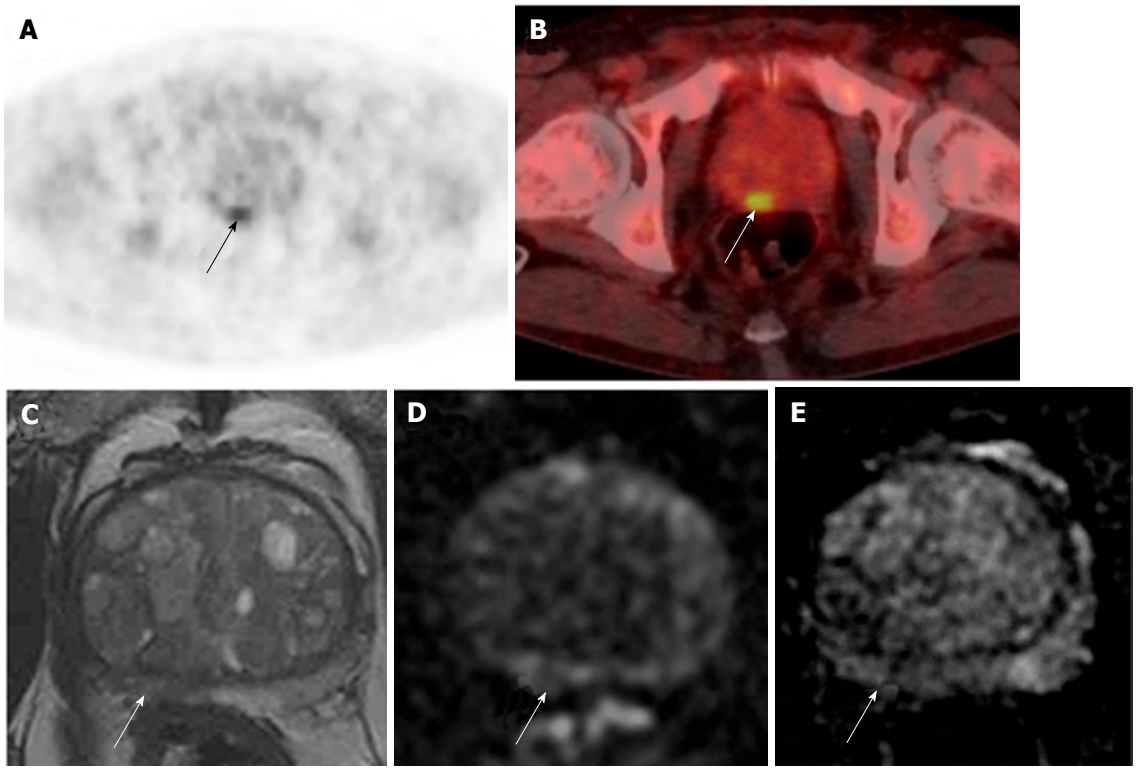

Figure 4 Incidental prostatic ^{18}F-labelled fluorodeoxyglucose uptake in a 67-year-old patient with Stage Ⅳ diffuse large B-cell lymphoma. A, B: Focal uptake in the posterior right peripheral zone of the prostate at the level of the mid-gland as demonstrated on PET (A) and fused PET/CT (B); SUVmax = 4.5; C-E: Prostate MRI shows non-specific geographical intermediate signal on T2-weighted imaging (C), but with no matching restricted diffusion on b-1400 diffusion-weighted images (D) or ADC maps (E). The MRI findings are low probability for tumour. Subsequent transrectal ultrasound-guided biopsy showed no cancer. PET/CT: Positron emission tomography/computed tomography; MRI: Magnetic resonance imaging; ADC: Apparent diffusion co-efficient.

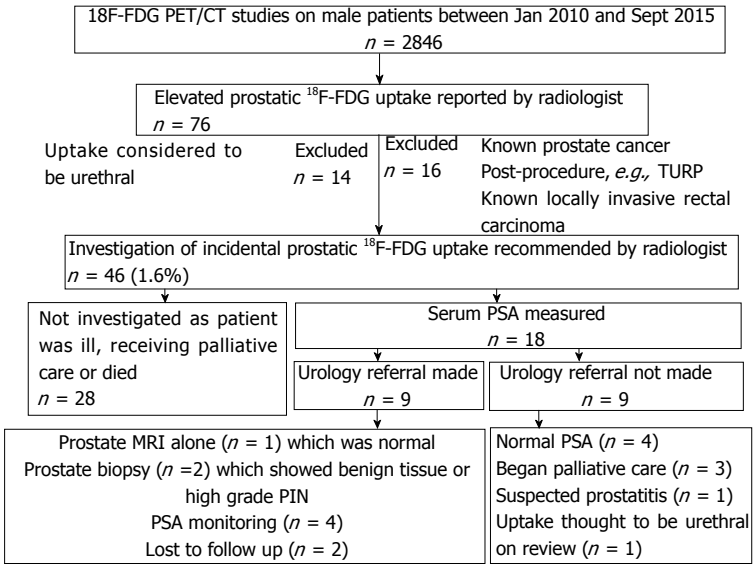

Figure 5 Flowchart showing clinical outcomes in patients with elevated prostatic ^{18}F-labelled fluorodeoxyglucose uptake.

DISCUSSION

Prostate cancer is the commonest male cancer[15]. There is therefore a potentially high incidence of synchronous prostatic tumour in patients undergoing ^{18}F-FDG PET/CT for other indications. However, PET/CT lacks specificity and sensitivity for primary detection of prostate cancer; consequently it is unclear how patients with incidental tracer uptake in the prostate should be managed. Our study has shown that focal ^{18}F-FDG uptake is not indicative of prostate cancer in this cohort, with SUV_{mean} and SUV_{max} values significantly overlapping between malignant and benign conditions, and that the reporting of incidental prostatic uptake

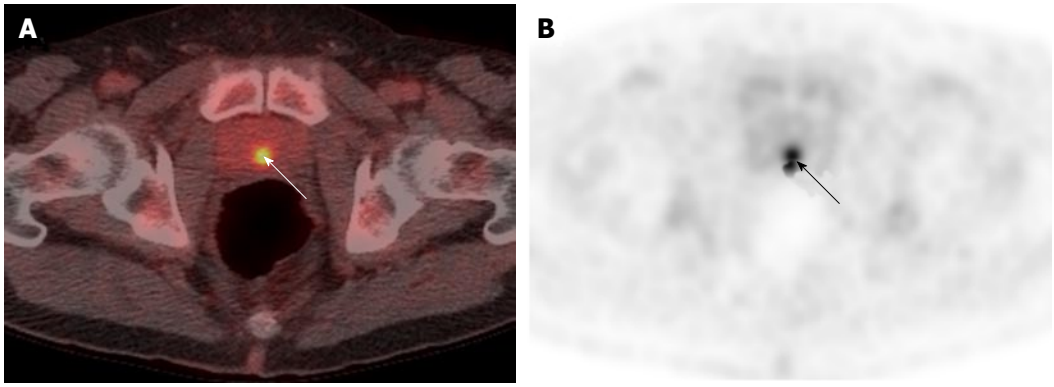

Figure 6 Midline uptake on ^{18}F-labelled fluorodeoxyglucose positron emission tomography/computed tomography in a 71-year-old man with oesophageal carcinoma and serum prostate specific antigen of 4.58 ng/mL. A, B: Fused PET/CT and PET-only imaging shows focal uptake in the midline of the prostate (arrowed). The uptake was considered to be tracer in the urethra given its anatomical location. PET/CT: Positron emission tomography/computed tomography.

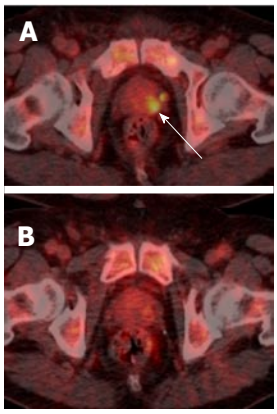

Figure 7 Resolving focal prostatic uptake in a 61-year-old man with Stage IV high-grade non-Hodgkin's lymphoma and serum prostate-specific antigen of 2.85 ng/mL. A: Fused PET/CT imaging performed after 2 cycles of chemotherapy shows focal uptake (arrowed) in the left side of the prostate at the level of the midgland on fused PET/CT; B: Repeat PET/CT performed 4 mo later following completing of 6 cycles of chemotherapy demonstrates resolution of this focal uptake. PET/CT: Positron emission tomography/computed tomography.

did not affect subsequent clinical management of any patient in our institute over a 5-year period.

Sector-based analysis showed that, in individual patients, malignant prostatic sectors had a trend to higher ^{18}F-FDG uptake than benign sectors. However, this difference was not statistically significant and total prostate ^{18}F-FDG uptake in men with prostate cancer was comparable to that from age-matched controls. Comparison of ^{18}F-FDG uptake across patient subgroups showed no correlation between ^{18}F-FDG uptake and histopathological findings. Although some authors have suggested that ^{18}F-FDG uptake weakly correlates with Gleason score, the small numbers in our study did not demonstrate this finding[9,16]. In fact, we observed a higher SUV_{max} and SUV_{mean} in patients with no biopsy, benign biopsy or high grade PIN than in patients with prostate cancer. This may be partially explained by increased ^{18}F-FDG uptake in prostatitis, where there is also increased glucose uptake within the inflammatory tissue[17].

Incidental and unexplained prostate uptake was found in 1.6% of all ^{18}F-FDG PET/CT studies in male patients, which is comparable to the rate reported previously[3-5]. These patients had a median SUV_{max} of 7.8, which is suspicious for tumour; other authors have suggested an SUV_{max} greater than 6.0 should be considered as a cut-off value for high-grade prostate cancer[9]. Only 40% of patients with incidental and unexplained prostatic uptake were investigated with a serum PSA. Twenty percent of patients were referred to a urologist, and only one-third of these patients underwent further investigation with either biopsy or MRI. This may reflect the fact that the existing cancer diagnosis is the primary factor in determining clinical prognosis, and that the subsequent detection of prostate cancer would not significantly affect patient management due to unsuitability for radical therapy. Another possibility is a reluctance to perform a transrectal prostate biopsy in patients undergoing chemotherapy due to the risk of sepsis. In some patients, incidental prostatic uptake was not investigated for different reasons, *e.g.,* uptake was thought to represent tracer in the urethra upon review (Figure 6), or uptake resolved on repeat PET/CT (Figure 7). Ultimately over a 5-year period in our centre, involving nearly three thousand ^{18}F-FDG PET/CT studies, no change in patient management occurred as a result of an incidental finding of elevated prostatic ^{18}F-FDG uptake. Therefore, our retrospective study questions the need to investigate incidental prostatic uptake of ^{18}F-FDG in men undergoing PET/CT.

Our study has some limitations. Firstly, as a retrospective study our population consisted of patients who underwent ^{18}F-FDG PET/CT primarily for other malignancies, and therefore the time difference between PET/CT and MRI was long in some cases (up to 46 mo). This timescale is similar to previously reported retrospective studies and given that the natural history of prostate cancer is one of a slow-growing tumour, most prostate cancers will be present for years before clinical presentation[10,18]. Secondly,

the number of eligible patients in our study was small. Thirdly, patients in our study had ultrasound-guided biopsy or MRI/ultrasound fusion biopsy, which are less sensitive in detecting prostate cancer than whole-mount histology derived from prostatectomy samples.

In conclusion, ^{18}F-FDG uptake has low clinical utility in distinguishing benign and malignant prostatic disease. Reporting incidental prostatic uptake did not affect subsequent patient management or clinical outcomes in this cohort of patients. This study suggests there may be little benefit in investigating incidental elevated prostatic ^{18}F-FDG uptake on PET/CT which should be addressed with future large prospective studies.

COMMENTS

Background

^{18}F-labelled fluorodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography/computed tomography (PET/CT) is used extensively in the diagnosis, staging and monitoring of many cancers. Incidental elevated prostatic ^{18}F-FDG uptake is found in a significant proportion of men undergoing PET/CT for unrelated reasons. ^{18}F-FDG PET/CT is not routinely used in prostate cancer because of the relatively low metabolic activity of prostate cancer, the proximity to tracer in the urethra and the presence of significant ^{18}F-FDG uptake in benign and inflammatory prostatic disease.

Research frontiers

The significance of incidental prostatic uptake, together with the need for further investigation, is unclear.

Innovations and breakthroughs

The results suggest that incidental prostatic uptake has no significant correlation with prostate magnetic resonance imaging or biopsy findings. In a cohort of nearly 3000 men over 5 years, reporting incidental prostatic ^{18}F-FDG uptake did not alter patient management or clinical outcomes.

Applications

The results suggest there is little benefit in investigating incidental elevated prostatic ^{18}F-FDG uptake.

Peer-review

This is an interesting study which investigates the clinical significance of incidental FDG uptake. Although the number of eligible patients was small, this is an well written retrospective study.

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ORIGINAL ARTICLE

Retrospective Study

Reliability of the pronator quadratus fat pad sign to predict the severity of distal radius fractures

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Institutional review board statement: This study was reviewed and approved by the University Hospital of Schleswig-Holstein.

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Conflict-of-interest statement: The authors certify that they have no affiliations with or involvement in any organization or entity wwith any financial interest, or any non-financial interest in the subject matter or materials discussed in this manuscript.

Data sharing statement: Thchinical ppendix, statistical code, and dataset available from the corresponding author at j.loesaus@gmail.com. Participants gave informed consent for data sharing.

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Abstract

AIM

To evaluate the reliability of pronator quadratus fat pad sign to detect distal radius fracture and to predict its severity.

METHODS

Retrospectively we identified 89 consecutive patients (41 female, mean age 49 ± 18 years) who had X-ray (CR) and computed tomography (CT) within 24 h following distal forearm trauma. Thickness of pronator quadratus fat pad complex (PQC) was measured using lateral views (CR) and sagittal reconstructions (CT). Pearson's test was used to determine the correlation of the PQC thickness in CR and CT. A positive pronator quadratus sign (PQS) was defined as a PQC > 8.0 mm (female) or > 9.0 mm (male). Frykman classification was utilized to assess the severity of fractures.

RESULTS

Forty-four/89 patients (49%) had a distal radius fracture (Frykman Ⅰ n = 3, Ⅱ n = 0, Ⅲ n = 10, Ⅳ n = 5, Ⅴ n = 2, Ⅵ n = 2, Ⅶ n = 9, Ⅷ n = 13). Mean thickness of the PQC thickness can reliably be measured on X-ray views and was 7.5 ± 2.8 mm in lateral views (CR), respectively 9.4 ± 3.0 mm in sagittal reconstructions (CT), resulting in a significant correlation coefficient

of 0.795. A positive PQS at CR was present in 21/44 patients (48%) with distal radius fracture and in 2/45 patients (4%) without distal radius fracture, resulting in a specificity of 96% and a sensitivity of 48% for the detection of distal radius fractures. There was no correlation between thickness of the PQC and severity of distal radius fractures.

CONCLUSION

A positive PQS shows high specificity but low sensitivity for detection of distal radius fractures. The PQC thickness cannot predict the severity of distal radius fractures.

Key words: Pronator quadratus fat pad sign; Pronator quadratus complex; Distal radius fracture; Frykman classification; Conventional radiograph; Computed tomography

Core tip: This study evaluated reliability of pronator quadratus fat pad sign (PQS) to detect distal radius fracture and to predict its severity. Therefore correlation of measurements of pronator quadratus complex (PQC) on conventional lateral radiographs (CR) and sagittal reconstructions of computed tomographies (CT), also regarding the severity of fractures were analyzed. In conclusion PQC thickness can reliably be measured on lateral CR and correlates with CT. Sensitivity of PQS for detecting fractures is low, but specificity is high. Therefore a positive PQS in putative negative radiograph should trigger further investigations, *e.g.*, CT scan. PQC thickness cannot predict severity of wrist fractures.

Loesaus J, Wobbe I, Stahlberg E, Barkhausen J, Goltz JP. Reliability of the pronator quadratus fat pad sign to predict the severity of distal radius fractures. *World J Radiol* 2017; 9(9): 359-364 Available from: URL: http://www.wjgnet.com/1949-8470/full/v9/i9/359.htm DOI: http://dx.doi.org/10.4329/wjr.v9.i9.359

INTRODUCTION

Soft tissue alterations or signs may be helpful when radiographs are assessed for fractures and have been used to detect occult bone injuries[1]. Regarding the wrist the "navicular fat stripe" and the "pronator quadratus sign" (PQS) have been described. Mac Ewan was first to characterize the pronator quadratus fat pad sign consisting of a radiolucent (fat containing) stripe which runs parallel to the pronator quadratus muscle covering the distal radius and ulnar (Figure 1)[1,2]. Studies on healthy subjects have shown that thickness of the pronator quadratus complex (PQC) is significantly greater in men (values up to 9 mm) than in women (values up to 8 mm) and increases with age[3,4].

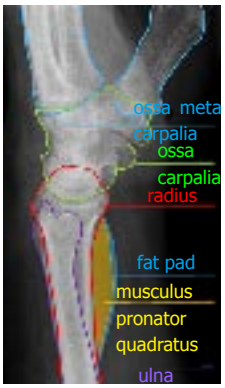

Figure 1 Anatomical sketch of conventional radiograph on lateral view of wrist.

In the case of a trauma to the distal radius or ulna this radiolucent stripe may be deformed or displaced, probably related to edema or hematoma within the pronator quadratus muscle[5,6]. In the majority of lateral conventional radiographs this fat pad can be identified. In the past several studies have analyzed the usefulness of the PQS to detect subtle fractures or inflammation of adjacent e in their detecting[7]. Sensitivity of the PQS measured on lateral X-rays to detect occustructures[3,4,5,7]. While earlier studies described the PQS as a useful adjunctive to detect subtle fractures[1], more recent studies, which used MRI as a reference, have found this sign to be unreliablt distal forearm fractures has been reported to range between 26% and 65%. Specificity however has been found to be 69%-70%[4,8], indicating that absence of the PQS does not necessarily exclude an (occult) fracture, while its presence should trigger further investigations to rule out an underlying pathology. More recent data suggest that a certain muscle-to-bone ratio (maximum pronator quadratus thickness and distal radial thickness at same levels) might be a useful index for the diagnosis of non-displaced and occult distal forearm fracture[9]. Besides detection of a distal radius fracture, classification and evaluation of the injury extent play a role during work-up of extremity trauma cases. So far conventional X-ray underestimates the severity of distal radius fracture when compared to computed tomography or the intraoperative situs[10,11]. In this context the PQS has not been evaluated for predicting the severity of an underlying fracture to the distal radius up to today.

Therefore the presented study analyzes: (1) the correlation of measurements of the pronator quadratus complex on conventional lateral radiographs and sagittal reconstructions of computed tomographies; (2) the sensitivity and specificity of the PQS on conventional lateral radiographs with computed tomography as the reference; and (3) the reliability of the PQS to predict the severity of an underlying fracture.

Table 1 Distribution (n = 44) of distal radius fractures according to the Frykman classification

Frykman-classification	
I	3
II	0
III	10
IV	5
V	2
VI	2
VII	9
VIII	13

Table 2 Thickness of the pronator quadratus complex measured on lateral conventional radiographs and sagital reconstructions of a computed tomography

	Total (n = 89)	With fracture (n = 44)	Without fracture (n = 45)
CR (mm)	7.5 ± 2.8	8.8 ± 2.9	6.2 ± 1.8
CT (mm)	9.4 ± 3.0	10.9 ± 3.1	7.8 ± 2.0
Correlation coefficient	0.795	0.74	0.695

CR: Conventional radiographs; CT: Computed tomography.

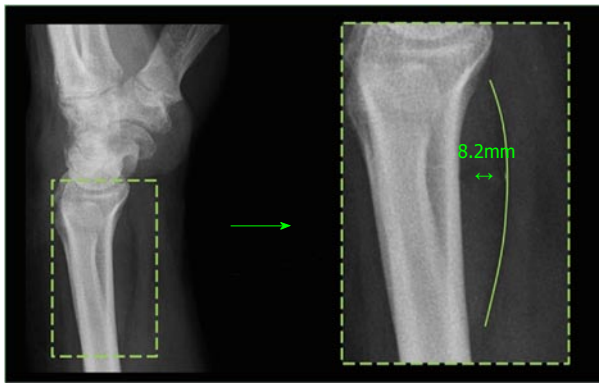

Figure 2 Measurement of the pronator quadratus complex on a lateral conventional radiograph.

MATERIALS AND METHODS

Institutional Review Board approval (Ethic votum No. 15-097A) was granted. Between 01/2010 and 08/2013 we retrospectively identified 89 patients (41 women, 48 men, mean age 49 ± 18 years) with conventional radiographs of the wrist, who had undergone an additional computed tomography within 24 h after suffering a forearm trauma. Inclusion criteria for this study were a distal forearm trauma in patients older than 18 years who had both a conventional X-ray as well as a CT scan of the wrist within 24 h of the time of trauma. Exclusion criteria included age below 18 years, diabetic patients, patients under treatment with corticosteroid, patients with previous forearm fractures as well as musculo-skeletal (muscular dystrophy osteoporosis) and neurological disorders (polyneuropathy, multiple sclerosis).

Thickness of the pronator quadratus complex was measured by two radiologists (three and eight years of experience with musculoskeletal imaging) on lateral radiographs (Figure 2) and on sagittal reconstructions of CTs (Figure 3). The thickest part of the pronator quadratus complex was identified, and the musculus pronator quadratus as well as the adjacent layer of fat were measured together. Inter-observer variability between the two readers was analyzed using Cohen's kappa.

Correlation of measurements of the pronator quadratus complex on conventional lateral radiographs and sagittal reconstructions of computed tomographies was evaluated using the Pearson product-moment correlation coefficient. The Pearson product-moment correlation coefficient is a dimensionless parameter of the strength of the linear relationship between two variables. It can take values between -1 and +1, where +1 (or -1) is a completely positive (or negative) linear relationship between the observed values. Values at 0 indicate no linear correlation.

A (positive) pronator quadratus sign was defined if the pronator quadratus complex measured more than 8 mm in women or 9 mm in men[4]. Severity of distal radius fractures was classified using the Frykman classification[12].

For statistical analysis SPSS (Statistics 21, SPSS Inc, IBM Company) was used. Significance level was set at 0.05. Sensitivity, specificity, positive and negative predictive values for a positive fat pad sign were calculated.

RESULTS

Of 89 patients 44 (49%) had a distal radius fracture. Of these, 24 (55%) patients had a Colles-fracture and ten (23%) patients had a Smith-fracture. Furthermore there were four (9%) patients with dorsal Barton fracture and one (2%) patient with reversed Barton fracture. Two (5%) patients had a Chauffeur fracture and two (5%) had a compressed plurifragmentary fracture. Figures 4 and 5 highlight case examples from the analyzed patient cohort. Table 1 highlights the distribution of fractures according to the Frykman classification.

The group without fractures included 45 patients (21 female, 24 male) and served as control group. Mean age was 47.0 ± 17.5 years. One patient had an underlying malignant disease. The group with a fracture consisted of 44 patients (20 female, 24 male) with a mean age of 51.8 ± 18.2 years.

Mean thickness of the pronator quadratus complex on lateral radiographs was 7.5 ± 2.8 mm and 9.4 ± 3.0 mm on sagitally reconstructed CT respectively. Table 2 depicts measurements in patients with and without an accompanying fracture. Cohen's kappa was used and showed an almost perfect agreement between the measurement of the two radiographs (0.887, $P < 0.01$).

Regarding thickness measurements we found a

Table 3 Frequency of a positive and negative fat pad sign depending on the absence or presence of a fracture

		CR pronator quadratus fat pad sign		
Radius fracture		Positive	Negative	Total
	Yes	21	23	44
	No	2	43	45
	Total	23	66	89

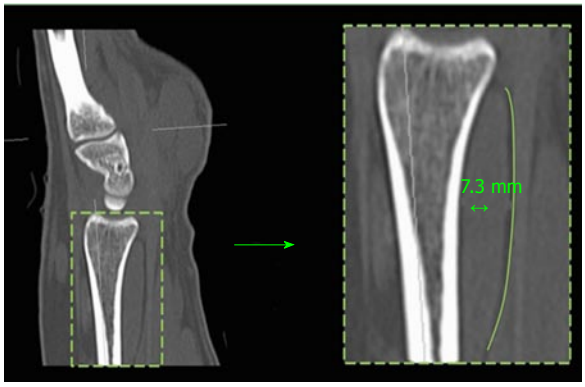

Figure 3 Measurement of the pronator quadratus complex on a sagittal reconstructed computed tomography.

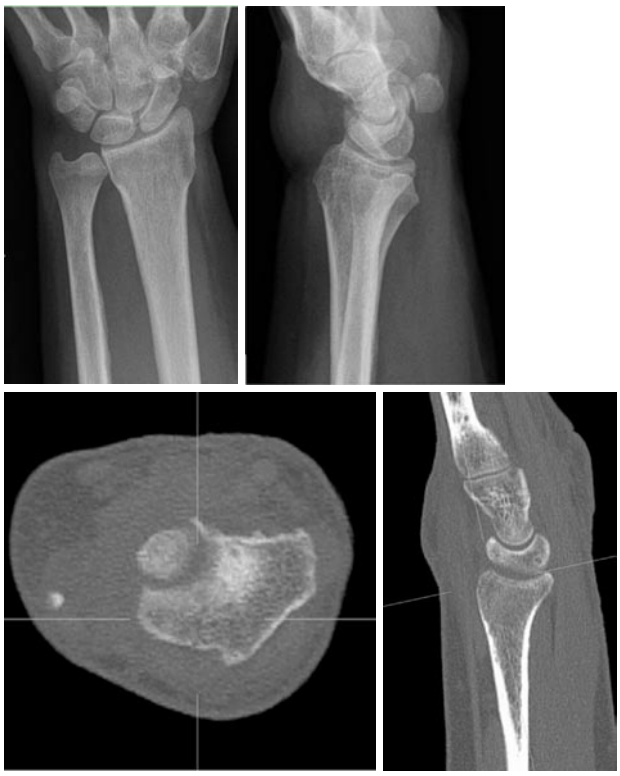

Figure 4 No fracture on lateral radiographs (A), but positive fad pad sign and confirmed fracture on computed tomography study (B). A 48-year-old lady, who had a distal forearm trauma. On lateral radiographs no fracture can be detected, but detailed analysis of the CR shows a thickened pronator quadratus complex measuring 8.5 mm (positive fad pad sign without verification of a wrist fracture on CR) (A). Computed tomography however reveals a fissurale epiphysial fracture (B).

significant correlation ($P < 0.01$) with a Pearson product-moment correlation coefficient of 0.795 between lateral radiographs and sagittal reconstructions of the CT scans.

Table 3 depicts the distribution of a normal or increased thickness (positive fad pad sign) of the pronator quadratus complex depending on the presence of a fracture (as confirmed or excluded by CT). On lateral radiographs 21/44 patients (47.7%) with a fracture had a positive fad pad sign. On the other hand we found 2/45 patients (4.4%) with a positive fad pad sign in the group without a fracture. Sensitivity and specificity were 48% and 96%, respectively. Positive and negative predictive values for detection of fracture using the fad pad sign was 91% and 65%, respectively (Tables 3 and 4). No significant correlation was found if the thickness of the pronator quadratus complex was used to determine the severity of a fracture, neither on lateral radiographs (Pearson product-moment correlation coefficient 0.038) nor on sagittal reconstructions of CT (0.006) scans.

DISCUSSION

Based on the results of our study we consider two messages to be of importance: A positive fat pad sign has a high specificity but low sensitivity for detection of a wrist fracture. We found no significant correlation between the thickness of the PQC and the severity of a fracture.

Early reports have suggested that a positive PQS should arouse suspicion of an occult fracture[7]. However more recent studies have reported sensitivity for the positive fat pad sign to detect an occult fracture as low as 26%-65%[4,8], judging it unreliable. One reason may be that in those studies MRI was used as reference - a method which is very sensitive for depicting bone injuries. Moreover, false negative results may be attributed to a dorsal location of the fracture which would not displace the pronator quadratus muscle, or to a poor image quality of the radiographs which do not allow evaluation of the fad pad sign and, last but not least, to a short interval between the injury and the generation of the radiographs so that the soft tissue is not swollen to such a degree that it may be detectable[1]. A recent study has suggested utilization of a muscle-to-bone ratio (maximum pronator muscle thickness divided by the maximum bone thickness of the distal radius at corresponding levels): With a ratio above 0.4 an occult distal forearm trauma seems likely and should be further evaluated[9].

For the first time, but in a setting similar to the above-mentioned studies, the presented evaluation used computed tomography scans as reference standard. CT is also known to be sensitive in detecting fractures and we too found a poor sensitivity of 46% for a positive PQS in predicting a distal radius fracture. Specificity of a positive PQS however has been calculated around 70%[4,8] and thus found to

Table 4 Sensitivity and specificity of the positive fat pad sign for detection of a fracture

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Positive fat pad sign for detection of a fracture	48.00%	96.00%	91.00%	65.00%

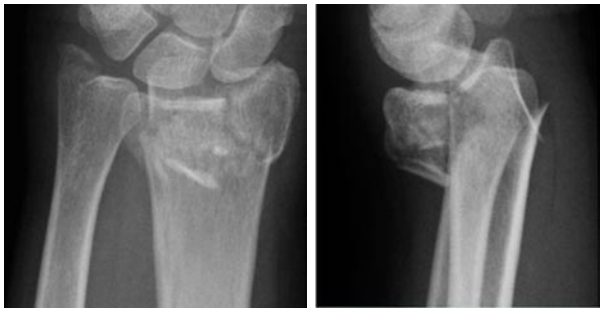

Figure 5 Non-thickened pronator quadratus complex (7 mm) in spite of an obvious fracture in a 27-year-old patient following distal forearm trauma.

range higher than sensitivity. In our study specificity was 96%, indicating that absence of the PQS does not necessarily exclude an (occult) fracture, while presence of it should trigger further investigations to rule out an underlying pathology, as proposed by others[13].

So far correlation of the PQS on conventional X-rays and CT or MRI has not been evaluated: In this context the presented study found a significant correlation of the thickness of the pronator quadratus complex on lateral radiographs and sagittal reconstruction of CT scans of the wrist. From this one may conclude that measurements on lateral radiographs are reproducible and may therefore be used for further studies.

Radiographs in a.p. and lateral views have been used as standard and been judged to be sufficient for evaluation of wrist fractures[10]. Several classifications have been used to group wrist fractures, with AO and Frykman classification as the most common. However both classifications are unreliable regarding reproducibility[14]. Moreover it has been reported that these systems, when compared to CT or intraoperative evaluation, underestimate the severity of wrist fractures, *e.g.*, involvement of bearing areas, which again may be associated with worse outcome for involved patients[10,11]. In this context the present study aimed at evaluation of PQS as an aid to the assessment of lateral radiographs by predicting the severity of an underlying wrist fracture. As no correlation could be found between the thickness of the PQC and the severity of the underlying fracture as assessed by Frykman classification, there seems to be no relevant role for the evaluating of the PQS in predicting the grade or severity of a wrist fracture.

There are main limitations to this study. First, the sample size is small, which prevents us from generalizing on the basis of the results of our series. Second, this study is retrospective and lacks randomization. Therefore a patient selection bias may have played a role. Third, true lateral radiographs of the distal radius might be hard to achieve constantly throughout a study collective and this circumstance might therefore be a slight source of error.

In conclusion, there is a strong correlation of measurements of the pronator quadratus complex on lateral radiographs and sagittal reconstructions from computed tomography scans. Sensitivity of the PQS for detecting wrist fractures is low, but specificity is high. Therefore a positive PQS in a putative negative radiograph should trigger further investigations, *e.g.*, a CT scan. The thickness of the PQC does not correlate with the severity of wrist fractures.

COMMENTS

Background

Conventional radiography is a fast, easy and feasible diagnostic tool to detect fractures. Indirect fracture signs which can be detected on conventional X-ray studies play their role in the detection of occult bone injuries, and might trigger further investigations as, *e.g.*, a computed tomography (CT) scan. The present study evaluates the reliability of such an indirect sign, namely the pronator quadratus fat pad sign, for the detection of distal radius fractures and prediction of its severity.

Research frontiers

The main conclusion of the present study is that a positive pronator quadratus sign (PQS) shows high specificity but low sensitivity for detection of distal radius fractures and that the Pronator quadratus complex (PQC) thickness cannot predict the severity of distal radius fractures. However, there are main limitations to this study. First, the sample size is small, which prevents us from generalizing on the basis of the results of our series. Second, this study is retrospective and lacks randomization. Therefore a patient selection bias may have played a role.

Innovations and breakthroughs

For the first time, but in a setting similar to other studies, the presented evaluation used computed tomography scans as reference standard. When compared to other studies we too found a poor sensitivity of 46% for a positive PQS in predicting a distal radius fracture. In this study specificity was 96%, indicating that absence of the PQS does not necessarily exclude an (occult) fracture, while presence of it should trigger further investigations to rule out an underlying pathology, as proposed by other articles. However configuration of the PQS does not give any information on the severity of an underlying fracture.

Applications

There is a strong correlation of measurements of the pronator quadratus complex on lateral radiographs and sagittal reconstructions from computed tomography scans. It can therefore be reliably used for further research purposes regarding this topic. Sensitivity of the PQS for detecting wrist fractures is low, but specificity is high. Therefore a positive PQS in a putative negative radiograph should trigger further investigations, *e.g.*, a CT scan. A certain thickness of the PQS cannot help to adjudicate the severity of the underlying fracture.

Terminology

There are two terms which are important for a clear understanding of this article. First, this study pays attention to the PQC, which consists of the pronator quadratus muscle covering the distal radius and ulnar and can be identified on the lateral view of the wrist and a radiolucent (fat containing) stripe, which runs parallel to the pronator quadratus muscle. Second, the authors analyzed a positive (and negative) PQS. A positive pronator quadratus sign is defined as thickness of the pronator quadratus complex above 9 mm in men and below 8

mm in women.

Peer-review

It is very interesting study which investigated the relationship between pronator quadratus fat pad sign and distal radius fractures.

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CASE REPORT

Imatinib response of gastrointestinal stromal tumor patients with germline mutation on *KIT* exon 13: A family report

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Author contributions: Engin G analysed data, designed and wrote the paper; Eraslan S performed molecular analysis and made the last revision of the report; Kayserili H performed genetic work-up and made the last revision of the report; Kapran Y performed the pathologic analyses; Akman H performed the computed tomography; Akyuz A performed surgical operations and Aykan NF collected the clinical data of patients, performed medical treatments and made the last revision of the report.

Institutional review board statement: This case report was approved by the Institutional Review Board of Istanbul University Oncology Institute in Istanbul.

Informed consent statement: The patients involved in this study gave their written informed consent authorizing use and disclosure of them protected health information.

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Abstract

Familial gastrointestinal stromal tumor (GIST) is a rare autosomal dominant disorder associated with mutations in the *KIT* gene in the majority of cases. Although, exon 11 appears to be the hot spot region for approximately 95% of germline mutations, pathogenic variations have also been identified in exon 8, 13 and 17. Exon 13 germline mutations are extremely rare amongst familial GISTs and seven families with a germline mutation have been reported to date. Moreover, the role of imatinib mesylate in this rare familiar settings is not completely known so far. We describe here clinical, imaging, pathological and genetic findings of a family with four affected members; grandmother, his son and two grand-sons having a germline gain-of-function mutation of *KIT* in exon 13 and discuss the imatinib mesylate treatment surveillance outcomes towards

disease management.

Key words: Gastrointestinal stromal tumor; Familial; Germline mutation; Imatinib; Response

Core tip: Familial gastrointestinal stromal tumor (GIST) with exon 13 germline mutations are extremely rare. Moreover, there are only a few reports describing the response to imatinib in familial GISTs. The data on the role of imatinib in familial GISTs is still limited. Understanding the role of imatinib is important for the appropriate management of mutation positive familial GISTs. It is also crucial to be able to determine the role of specific germline *KIT* mutations in. We hereby report our findings in consideration of up-to-date information.

Engin G, Eraslan S, Kayserili H, Kapran Y, Akman H, Akyuz A, Aykan NF. Imatinib response of gastrointestinal stromal tumor patients with germline mutation on *KIT* exon 13: A family report. *World J Radiol* 2017; 9(9): 365-370 Available from: URL: http://www.wjgnet.com/1949-8470/full/v9/i9/365.htm DOI: http://dx.doi.org/10.4329/wjr.v9.i9.365

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors originating in the gastrointestinal tract. GISTs constitute 1%-3% of all malignant gastrointestinal tumors and the majority of cases are sporadic[1]. Familial GIST is an extremely rare autosomal dominant condition which is predominantly due to germline gain-of-function mutations of *KIT* and to a lesser extent of *PDGFRA*[2]. Diffuse proliferation of interstitial cells of Cajal (ICCs) in the myenteric plexus layer of the intestine has been described in patients with familial GISTs[3].

Familial GISTs, associated with germline gain-of-function mutations of *KIT* have been described in 35 families[2,4,5]. Somatic *KIT* mutations are reported in approximately 60% of all sporadic GISTs, and almost 95% of all mutations are located in exon 11[6]. In patients with familial GISTs, most germline mutations are also located in exon 11[4]. Familial GISTs with exon 13 mutations are extremely rare, the range of frequency of exon 13 mutations is between 0.8% to 4.1%. Seven families with a germline gain-of-function mutation of *KIT* in exon 13 have been reported to-date[7-12].

Surgery is the primary treatment for localized GISTs. Imatinib mesylate, which is a tyrosine kinase inhibitor, is administered as adjuvant therapy for high-risk groups after the operation or as neoadjuvant therapy for the management of advanced GISTs which are not candidates for surgery at initial diagnosis[13,14]. There are only a few reports describing the response to imatinib in familial GISTs confirming it as a promising therapeutic option[4,5,10].

We here describe clinical, imaging, pathological and genetic findings of a family with four affected members, grandmother, his son and two grandsons having a germline gain-of-function mutation of *KIT* in exon 13 and discuss the imatinib treatment surveillance outcomes towards disease management.

CASE REPORT

We describe a family, father and two sons, with multiple GISTs. Grandmother was reported as being operated at the age of 62 and staged as advanced GIST. Genetic analysis was carried out on DNA obtained from peripheral blood samples from three affected individuals, and there was no DNA available from the grandmother (Figure 1). Sequence analysis of *KIT* gene (RefSeq ID: NM_000222.2; NP_000213.1) revealed a heterozygous exon 13 c.1924A>G (p.Lys642Glu; p.K642E) gain-of-function mutation in all three cases (Figure 2). This result was in concordance with the familial GIST diagnosis.

All three had been operated and found to have low risk, grade 1 multiple GISTs (T2N0M0). Immunohistochemical studies of the tumors showed strong positivity for CD117 (c-kit) (Figure 3). The father and older sibling were treated with imatinib for rest tumors after resection and showed a partial response to treatment.

Patient 1 (Ⅲ-1; 36 years)

The patient has been hospitalized due to massive GIS bleeding at the age of 20 and was operated at the age of 27 after an intensive rectal bleeding. Mesenteric angiography showed bleeding from proximal jejunal branches and tumoral staining. The bleeding branches embolized. Abdominal computed tomography (CT) revealed proximal jejunal wall thickening and nodular solid lesions with 2.5 cm in diameter. Laparoscopic jejunal resection was made and histopathological examination showed low risk grade 1 GIST with strong positivity for CD117(c-kit) (pT2N0M0). Postoperative follow-up PET-CT demonstrated normal findings. He was, thereafter, treated with imatinib (400 mg/d) for five years due to residual multiple, milimetric GISTs and annual follow-up PET-CT showed no recurrence during that period. Imatinib treatment was terminated upon patient's request, end of five years treatment, in 2012. A recent follow-up PET-CT scan identified two nodular lesions in jejunum, 2 cm (SUVmax: 4.69) and 1.5 cm (SUVmax: 1.68) in diameters, which were consistent with GIST recurrence (Figure 4). Abdominal CT revealed multiple duodenal, jejunal and ileal contrast enhanced solid, nodular lesions with maximum 3 cm in diameter. The patient rejected the operation and preferred the re-treatment of imatinib (400 mg/d). A partial response was obtained again in the following 3 mo (Figure 5). The proband had multiple nevi on palms and soles which showed

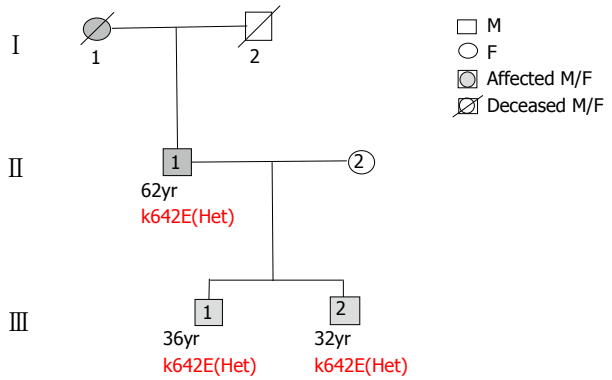

Figure 1 Pedigree of the family shows vertical transmission of *KIT* exon 13 c.1924A>G (p.Lys642Glu; p.K642E) mutation. Het: Heterozygous.

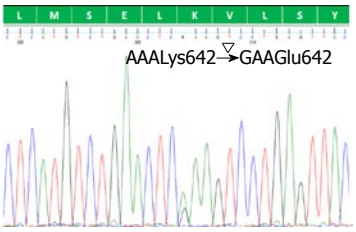

Figure 2 Electropherogram shows exon 13 c.1924A>G missense mutation leading to a change of lysine at position 642 to glutamine (p.Lys642Glu; p.K642E) (dbSNP: 121913512) of *KIT* gene at heterozygote state in three affected family members.

regression after the initiation of the treatment and had hypopigmentation of skin in general.

Patient 2 (Ⅲ-2; 32 years)

He was referred due to abdominal distension and dysphagia at the age of 32. Gastroduodenal endoscopic examination and endoscopic ultrasonography (EUS) showed a gastric submucosal 1.4 cm tumor in diameter on the small curvature of prepyloric antrum. Colonoscopy showed normal findings. ^{18}F-FDG PET-CT revealed two lesions, one at the prepyloric antrum 1.5 cm in diameter with a SUVmax: 5.0 and another at jejunum 2.2 cm in diameter with a SUVmax: 5.39. Abdominal CT showed multiple solid, contrast enhanced mass lesions maximum 3.5 cm in diameter located at the jejunum in addition to the prepyloric antral mass. Partial jejunal resection, multiple wedge resection of stomach and jejunum was performed. Histopathological examination showed low risk grade 1, multifocal masses, two, in stomach at 2.5 cm in diameter and multiple in jejunum, more than 20 with a maximum diameter of 4 cm). Tumors showed strong positivity for CD117 (c-kit) (pT2N0M0). The patient opted for no adjuvant therapy and decided to be followed up by routine annual PET-CT.

Patient 3 (Ⅲ-3; 62 years)

The father had been treated for gastrointestinal bleeding at the age of 18 and preoperatively diagnosed as GIST at the age of 25. He had Billroth operation at the age of 28 and had bleeding episodes thereafter and is on imatinib for the past eight years. At the age of 53, abdominal CT revealed multiple solid lesions with heterogenous contrast enhancement at the distal duodenum, max 5.2 cm in diameter, proximal and middle jejunum, max 5.0 cm in diameter. Three similar solid lesions were further identified at the esophageal wall of the esophago-gastric junction level (2.0 cm in diameter), at the colonic wall of the splenic flexura level (1.2 cm in diameter) and of the rectosigmoid junction level (1.0 cm in diameter), respectively. There was no additional pathologic finding in the liver, peritoneal or retroperitoneal areas. Partial jejunal resection and multiple wedge resections from the esophagus, colon and rectum were performed. Histopathological examination showed low risk grade 1 multifocal GIST with strong positive CD117 (c-kit) (pT2N0M0). After the operation, the patient has been treated with imatinib (400 mg/d) for 8 years due to residual multiple, milimetric GISTs without recurrence on annual follow-up PET-CT.

DISCUSSION

We present an extremely rare condition of autosomal dominant familial GIST with heterozygous c.1924A>G (p.Lys642Glu; p.K642E) germline *KIT* mutation in exon 13 (K642E). All three patients had been operated and two of them were treated with imatinib due to residual multiple, milimetric GISTs to which they all showed partial response.

Surgery is the initial treatment for primary and localized GISTs, targeting complete resection with macroscopic and microscopic negative margins and functional preservation by wedge resection, whenever applicable. The management of a positive microscopic margin after macroscopic complete resection is not well defined, and options may include re-excision, watchful waiting, and adjuvant imatinib therapy. Imatinib mesylate is a first-line standard therapy for inoperable, metastatic, or recurrent GISTs. It is also indicated as adjuvant treatment for intermediate or high risk group of GISTs[14].

Only about half of the patients with sporadic GIST respond to imatinib treatment; 12%-14% show primary resistance to imatinib, and 40%-50% experience secondary resistance and disease progression within 2-3 years from the beginning of therapy[5]. With regard to familial GISTs, there are only 12 reports on the use of imatinib in 24 patients with *KIT* germline mutations[8,10,15-24].

The effect of imatinib on the inhibition of *KIT* activation is dependent on the site of the mutation within the *KIT* gene[5,25]. Previous studies described that the best responses were obtained in GISTs with exon 11 mutations with a daily dose of 400 mg while a daily double dose of 800 mg is required in cases with exon 9 mutation[5,26,27]. Clinical data on the effect of imatinib against sporadic GISTs with exon 13

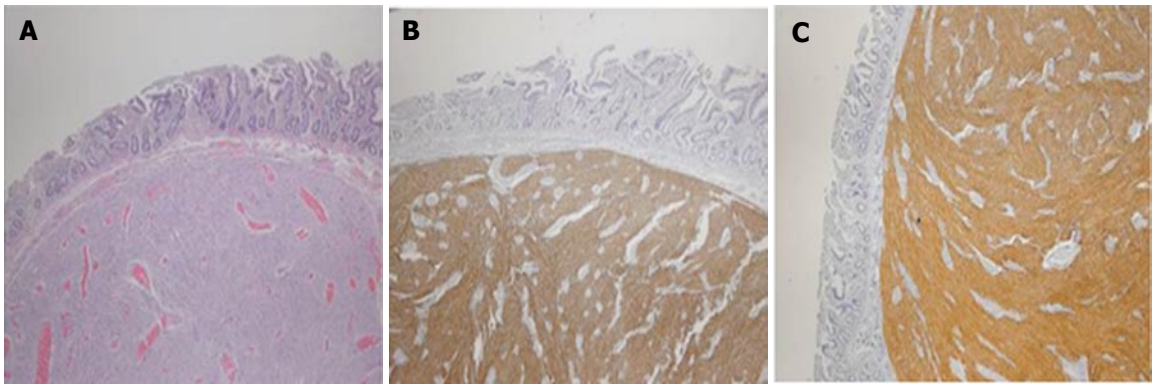

Figure 3 Microscopic findings of gastrointestinal stromal tumor located in the proximal jejunum. Hematoxylin and Eosin staining revealed spindle cells in small bowel submucosa and wall (A). Immunohistochemistry for DOG1 (B) and c-KIT (C) showed immun activity in the tumor cell (original magnification: A, B and C, 40 ×).

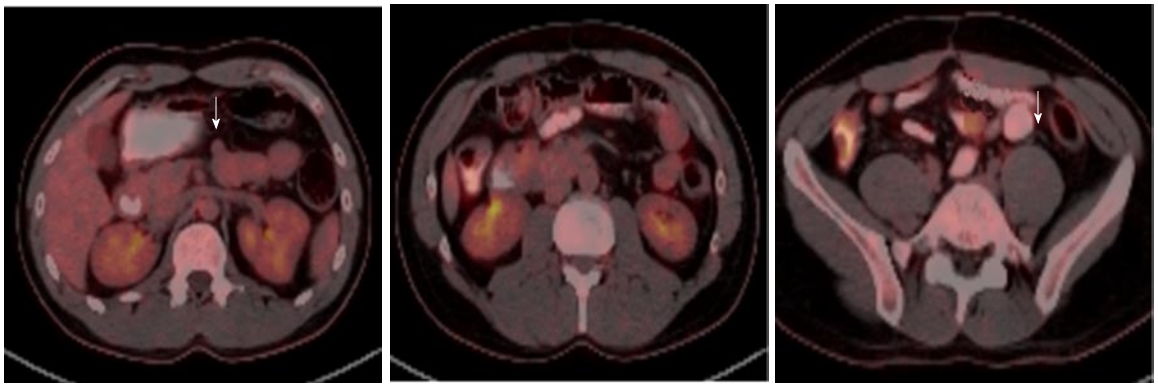

Figure 4 ^{18}F-fluorodeoxyglucose positron emission tomography-computerized tomography scans of the gastrointestinal stromal tumors recurrence. Serial ^{18}F-FDG PET-CT scans showed submucosal, solid lesions in jejunum (SUVmax: 1.68-1.50) (A, B) and ileum (SUVmax: 4.69) (C) with maximum 2 cm in diameter, consisted with GIST recurrence on the follow-up (arrows). ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; PET-CT: Positron emission tomography-computerized tomography; GIST: Gastrointestinal stromal tumors.

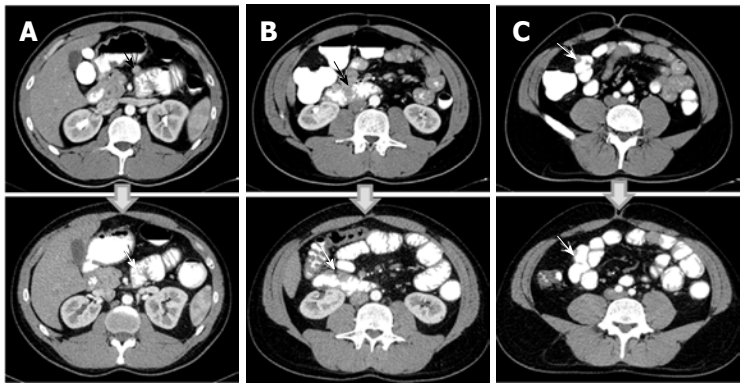

Figure 5 Imatinib response evaluation of the gastrointestinal stromal tumors using contrast-enhanced abdominal computerized tomography. Pre- and post-treatment CT images are shown on upper and lower series respectively. A partial response is seen in jejunal (A, B) and ileal (C) GISTs in the following 3 mo after imatinib therapy (arrows). CT: Computerized tomography; GIST: Gastrointestinal stromal tumors.

mutations are limited. However, it has been proven that imatinib is effective in controlling the progression of sporadic GISTs in patients with K642E mutation. *In vitro* assays also showed that activation of K642E is inhibited by imatinib[26,27].

Several research and follow-up studies has shown that twelve exon 11 positive patients on 400 mg/d imatinib had stable outcome, lasting from 12 to 58 mo[10,19-21,23]. Three out of four exon 17 mutated patients[22,24], two out of three exon 13 mutated patients[8,10] and one exon 8 mutated patient[15] also reported to be stable after imatinib treatment initiation.

In our family, the father and the older son were treated with imatinib (400 mg/d) without recurrence.

There were no signs of recurrence in the father. However, the older son showed recurrence four years after the cessation of imatinib treatment upon patient's request. Imatinib was re-administered with a daily dose of 400 mg and CT scan showed a significant decrease in the tumor size, after three months of the treatment.

We conclude that, *KIT* mutation analysis is advisable prior to initiation of imatinib treatment, as it can help predicting the tumor response. However, data on the role of imatinib in familial GISTs is still limited. We believe that case studies will contribute to our understanding the significance of mutation analysis in regard to the drug dosage, duration of treatment, drug response and follow-up studies of imatinib therapy in familial GISTs. The prognostic comparison of the outcome of imatinib treatment in sporadic GISTs and familial GISTs may play a role in defining the underlying mechanisms and pathways.

COMMENTS

Case characteristics

A family, a father (62-year-old) and two sons (32 and 36 years old) having multiple gastrointestinal stromal tumor (GIST) are described.

Clinical diagnosis

Massive GIS hemorrhage in the father and his older son, abdominal distension and dysphagia in the younger son.

Differential diagnosis

Gastric varices, Mallory-Weiss tear, neoplasm and hemorrhagic gastritis in upper GIS; bleeding, diverticulosis, angiodysplasia, colitis (infectious or ischemic), inflammatory bowel disease, colon cancer in lower GIS bleeding. Dysphagia can be seen in mechanical obstruction or neuromuscular motility disorders.

Laboratory diagnosis

All labs were within normal limits.

maging diagnosis

Imaging computed tomography showed multiple, submucosal, solid masses in 2-5 cm sizes in the upper and lower gastrointestinal tract. ^{18}F-FDG PET-CT revealed high FDG activity (SUVmax 5.0-5.4) in the solid lesions.

Pathological diagnosis

Immunohistochemistry for DOG1 and c-kit showed immun activity in the tumor cell. Sequence analysis of *KIT* gene revealed a heterozygous exon 13 c.1924A>G gain-of-function mutation in all three cases in concordance with the familial GIST diagnosis.

Related reports

Exon 13 germline mutations are extremely rare amongst familial GISTs and seven families with a germline mutation have been reported to date. Moreover, there are only a few reports describing the response to imatinib in familial GISTs confirming it as a promising therapeutic option.

Term explanation

Familial gastrointestinal stromal tumor (GIST) is a rare autosomal dominant disorder associated with mutations in the *KIT* gene in the majority of cases presents multiple GIST. Although surgery is the primary treatment for localized GISTs, imatinib mesylate is used as adjuvant or neoadjuvant therapy in high risk or advanced GIST groups.

Experiences and lessons

We conclude that *KIT* mutation analysis is advisable prior to initiation of imatinib treatment in familial GIST, as it can help predicting the tumor response. We believe that case studies will contribute to our understanding the significance of mutation analysis in regard to the drug dosage, duration of treatment, drug response and follow-up studies of imatinib therapy in familial GISTs.

Peer-review

The authors describe three members of a family treated with surgery and imatinib due to a familiar GIST with a rare mutation. The role of imatinib in this rare familiar settings is not completely known so far. The paper is interesting, addresses a novel topic and adds further knowledge to literature.

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