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Diagnostic modalities for the occult scaphoid fracture

Andele Dirk de Zwart

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Chapter 1

Introduction and outline of this thesis

Introduction

The discussion about diagnostic modalities for scaphoid fractures seems to be a never-ending story. The dilemmas and challenges are illustrated by the fact that a Pubmed search (dd 12-08-2017) on "scaphoid AND diagnosis'' results in more than 3000 hits. On average, at least one relevant paper on the topic is published every two weeks. The diagnosis of a scaphoid fracture is still subject of debate and probably will be for the next decades.

The aim of this thesis is to add new data and to review the current literature per specific part of the discussion. This thesis will summarize existing statements and provide evidence based new ones. Moreover will it be a guide towards a consensus in the diagnostic work up for occult scaphoid fractures.

The incidence of scaphoid fractures varies between 1,5 to 121 per 100.000 persons and the fracture predominantly occurs in young active males.(1) The scaphoid plays a central role in wrist function and is easily injured.(2) Of the patients visiting the emergency department with a clinical suspected scaphoid fracture after a fall on the outstretched hand, 21 to 28% are diagnosed with a scaphoid fracture.(3-5) Between 10 to 20% of these fractures are not visible on the initial scaphoid radiographs and are so called the ''occult scaphoid fracture''.(6,7)
Because of the limited and partially retrograde blood supply, in combination with the multidirectional forces applied on the bone during wrist movement, the scaphoid bone has a low tendency to heal.(8,9) Therefore a scaphoid fracture can result in a non-union, avascular necrosis, carpal instability and osteoartritis.(10-13)
Scaphoid fractures have a non-union rate of 15% and displacement of 2 mm seems to be the predictor for developing a non-union.(14,15) If a scaphoid fracture is not displaced, proximal pole have worse outcome than midwaist and distal pole fractures because of the predominantly retrograde blood supply.(16,17) To improve outcome, these displaced and proximal pole fractures can be treated with internal fixation.(15) Non-displaced fractures can safely be treated with cast immobilisation and union rates are up to 100%.(15) However, a tendency arises to also treat these fractures operatively.(18) Benefits are early return to work and avoidance of cast immobilisation. However long term outcome does not differ and complication rates of operative treatment are up to 30% (mostly minor wound problems).(10,11,19,20)
Most studies concerning non-unions after scaphoid fractures, included fractures that were visible on initial scaphoid radiographs. Occult fractures, diagnosed with techniques like CT, MRI or bone scintigraphy in patients with a clinically suspected scaphoid fracture and no fracture on scaphoid radiographs, are mostly treated with cast immobilisation and non-unions are not described in literature. There is no data available if these fractures also could lead to adverse outcome without treatment. However, as there are relatively high percentages of occult fractures and the consequences of a non-union, it is believed there is place for advanced diagnostic methods.(21,22) There is however controversy what is the best diagnostic modality to detect these occult fractures.

The remarkable wide incidence ranges (between 1,5 and 121 per 100.000) published in literature may well result from different definitions used for (occult) scaphoid fractures. The absence of a 100% reliable reference standard on the diagnosis of a scaphoid fracture is one of the main reasons for this difficulty in defining true scaphoid fractures. In other words, depending on the type of radiographic

modality that you use to diagnose scaphoid fractures, you will find difference in incidences. In literature different reference standards are being used. Some use repeated radiographs, others CT, MRI or bone scintigraphy. However these diagnostic modalities all have their specific advantages and shortcomings. These will be further investigated in this thesis.
The low prevalence of true scaphoid fractures among suspected fractures does not help either.(23) Low percentages of false positive outcomes will lead to many patients who will be overdiagnosed and consequently overtreated, as most patients will have no fracture. Furthermore prospective studies need large sample sizes to have a sufficient amount of fractures.

In the last decades much effort has been done to solve these diagnostic problems. Latent class analysis and clinical prediction rules are the latest developments in order to improve the clinical diagnosis of a scaphoid fracture.(24-28)

The research described in this thesis has started in 2010. Bone scintigraphy was then widely used as additional imaging in clinically suspected scaphoid fractures with no evidence of a fracture on radiographs. The estimated sensitivity and specificity was 100% and 90% respectively.(29-31) In addition to a specificity of 90%, bone scintigraphy was found to have other shortcomings. Nuclear imaging is time-consuming, invasive and the radiation exposure is around 4 mSv.(32) Moreover CT and MRI became more available for musculoskeletal imaging in isolated extremity trauma. In 2010 studies focused on the value of MRI. The accuracy of MRI was promising and the estimated sensitivity and specificity were 98% and 99% respectively.(23) However these results were not consistent and also lower sensitivities of around 80% have been described.(33) At that time, literature that evaluated the role of the CT in diagnosing occult fractures was scarce. Only three studies had been performed with small sample sizes.(34-36) CT however had the advantage of being quick and readily available in a daily clinical setting. A disadvantage of the CT scan was the radiation exposure.

In this thesis the diagnostic characteristics of CT, MRI, bone scintigraphy and SPECT/CT is investigated in patients with clinically suspected scaphoid fractures, that were not visible on standard scaphoid radiographs.

Outline and research questions of this thesis

Chapter 2

MRI is often being suggested to have the best diagnostic value for detecting occult scaphoid fractures. Therefor MRI is frequently being used as a reference standard. To date, no study has reported a specificity below 99% for MRI in diagnosis of scaphoid fractures.(23,31,37,38) If we know that the diagnosis is ''no fracture'' on beforehand, it is possible to study the specificity without a reference standard. Therefore we have used a group of healthy volunteers with no complaints and no history of trauma. The questions to be answered in this chapter are

- What is the specificity of MRI?
- Can MRI be used as a reliable reference standard?

Chapter 3

A missed scaphoid fracture can lead to serious complications. Therefor a diagnostic modality for the detection of an occult scaphoid fracture needs to be highly sensitive. Bone scintigraphy has proven to be a sensitive diagnostic modality.(34,36,37) CT has several advantages over bone scintigraphy: it is readily available, has probably less radiation exposure and is less time-consuming. In chapter 3 the diagnostic value of CT compared with bone scintigraphy is investigated. The question this chapter aims to answer is

- What is the diagnostic value of CT compared to bone scintigraphy?

Chapter 4

For a diagnostic modality to be accurate, the interobserver variability needs to be low. In chapter 4 we have studied interobserver agreement of radiologists evaluating CT's of patients with a clinical suspicion of a scaphoid fracture and no fracture on conventional radiographs. The main question to be answered in chapter 4 is

- What is the interobserver variability of CT's for the diagnosis of scaphoid fractures, not visible on conventional radiographs?

Chapter 5

An often suggested disadvantage of the CT is the radiation exposure. There is controversy around the harmfulness of low dose radiation exposure.(39)

So far, only indirect measurements of radiation exposure concerning a CT of the wrist, are known in the literature.(40) In chapter 5 the radiation exposure of a CT of the wrist, including scatter radiation, is quantified using a phantom (direct measurements). Moreover the difference in radiation exposure of scanning with -and without a plaster cast is evaluated. The questions to be answered in this chapter are

- What radiation exposure does a CT of the wrist induce?
- Is there a difference in radiation exposure during CT of the wrist with and without a plaster cast of the wrist?

Chapter 6

MRI, CT and bone scintigraphy all have advantages and disadvantages. To date, no other study has been performed comparing these three diagnostic modalities in the same patient group. In chapter 6 an unique comparative prospective cohort study is presented in which MRI, CT and bone scintigraphy are compared in diagnosing occult scaphoid fractures. The questions to be answered in this study are

- Are MRI, CT and bone scintigraphy comparable in diagnosing occult scaphoid fractures?
- What are the discrepancies in these advanced diagnostic methods and how should they be interpreted?

Chapter 7

Recently, SPECT/CT has become a more commonly used imaging tool in orthopedic trauma surgery. (41) Chapter 7 is a pilot study investigating the role of SPECT/CT in the diagnostic work up for scaphoid fractures. Moreover the role of SPECT/CT as reference standard is being investigated.

- Does SPECT/CT have place in the diagnostic work up for scaphoid fractures?
- Could SPECT/CT serve as a reference standard in future studies?

In **Chapter 8** the outcome of this thesis is being discussed, the latest literature is being reviewed and future perspectives are being evaluated.

Chapter 9 presents the summary of this thesis in English.

Chapter 10 presents the summary in Dutch.

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Chapter 2

MRI as a reference standard for suspected scaphoid fractures

De Zwart AD, Beeres FJP, Ring D, Kingma LM, Coerkamp EG, Meylaerts SA, Rhemrev SJ.
Br J Radiol. 2012 Aug;85(1016):1098-101.

Abstract

Objectives Some have suggested that MRI might be the best reference standard for a true fracture among patients with suspected scaphoid fractures. The primary aim of this study was to determine the rate of false-positive diagnosis of an acute scaphoid fracture in a cohort of healthy volunteers.

Methods In a prospective study, 33 healthy volunteers were recruited and both wrists of each were scanned, except for two volunteers for whom only one wrist was scanned. To simulate the usual clinical context the 64 scans of healthy volunteers were mixed with 60 MRI scans of clinically suspected scaphoid fractures but normal scaphoid radiographs. These 124 MRI scans were blinded and randomly ordered. Five radiologists evaluated the MRI scans independently for the presence or absence of a scaphoid fracture and other injuries according to a standard protocol.

Results To answer the primary question, only the diagnoses from the 64 scans of healthy volunteers were used. The radiologists diagnosed a total of 13 scaphoid fractures; therefore, specificity for diagnosis of scaphoid fracture was 96% (95% confidence interval: range 94–98%). The five observers had a moderate interobserver agreement regarding diagnosis of scaphoid fracture in healthy volunteers (multirater k50.44; p=0.001).

Conclusions The specificity of MRI for scaphoid fractures is high (96%), however false positives do occur. Radiologists have only moderate agreement when interpreting MRI scans from healthy volunteers. MRI is not an adequate reference standard for true fractures among patients with suspected scaphoid fractures.

Introduction

The American College of Radiologists (ACR) recommends MRI for diagnosis of true fractures among suspected scaphoid fractures.(1) A number of published studies cite sensitivities and specificities approaching 99%,(2-9) but other studies have reported a lower sensitivity (80%) and substantial interobserver variation for the diagnosis of a scaphoid fracture.(2,7) It has been difficult to agree upon a reliable reference standard for true fractures among suspected scaphoid fractures and these studies often use only repeated radiographs six weeks after trauma as reference standard. However, it is also known that not all occult scaphoid fractures become apparent on repeated radiographs. It is not clear how to distinguish true fracture from other changes in bone signal that are detected with MRI. We propose that MRI of the wrists of healthy volunteers with no history of wrist or hand injury represents a reliable reference standard for the absence of an acute fracture of the scaphoid waist. By evaluating MRI scans of healthy volunteers, we may learn more about the diagnostic performance characteristics of MRI for suspected scaphoid fracture. A set of MRI scans with a reliable reference standard would also provide useful information about the reproducibility of the interpretation of MRI for suspected scaphoid fracture. The primary study question was to investigate the occurrence of false-positive diagnosis of an acute scaphoid fracture on MRI using a reliable reference standard (healthy volunteers). Secondarily we also investigated the interobserver variation of diagnosis of scaphoid fracture on MRI in healthy volunteers.

Methods and materials

This is a prospective cohort study approved by our institutional review board.

Healthy volunteers

Healthy volunteers were recruited from acquaintances of the main study investigators. Before inclusion one of the investigators assessed an interview concerning whether there was:

1. Any history of wrist or hand injury
2. Any history of wrist pain or arthritis
3. Any contraindication for an MRI scan

If any of these questions were positive the volunteer was excluded. All healthy volunteers were aware of the primary aim of the study and gave oral informed consent. They volunteered and there was no form of compensation.

62 MRI scans were made of both wrists of 31 healthy volunteers. Two healthy volunteers had an MRI scan of one wrist because they had a history of wrist trauma on one side. There were 44 MRI scans of males and 20 MRI scans of females, with a mean age of 28 years (range 19–53 years).

Suspected scaphoid fractures

To simulate the clinical context, we mixed the MRI scans of the healthy volunteers with MRI scans from a cohort of patients with a suspected scaphoid fracture from a database of a previous study.(2) All patients with a suspected scaphoid fracture had a recent trauma, a tender anatomical snuffbox and pain when applying axial pressure on the thumb or index finger. Of the group of 60 scans of patients with suspected scaphoid fractures, there were 32 males and 28 females with a mean age of 38 years (range 16–70 years). According to the reference standard used in this study,15 patients were diagnosed with a scaphoid fracture, 20 with other fractures, two with contusions of os triquetrum, three with contusion of os scaphoid and 20 without any injury.(2) This study was performed in the same clinic with an identical MRI protocol to our current study, but with the participation of different radiologists. In total there were 124 MRI scans, of which 64 were from healthy volunteers and 60 from the used cohort study.

Evaluation

All MRI scans were stripped of patient identifiers and presented in random order to five radiologists that specialise in musculoskeletal radiology. Five radiologists participated in the study. Radiologist 1 was a resident in the USA with two years of experience. Radiologists 2 and 3 were fellows in skeletal radiology in the USA. Radiologists 4 and 5 were established radiologists in the Netherlands with 14 years and 18 years of experience, respectively. The radiologists were aware that the MRI scans were obtained from both healthy volunteers and patients with suspected scaphoid fracture; however, they were not aware about the size of each group. Each radiologist independently rated each MRI scan using a standardised scoring sheet containing the following four items:

1. Scaphoid fracture (yes/no)
2. Other fracture (yes/no; if yes, metacarpal, other carpal or distal radius fracture)
3. Other lesions
4. No injury (yes/no)

There were no specific criteria for diagnosis of a fracture determined by the investigators before the start of the study.

MRI protocol

A 1.5 T MRI scanner (SymphonyTM; Siemens, Erlangen, Germany) was used. The patient lies prone on the scanner table with the hand extended forward, palm down, over the patient's head. A flexible surface coil was wrapped around the wrist. The MRI protocol included coronal T1 weighted turbo spin-echo images with a repetition time (TR) of 450 ms, an echo time (TE) of 13 ms, a field of view of 1806115. 2 mm (64%), a base resolution of 512, two averages, a slice thickness of 3 mm with a distance factor of 10% and a scan time of 2.17 min. The parameters for the coronal fat-suppressed T2 weighted fast spin-echo images were a TR of 5220 ms, a TE of 73 ms, a field of view of 2206141. 46 mm (64.3%), a base resolution of 448, 3 averages, a slice thickness of 3 mm with a distance factor of 10% and a scan time of 4.33 min. Both wrists of the healthy volunteers were scanned.

Statistical methods

For data analysis we excluded 60 scans of the suspected scaphoid fractures as this was not the main goal of this study. Statistics are based on the 64 scans of the healthy volunteers. As one of the radiologists did not rate one of the healthy scans, the data set contained 319 diagnoses/ratings (64 healthy scans rated by four radiologists and 63 scans rated by one radiologist). Among the healthy volunteers, we calculated the specificity (the proportion of healthy volunteers correctly diagnosed as having no scaphoid fracture) based on a binomial-based robust estimator (method of Clopper and Pearson). To get a robust estimate of specificity with 95% confidence interval, we used repeated-measures terms in the logistic regression model using generalised linear models. Here we accounted for multiple wrists from the same patient as a repeated measure and different MRI scans read by the same radiologist as another repeated measures parameter.(10) In addition, we calculated the interobserver agreement. A multirater macro was used to determine interobserver agreement while accounting for five independent observers. Left and right wrists were evaluated separately and then pooled together. To account for multiple raters and wrists from the same patient, the independent working correlation structure worked best and model fit was better treating both healthy volunteer and radiologist as subject effects, as opposed to either one alone.(11)

Results

Among the 319 rated MRI scans in healthy volunteers, 247 were diagnosed with no injury, 13 with scaphoid fracture, 23 with other fracture and 36 as a ‘‘bone bruise’’ (Figure 1). Of the 36 bone bruises, 10 involved the scaphoid and 26 involved other bones (carpus, metacarpus or distal radius). Four out of five radiologists diagnosed a total of 13 scaphoid fractures (Table 1). On average the five radiologists diagnosed 2.6 (range 0–5) scaphoid fractures. The 13 scaphoid fractures were diagnosed in six scans. For three scans the diagnosis was supported by only one radiologist; two scans were supported by three radiologists; and one scan was supported by four radiologists. In these six scans ten bone bruises of the scaphoid were diagnosed by radiologists who did not diagnose a fracture. Three scaphoids were diagnosed by all five radiologists as either fractured or bruised (Table 2). Based on these data, the specificity of MRI was estimated as 95.9% (95% confidence interval: range 93.8–98.1%). The multirater kappa value was 0.47 for all the right wrists and 0.359 for all the left wrists. The kappa value based on presence or absence of scaphoid fracture of the five observers was 0.44 (p,0.001), which is considered moderate interobserver agreement.(10)

Table 1. Agreement between five radiologists in the presence or absence of a scaphoid fracture in 64 MRI scans of healthy volunteers

Radiologist	Scaphoid fracture	No scaphoid fracture	Specificity (95% confidence interval)
1	3	61	95% (87-99%)
2	1	63	98% (91-100%)
3	0	63	100% (94-100%)
4	5	59	92% (84-98%)
5	4	60	94% (91-100%)
Total	13	306	96% (93-98%)

Table 2. MRI findings in six healthy volunteers, in whom one or more radiologists diagnosed scaphoid fracture (13/319 scans), scaphoid bone bruise (n=10) or no abnormality (n=7).

Volunteer	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist 4	Radiologist 5
1	No abnormality	No abnormality	No abnormality	Fracture	Bone bruise
2	No abnormality	No abnormality	No abnormality	Fracture	No abnormality
3	Fracture	Fracture	Bone bruise	Fracture	Fracture
4	Fracture	Bone bruise	Bone bruise	Fracture	Fracture
5	Fracture	Bone bruise	Bone bruise	Fracture	Fracture
6	Bone bruise	Bone bruise	Bone bruise	Bone bruise	Fracture

Figure 1. All diagnoses of the 64 healthy volunteers scored by five radiologists (n=319).

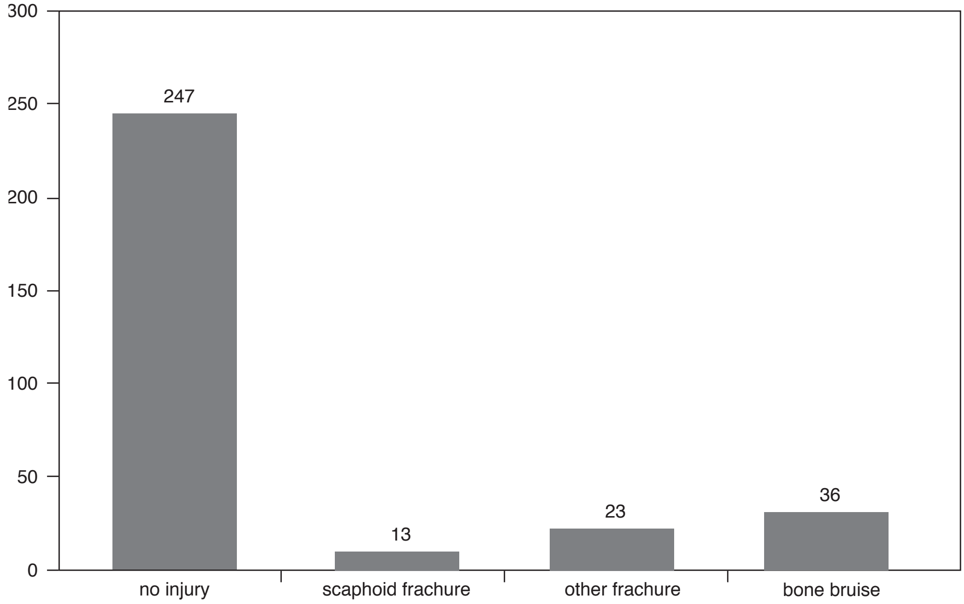
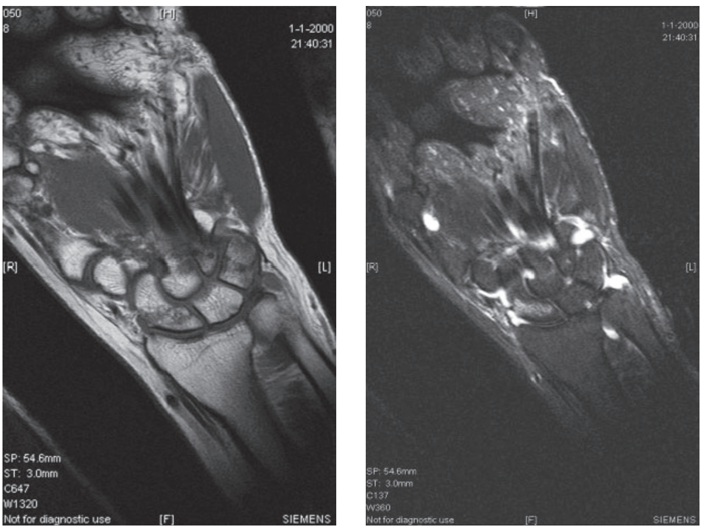


Figure 2. Four radiologists scored this MRI scan of a healthy volunteer as a scaphoid fracture. (a) T1 sequence; (b) T2 sequence.



(a) (b)

Discussion

MRI cannot be used as the reference standard for true fractures among suspected scaphoid fractures because, even in healthy volunteers with no history of wrist trauma, there are signal changes that radiologists sometimes interpret as a fracture or a bone bruise (Figure 2). The use of a reliable reference standard for no fracture (healthy volunteers) allows us to estimate the specificity of MRI for scaphoid fracture as approximately 96%, which is good, but not perfect. Given that the prevalence of true fractures among suspected scaphoid fractures is low, even small imperfections in diagnostic tests are magnified.(7) False-positive diagnosis in our cohort may be due to: 1. scoring a bone bruise as a fracture (some authors do this, while others require an interruption of the cortex or a clear fracture line); 2. the use of an abbreviated scanning protocol with only coronal plane images; and 3. training and experience (our impression is that radiologists with greater specialisation in musculoskeletal MRI have fewer false-positives). With respect to the influence of the MRI scanning protocol, a limited and fast (7 min) protocol was used in order to evaluate a protocol that is easily implemented in a busy daily clinic (this protocol is routinely used in our clinic). Additional views or additional sequences might influence the diagnostic performance. Partial volume artefact within the limited scanning protocol could have contributed to false-positive findings. Additional research is needed to determine optimal diagnostic criteria for a scaphoid fracture on MRI and what defines an adequate MRI scan for diagnosis of scaphoid fracture. Given that our most sophisticated imaging techniques are imperfect, it must be accepted that there is no reference standard for true fracture of the scaphoid among patients with a suspected fracture. It is conceivable that certainty regarding the diagnosis of scaphoid fracture may be elusive. It may be more appropriate to treat patients and perform research based on the probability of a fracture. Latent class analysis—an alternative statistical method for calculating diagnostic performance statistics in the absence of a consensus reference standard—may be more appropriate in this context.(12)

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Chapter 3

Early computed tomography compared with bone scintigraphy in suspected scaphoid fractures

De Zwart AD, Rhemrev SJ, Kingma LM, Meylaerts SAG, Arndt JW, Schipper IB, Beeres FJP.
Based on Clin Nucl Med 2012 Oct;37(10):981 and Clin Nucl Med 2010 Dec;35(12):931-934.

Abstract

Objectives This study examined whether Computed Tomography (CT) is superior to bone scintigraphy for diagnosis of an occult scaphoid fracture.

Methods In a study period of 39 months, 159 consecutive patients with a clinically suspected scaphoid fracture and no fracture on scaphoid radiographs, were evaluated with CT within 24 hours after injury and bone scintigraphy between three and five days after injury. The reference standard for a true (radiographic occult) scaphoid fracture was either (1) diagnosis of fracture on both CT and bone scintigraphy or (2) in case of discrepancy, clinical and/or radiographic evidence of a fracture during follow-up.

Results CT showed 15 scaphoid fractures and 35 other fractures. Bone scintigraphy showed 28 scaphoid fractures and 57 other fractures. According to the reference standard, there were 20 scaphoid fractures. CT had a sensitivity of 70%, specificity of 99%, accuracy of 96%, a positive predictive value of 93% and a negative predictive value of 96%. Bone scintigraphy had a sensitivity of 95%, specificity of 94%, accuracy of 94%, a positive predictive value of 68% and a negative predictive value of 99%.

Conclusion This study could not confirm that early CT imaging is superior to bone scintigraphy for suspected scaphoid fractures.

Introduction

Ever since its first description in 1905, diagnosing suspected scaphoid fractures has been recognized as a problem.(1) Patients with a history of acute trauma, clinical signs of a scaphoid fracture but no evidence of a scaphoid fracture on plain radiography have a scaphoid fracture in up to 15%.(2-6) Even though these fractures are occult, they can lead to complications such as osteonecrosis, nonunion, carpal instability and functional impairment. Moreover, a delay in treatment increases the risk of these complications.(7-12) Therefore, there is a clear need for a fast and reliable diagnostic method, to initiate the appropriate treatment as early as possible. Bone scintigraphy has been widely used in the diagnostic management of scaphoid fractures. It has a known sensitivity of up to 100% and a specificity of approximately 90%.(2,5,12-14) Nuclear imaging, however, requires intravenous radioactive isotopes and a delay of at least 72 hours after injury. Moreover, a bone scintigraphy has a radiation dose of four mSv, which is equivalent to approximately two years of natural background radiation.

The American College of Radiology currently deems Magnetic Resonance Imaging (MRI) and radiographs as the most appropriate investigation in imaging acute scaphoid trauma.(15) MRI has a suggested sensitivity and specificity approximating 90% and 100%, respectively.(4,6,13,16-19) In a recent prospective trial comparing MRI with bone scintigraphy, MRI was found not to be superior.(6) The United Kingdom's Royal College of Radiologists gives equal merit to MR imaging, computed tomography (CT) and bone scintigraphy in the imaging of acute scaphoid trauma when scaphoid radiographs are negative. There is currently insufficient scientific evidence regarding the ideal imaging technique in acute scaphoid trauma.(20) CT has been claimed a useful technique to identify communition, displacement and alignment in radiographic evident fractures. The radiation dose of CT used for imaging scaphoid fractures is less than 0.03 mSv.(21) In addition, CT is superior to MRI in the evaluation of cortical involvement of occult scaphoid fractures.(18) However, both false positive and false negative results of CT in occult scaphoid fractures have been described. In addition, there is evidence that CT is less sensitive than bone scintigraphy.(22) Data regarding CT are limited and till now the value of CT for the detection of suspected scaphoid fractures has not yet been evaluated properly.(20) Proper analyses is important, since early CT could obviate many of the disadvantages of bone scintigraphy. The objective of the present study was to evaluate if early CT is superior to bone scintigraphy for definitive diagnosis of suspected scaphoid fractures.

Methods and materials

Patients

This prospective study was approved by the regional Ethical Committee. Between November 2007 and July 2009, all consecutive patients visiting the emergency department with a suspected scaphoid fracture were included for analyses, after written informed consent. Patients were eligible if they had a suspected scaphoid fracture (tender anatomic snuffbox and pain in the snuffbox when applying axial pressure on the first or second digit), a recent trauma (within 48 hours) and no evidence of a fracture on scaphoid radiographs. Polytrauma patients, patients younger than 18 years and those with contraindications for bone scintigraphy or CT were excluded.

Study Protocol

After inclusion, all patients were physically examined and scaphoid radiographs were made. CT of the hand and wrist was performed within 24 hours after the initial presentation at the emergency department. Bone scintigraphy of the hand and wrist was performed between three and five days post-trauma.

Physical Examination

In the Emergency Department and at fixed intervals throughout follow-up, patients underwent a physical examination of the wrists and hands. Patients were asked to localize the "point of maximal tenderness" for pain. Subsequently, both wrist and hand were examined. Pressure was applied on the anatomic snuffbox, distal radius and other carpal bones. Next, axial pressure was applied on both the first and second digits.(23-25)

Scaphoid Radiographs

All radiographs were obtained by using a digital technique and a computed radiography system (Siemens Vertex 3D, Erlangen, Germany). Initial scaphoid radiographs were taken in following three planes: (1) a posteroanterior view with the hand in a neutral position, (2) an oblique view with the wrist in 10 degrees of supination and maximal ulnar deviation and (3) a true lateral view with the wrist resting in the ulnar position on the x-ray plate. First, all radiographs were reviewed by the attending resident surgeon in the emergency department and a resident radiologist. Subsequently, the consultant trauma surgeon and consultant radiologist evaluated the radiographs. All responses had to be negative to have an overall negative reading and to be eligible for study inclusion.

Computed Tomography

The CT scans were obtained with a scanner (General Electric Lightspeed Qx/I CT Scanner, Pewaukee, WI). The technique used is described by Sanders.(26) The patient lie prone on the scanner couch with the hand extended forward palm down over the patient's head, with the wrist in neutral flexion and neutral radial-ulnar deviation. Scout images were obtained to ensure that the scanning plane corresponded with the scans that provided a lateral view of the scaphoid bone as defined by the central longitudinal axis of the scaphoid. Coronal plane images defined as images that provided a posteroanterior view of the scaphoid in the anatomic plane and in line with the axis of the scaphoid were obtained by supinating the forearm 90 degrees keeping the wrist in a neutral position. Slice thickness was 0.625 mm with reconstructions every 0.4 mm (120 per kV, 80 mA, noise index 34). For multiplanar reformatted images, parameters were 2 mm slice thickness, 2 mm interval.

Bone scintigraphy

Bone scintigraphy was performed between three and five days after trauma, using a standard protocol of images of the early static phase,on a SKYLight gamma camera (Philips, Eindhoven, The Netherlands). Palmar and dorsal images of both wrists were performed between two and a half and four hours after the intravenous injection of 500 MBq of Tc-99m-HDP (Tc-99m hydroxymethylene diphosphonate) visualizing the osteoblastic activity with a planar collimator. Each image took 10 minutes.

Image Analysis

A resident and consultant radiologist evaluated the radiographs and CT images. A consultant clinical nuclear physician evaluated all bone scintigraphs. For both the CT and the bone scintigraphy, observers filled in a standard form blind to each other and blind to all other data. Each observer scored as follows:

1. Scaphoid fracture (yes-no)
2. Other fracture (yes-no)

The observers also evaluated the presence or absence of arthrosis and other lesions.

Management of Injury

Patients with a scaphoid fracture either on CT or bone scintigraphy were treated with a scaphoid forearm cast. Standard scaphoid radiographs were made six weeks after injury. All patients were clinically re-examined at fixed intervals throughout follow-up: two, six and eight weeks and three and six months after injury. Patients with no fracture or another fracture were treated according to the local trauma protocol.

Reference standard

A final diagnosis was performed after final discharge according to the following reference standard:

- If CT and bone scintigraphy showed a fracture, the final diagnosis was fracture.
- If CT and bone scintigraphy showed no fracture, the final diagnosis was no fracture.
- In case of discrepancy between CT and bone scintigraphy, both radiographic (six weeks after injury) and physical reevaluation during follow-up were used to make a final diagnosis.
- In case of radiographic evidence of a scaphoid fracture six weeks after injury, the final diagnosis was fracture.
- In case of no radiographic evidence of a scaphoid fracture six weeks after injury but there were persistent clinical signs of a scaphoid fracture after two weeks, the final diagnosis was fracture.
- If there was no radiographic evidence of a scaphoid fracture six weeks after injury and there were no longer clinical signs of a scaphoid fractures throughout follow-up, the final diagnosis was no fracture.

Power analysis

The sensitivity of bone scintigraphy is approximately 98% and its specificity is about 90%, resulting in a suspected chance of a correct diagnosis on bone scintigraphy of 0.15*0.98 + 0.85*0.90 = 0.912, with a prevalence of 15%(2;3). Our hypothesis was that CT had an sensitivity of 90% and a specificity of 100%. This resulted in a chance of 0.15*0.9 + 0.85*1 = 0.98 of a correct diagnosis using CT. In order to detect this difference in correct diagnosis with a power of 0.80 using a McNemar test ($\alpha = 0.05$, two-tailed),169 patients were needed. Due to the within-patient-design of this study, it is very likely that there is a positive correlation between the results of CT and bone scintigraphy and the number of patients can be reduced. Therefore the aim was to include 150 patients. According to the reference standard, the sensitivity, specificity, accuracy PPV and NPV were calculated for bone scintigraphy and CT scan. In addition percentages of sensitivity, specificity and correct predictions between the two diagnostic methods were compared with a McNemar test. A p-value < 0.05 was considered significant.

Table 1. Cross tables showing actual scaphoid fractures and related positive and negative CT's and bone scintigraphy's (BS).

	scaphoid # BS	no scaphoid # BS	totals
scaphoid #	19	1	20
no scaphoid #	9	130	139
totals	28	131	159

	scaphoid # CT	no scaphoid # CT	totals
scaphoid #	14	6	20
no scaphoid #	1	138	139
totals	15	144	159

 # fracture

Table 2. Tables showing sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) for CT and bone scintigraphy (BS).

Summary table BS		
sensitivity	95%	(85-100%)
specificity	94%	(90-98%)
accuracy	94%	(90-98%)
PPV	68%	(51-85%)
NPV	99%	(98-100%)

Summary table CT		
sensitivity	70%	(50-90%)
specificity	99%	(98-100%)
accuracy	96%	(93-99%)
PPV	93%	(80-100%)
NPV	96%	(93-99%)

Results

Patient Characteristics

In a period of 39 months, a total number of 159 consecutive patients with a suspected scaphoid fracture visited the Emergency Department. They were 79 men and 80 women, with a mean age of the 41 years (range 17 to 88). CT showed 15 scaphoid and 35 other fractures. Bone scintigraphy showed 28 scaphoid and 57 other fractures. According to the reference standard, there were 20 scaphoid fractures (Table 1). CT had a sensitivity of 70%, specificity of 99%, accuracy of 96%, a positive predictive value (PPV) of 93% and a negative predictive value (NPV) of 96%. Bone scintigraphy had a sensitivity of 95%, specificity of 94%, accuracy of 94%, a PPV of 68% and a NPV of 99% (Table 2). The percentages of sensitivities and accuracies did not differ significantly between CT and bone scintigraphy (respectively p=0.125 and p=0.629). Specificity did differ significantly (p=0.022) (table 3).

Table 3. Cross tables comparing CT and bone scintigraphy for sensitivity (a), specificity (b) and accuracy (c) using the McNemar test.

a.

Mcnemar Sensitivity		CT pos	CT neg	
BS	pos	13	6	19
BS	neg	1	0	1
		14	6	20

*Two-sided p-value: 0.1250

b.

Mcnemar Specificity		CT pos	CT neg	
BS	pos	129	1	130
BS	neg	9	0	9
		138	1	139

*Two-sided p-value: 0.0215

c.

Mcnemar accuracy		CT pos	CT neg	
BS	pos	142	7	149
BS	neg	10	0	10
		152	7	159

**Two-sided p-value: 0.6291*

** Result of the McNemar*

Discussion

This study is the largest to date to compare CT and bone scintigraphy for suspected scaphoid fractures. We demonstrated that the CT had a lower sensitivity but higher specificity for occult scaphoid fractures. In essence, the choice is overtreating patients without a scaphoid fracture (bone scintigraphy) and underdiagnosing patients with a scaphoid fracture (CT). It is postulated that a missed scaphoid fracture gives a higher risk of complications, but the exact rate of complications of these fractures is not known. Therefore, 100% sensitivity seems an essential criterion for a diagnostic tool. The false negative CT scans in this manuscript are therefore unfavorable.

In literature, there are three studies that compare CT with bone scintigraphy.(22,27,28) Two of these (27 and 28) are of recent date, but have a smaller sample size and they use different reference standards.

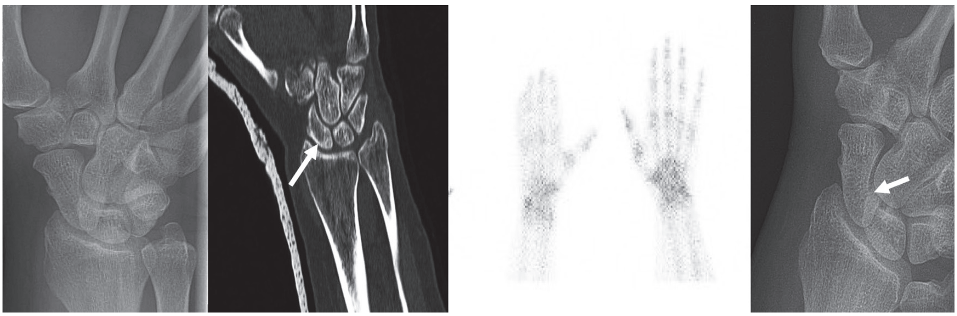
Our reference standard (radiographic and clinical follow-up) is open to debate. It is known that repeated radiographs have little added value in diagnosing occult scaphoid fractures. Despite the above, there are surgeons who suggest the use of late radiographs as the final arbiter.(29) Consequently, the three patients with a false negative CT (clinically suspected, negative initial and follow-up radiographs, negative CT, positive bone scintigraphy and positive clinical follow-up) could be considered to have a correct CT and false positive bone scintigraphy when using late radiographs as the sole reference standard. Sensitivity of CT would be 85% (17/20) using only repeated scaphoid radiographs as reference standard (Figure 1). The sole use of repeated radiographs is in our opinion not sufficient and a clinical follow-up was also added to our reference standard. The false negative bone scintigraphy was remarkable. According to the literature, bone scintigraphy has a near to 100% sensitivity.(2,7,30,31) Re-examination of this specific patient has led to debate between radiologists as there are radiologists who suggest that the CT and repeated x-ray is negative and therefore the bone scintigraphy would be correct (Figure 2). This debate underlines the diagnostic problem and diagnostic value of CT and radiographs in accordance to a substantial observer variation described.(32)

In conclusion, this study confirms that bone scintigraphy remains the gold standard to date.

Figure 1. (a) Initial radiograph of a patient with pain in the anatomic snuffbox after wrist trauma. (b) CT scan of the same patient, diagnosed as "no fracture." (c) Bone scintigraphy (after 72 hours) of the same patient, diagnosed as "scaphoid fracture." (d) Repeated radiograph of the same patient six weeks after wrist trauma. There is a clear fracture line. Conclusion: Final diagnosis was a scaphoid fracture and CT was false negative.

(a) (b) (c) (d)

Figure 2. (a) Initial radiograph of a patient with pain in the anatomic snuffbox after wrist trauma. (b) CT scan of the same patient, diagnosed as "scaphoid fracture." (c) Bone scintigraphy (after 72 hours) of the same patient, diagnosed as "no fracture." (d) Repeated radiograph of the same patient six weeks after wrist trauma. Diagnosis of the radiologist was fracture. Conclusion: Final diagnosis was a scaphoid fracture according to our reference standard and bone scintigraphy was false negative. However, there is debate about the repeated radiograph. As written in the discussion are there also radiologists who suggest that there is no evident fracture.



(a) (b) (c) (d)

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Chapter 4

Interobserver variability among radiologists for diagnosis of scaphoid fractures by computed tomography

De Zwart AD, Beeres FJP, Kingma LM, Otoide M, Schipper IB, Rhemrev SJ
J Hand Surg Am. 2012 Nov;37(11):2252-6.

Abstract

Objectives To determine the interobserver variability among radiologists for Computed Tomography (CT) diagnosis of scaphoid fractures.

Methods Four specialized musculoskeletal radiologists evaluated the CT scans of 150 consecutive patients who were clinically suspected of having sustained a scaphoid fracture but whose scaphoid-specific radiographs were normal. The radiologists were asked to determine the presence or absence of a scaphoid fracture and to localize the fracture. Interobserver agreement was calculated using the kappa statistic.

Results The radiologists diagnosed between 11 (7%) and 22 (15%) scaphoid fractures; the kappa value was 0.51.

Conclusion Agreement on the presence of a scaphoid fracture and its location on a CT scan was moderate among the 4 radiologists. This finding raises the question as to whether scaphoid fractures could be under- or overdiagnosed in daily practice when CT is used to exclude or confirm a fracture. This should be kept in mind when interpreting clinical and radiological results in patients with suspected scaphoid fractures.

Introduction

Twenty percent of all scaphoid fractures are not evident on initial radiographs.(1-3) An untreated or mistreated scaphoid fracture may give rise to osteonecrosis, nonunion, carpal instability with subsequent pain, or functional impairment.(4-9) To initiate appropriate treatment as soon as possible, the diagnostic method chosen must be accurate and allow for the accurate identification of scaphoid fractures among suspected fractures.CT is often advocated for the diagnosis of scaphoid fractures in patients who are clinically suspected of having a fracture but whose radiographs are negative. The primary aim of this study was to determine the interobserver variability in the use of CT for the diagnosis of true scaphoid fractures among suspected fractures. Interobserver variation in fracture localization was additionally evaluated because the location of a fracture could have distinct consequences on the choice of treatment.(10,11)

Methods and materials

Patients

This cross-sectional study was approved by the regional medical ethics committee. Between November 2007and March 2010, all eligible patients who had consecutively presented at the emergency department of our facility were included in the study after both oral and written informed consent had been obtained. The eligibility criteria were a suspected scaphoid fracture (a tender anatomic snuffbox and pain in the snuffbox when applying axial pressure on the thumb or index finger), recent trauma (within 48 h) and no evidence of a fracture on scaphoid radiographs. The scaphoid radiographs were taken on three planes: a posteroanterior view with the hand in a neutral position, an oblique view with the wrist in 10° of supination and maximal ulnar deviation and a true lateral view with the wrist resting in the ulnar position on the x-ray plate. Patients who had sustained multiple injuries, who were younger than 18 years of age, or in whom CT was contraindicated were excluded from the study.

CT protocol

The CT scans were obtained with a General Electric Lightspeed Qx/I CT Scanner (Pewaukee, WI). The technique used was described by Sanders.(12) A patient lay prone on the scanning table with the hand extended forward, palm down, over the head, with the wrist in neutral flexion and neutral radial-ulnar deviation. Scout images were obtained to ensure that the scanning plane corresponded with the scans that provided a lateral view of the scaphoid, as defined by the central longitudinal axis of the scaphoid. Coronal plane images, defined as images that provided a posteroanterior view of the scaphoid in the anatomic plane and in line with the axis of the scaphoid, were obtained by supinating the forearm 90° while keeping the wrist in a neutral position. Slice thickness was 0.625 mm with reconstructions every 0.4 mm (120 per kilovoltage, 80 mA, noise index 34). For multiplanar reformatted images, the parameters were a 2-mm slice thickness at a 2-mm interval. All scans were reconstructed in high kernel bone algorithms (high spatial resolution/low contrast resolution).

Observers

We asked four of our facility radiologists, experienced in musculoskeletal trauma radiology, to evaluate the CT scans of the patients included in the study for the presence or absence of a scaphoid fracture. If a fracture was diagnosed, we also asked for its exact location. The four radiologists had 36, 18, 16 and 12 years of clinical experience, respectively.

Evaluation

All CT images were blinded and uploaded into a workstation (GE Medical Systems IT, Zeist, The Netherlands, software Centricity Radiology RA 600 Standard v6.1 Build 1588 patch 05, 04, 02, 01). Both before and during evaluation of the CT scans, the radiologists had been aware of the fact that all patients were clinically suspected of having scaphoid fractures but whose radiographs had been negative. They did not have access to the radiographs or any other clinical data. Each radiologist independently rated each CT scan using a standardized scoring sheet containing the following items:

1. Scaphoid fracture (yes/no) and, if yes, its location (distal/waist/proximal)
2. Distal radius fracture (yes/no)
3. Other carpal fracture (yes/no)
4. No injury

Statistical analysis

Interobserver agreement among the four observers was calculated. For the presence or absence of a scaphoid fracture, the simple kappa coefficient was calculated. For the location of a scaphoid fracture, the weighted kappa coefficient was calculated because these data had been scored on an ordinal scale. For the interobserver variations, an overall kappa statistic along with the pairwise kappa statistics was provided. For the overall weighted kappa, an intraclass correlation coefficient was calculated. The kappa statistic is a chance-corrected measurement of agreement in data. A kappa value can range from +1 (perfect agreement) to -1 (absolute disagreement). A value of 0 indicates no more agreement than could be expected by chance alone. The interpretation of the kappa value was based on the guidelines of Landis and Koch,(13) which suggest that values between 0 and 0.2 represent slight agreement; between 0.21 and 0.40, fair agreement; between 0.41 and 0.60, moderate agreement; and between 0.61 and 0.80, substantial agreement. A value above 0.80 is considered to be an almost perfect agreement.

Results

A total of 162 patients with a clinically suspected scaphoid fracture were eligible for inclusion. Two patients who had not undergone CT scanning were excluded from the analyses, as well as 10 patients whose CT scans had not been carried out according to the protocol. There were 150 (93%) patients included with a mean age of 41 years (range, 18 – 89 y); 77 (51%) were male.

Interobserver agreement for the presence of scaphoid fracture

The four radiologists diagnosed 22, 16, 15 and 11 scaphoid fractures, respectively. Overall, kappa for presence of a scaphoid fracture was 0.51; the kappa between observers ranged from 0.36 to 0.68 (Table 1). Figure 1 contains a slice of the CT of the scaphoid upon which the radiologists agreed a scaphoid fracture was present. In this patient, a fracture line in the scaphoid became visible on the x-ray that was repeated six weeks after trauma. Figure 2 is an example of a CT scan on which the radiologists had not agreed. Two radiologists had scored “scaphoid fracture” and two radiologists had scored “no injury.” Interobserver agreement for the location of the scaphoid fracture Three radiologists reported “waist” most often as the location of the scaphoid fracture (Table 2). Overall, kappa for scaphoid fracture location among four observers was 0.48 and kappa ranged from 0.26 to 0.84 among observers (Table 3). Figure 3 gives examples of a CT scan in which the radiologists had not agreed on the location of the scaphoid fracture.

Other fractures

The four radiologists collectively diagnosed a total of 48 distal radius fractures and 97 other carpal fractures in the absence of any scaphoid fracture.

Table 1. Interobserver variation for 150 Computed Tomography Scans relating to the Presence or Absence of a Scaphoid Fracture. 95% confidence intervals in parentheses.

Observer	1	2	3	4
1	X	0.52 (0.36-0.68)	0.48 (0.32-0.64)	0.36 (0.21-0.51)
2		X	0.68 (0.52-0.84)	0.55 (0.39-0.71)
3			X	0.50 (0.34-0.66)
4				X

Table 2. Overview of the Location of the Scaphoid Fractures for the four Radiologists Independently

Location	Observer 1	Observer 2	Observer 3	Observer 4
proximal	1 (1%)	1 (1%)	6 (4%)	1 (1%)
waist	11 (7%)	9 (6%)	3 2%)	6 (5%)
distal	9 (6%)	6 (4%)	6 (4%)	4 (3%)
not reported	1 (0.7%)	0	0	0
no scaphoid fracture	128 (85%)	134 (89%)	135 (90%)	139 (93%)

Table 3. Interobserver Variation for 150 Computed Tomography Scans Relating to Localization of a Scaphoid Fracture. 95% confidence intervals in parentheses.

Observer	1	2	3	4
1	X	0.84 (0.34-1.0)	0.5 (0.12-0.88)	0.53 (0-1)
2		X	0.52 (0.15-0.89)	0.4 (0-0.88)
3			X	0.26 (0-0.77)
4				X

Figure 1. Coronal reformatted CT section of a patient with a suspected scaphoid fracture (arrow). Two radiologists diagnosed a scaphoid fracture and two radiologists did not.

Figure 2. Coronal reformatted CT section of a patient with a suspected scaphoid fracture (arrow). All four radiologists scored a scaphoid fracture as being present.

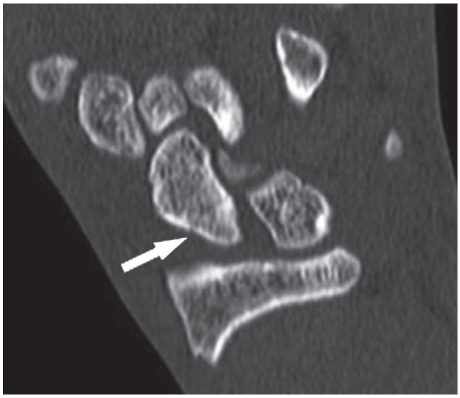
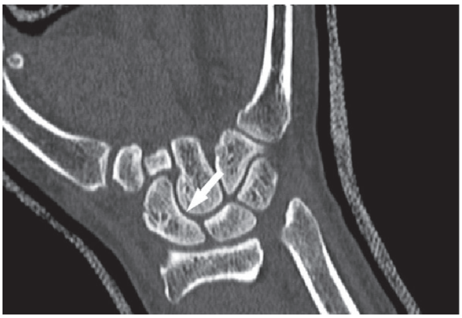
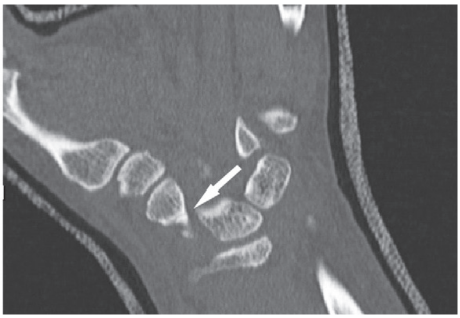


Figure 3. (a) Coronal reformatted CT section of a patient with a suspected scaphoid fracture (arrow) in which there was a discrepancy in the location of the fracture as judged by the radiologists. (b) Another coronal section of the same patient. The fracture line (arrow) in this image is still present, indicating there was a fracture.



(a)



(b)

Discussion

The primary aim of this study was to determine interobserver variability in the interpretation of CT scans in clinically suspected scaphoid fractures. Our study showed that agreement among the four radiologists for the presence of a true scaphoid fracture among clinically suspected patients was moderate, with a kappa value of 0.51. Agreement on the location of a scaphoid fracture on a CT scan was also moderate (kappa value, 0.48). Together, the four radiologists diagnosed a total of 48 distal radius fractures and 97 other types of carpal fractures in the absence of any scaphoid fracture. The presence of these injuries likely explained the clinical symptoms and initial suspicion of a scaphoid fracture. The literature reveals that an initial clinical suspicion of scaphoid fracture with no fracture seen on an initial radiograph results in the diagnosis of a different adjacent injury in 30% of cases.(14) The standard protocol for CT used in our clinic may present a limitation to this study. A different protocol with thinner slice reformations and higher resolution might increase the observer agreement. The current results, therefore, apply primarily to the CT protocol used in this study. Another limitation of this study is that the CT scans and their reviews were conducted in a single institution. Another study has investigated the interobserver variation of the use of CT for suspected scaphoid fractures.(15) They used eight observers who reviewed 30 CT scans of patients with suspected scaphoid fractures. That study revealed substantial interobserver agreement (average kappa value, 0.66 [95% confidence interval (CI), 0.58–0.72]).The different kappa value in comparison with our results may be due to a different CT protocol used in the two studies. Generally speaking, CT is advantageous for diagnosing scaphoid fractures in patients with suspected scaphoid fractures in several ways: it is readily available, is fast and costs less than Magnetic Resonance Imaging (MRI) or bone scintigraphy.(15-19) One disadvantage of CT is radiation exposure. If the diagnosis of a scaphoid fracture is missed and treatment is delayed or inadequate, it could lead to severe impairment; therefore, the examination method chosen should be highly sensitive. A meta-analysis by Yin et al. concerning the diagnostic performance of CT showed a sensitivity of 93% and a specificity of 96%.(20) Alternative diagnostic modalities that could be used for triaging suspected scaphoid fractures are MRI and bone scintigraphy. Sensitivity and specificity for these tools have been reported as being 96% and 99% for MRI, respectively and 97% and 89% for bone scintigraphy.(20) Observer agreement scores for MRI and bone scintigraphy are substantial.(21,22) Both MRI and bone scintigraphy, therefore, appear to result in better diagnostic performance than CT. Although interobserver agreement is just one aspect of diagnostic performance and does not indicate whether fractures are missed or overdiagnosed, the quest for a true reference standard for scaphoid fractures continues. The previously published results on sensitivity and specificity should, therefore, be interpreted with care. Clinicians who use CT to triage suspected scaphoid fractures should be aware of these results and should carefully deliberate before excluding a scaphoid fracture. If clinical doubt arises based on discrepancies between the CT results and the physical examination, additional imaging modalities such as MRI or bone scintigraphy may be helpful.

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Chapter 5

Radiation exposure due to CT of the scaphoid in daily practice

De Zwart AD, Beeres FJP, Pillay M, Kingma LM, Schipper IB, Rhemrev SJ
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Abstract

Objectives The aim of this study was to measure radiation exposure including scatter radiation, resulting from CT of the scaphoid in different settings as used in daily practice and to calculate the effective dose (ED) using a wrist phantom.

Methods The radiation exposure was quantified for five different CT protocols, all used in daily practice for the scaphoid CT. Two protocols concerned a CT of the scaphoid with a plaster cast of the hand and three protocols without. For all protocols the Computed Tomographic Dose Index weighted (CTDIw), the scatter dose to the brain and scatter dose to the torso were derived from the CT and measured externally with the Piranha dose meter.

Results The average CTDIw was 2.18 mGy. The average scatter to the brain and torso was 0.011 mSv. The average estimated ED was 0.02 mSv (range 0.02 to 0.04) of which 0.0008 mSv (range 0.0003 to 0.0012) was due to the scatter radiation. The two CT protocols of the scaphoid performed with a plaster cast resulted in a 90% higher ED, although the power of the study was too low to demonstrate this statistically.

Conclusion The CT protocols used for scaphoid analyses in a plaster cast immobilized hand may result in higher radiation exposure than without plaster cast. We therefore recommend, whenever possible, performing CT of the hand and wrist without a plaster cast.

Introduction

Computer Tomography (CT) is often used in the diagnostic workup of clinically suspected scaphoid fractures that are not evident on plain radiographs. CT is readily available, cheap and fast.(1) The assumed specificity is 99% and sensitivity 93%,(2) although a recent study showed a lower sensitivity of around 70%.(3) Despite its moderate sensitivity, CT remains the investigation of choice for the triage of suspected scaphoid fractures in many hospitals. A disadvantage of CT is the exposure to radiation. Since the damaging impact of radiation on tissue in the body is cumulative, radiation exposure should be kept as low as possible throughout a patient's life according to the philosophy of ALARA (As Low As Reasonably Achievable).(4) Moreover investigations have shown an increased risk of cancer after exposure to low dose radiation.(5) Radiology departments in Europe are obliged to abide by set reference levels of radiation exposure for each procedure according ICRP (International Commission for Radiation Protection) and the European EURATOM guidelines.(6) Diagnostic Reference Levels (DRL) for the extremities are currently being developed and, therefore, not yet available for CT of the scaphoid. Moreover, the DRL measurements do not include scatter radiation. This study was designed to determine the radiation exposure of a CT of the scaphoid, including the scatter radiation, mimicking different clinical settings (with and without a plaster cast) in a phantom. These findings are of interest for clinicians and patients who should be informed of the potential health hazards they are subjected to.

Materials and Methods

This study does not involve humans or animals. Therefor approvement by the regional Medical Ethics Committee was not needed.

Radiation measurements

The direct radiation exposure on PMMA (polymethylmethacrylate) wrist phantoms was measured. The construction of the phantom was based on the phantom description by Robertson et al. The phantom was constructed accordingly in our radiotherapy moldroom (Figure 1).(7) The radiation dose was measured in CTDIw using the Piranha dose meter with a SD16 ionising chamber. For the scatter measurements the Victoreen 451B ionizing chamber was used. The measurements were taken in two different settings. The CTDI measuring chamber was placed inside the wrist phantom for measurement of the radiation exposure due to the primary beam and the Victoreen 20 cm above the wrist phantom (where the head would be in a clinical situation) for measurement of the scatter to the head (Setting A). The CTDI measuring chamber was placed inside the wrist phantom for measurement of the radiation exposure due to the primary beam and the Victoreen dosemeter above the head phantom for measurement of the scatter to the rest of the body (setting B) (Figure 1). The Dose-Length Product (DLP), CT dose index (CTDi) and CT dose index volume (CTDivol) were taken from the CT scanner.

CT protocols

The radiation exposure was measured with the help of a phantom during five different CT protocols. These five protocols are commonly used for in-hospital imaging of the scaphoid. The parameters were chosen on the basis of best images for viewing the scaphoid, produced in the two radiological departments of our clinics. Three protocols concerned a CT of the scaphoid without a plaster cast and two described imaging of the scaphoid in a plaster cast. An overview of CT parameters for the five protocols is given in Table 1. For protocol one, four and five, three measurements were performed in setting A and three measurements in setting B. For protocol two and three, five measurements were performed in setting A and five in setting B (Figure 1). Conform our standard acute plaster protocol, a six layer plaster cast was used on the wrist phantom, in the way that it is normally applied in the acute setting. The CT was performed after the plaster had dried completely. The CT images were obtained with a multidetector scanner (General Electric Lightspeed Qx/I CT Scanner, Pewaukee, WI, USA), using the technique described by Sanders.(8) The phantom was positioned as if the patient lay prone on the scanner couch with the hand extended over the patients head. Section collimation was 0.625 mm with reconstructions every 0.4 mm (120 kVp, 80 mA, noise index 34). For multiplanar reformatted images, parameters were 2 mm slice thickness, 2 mm interval. All scans were obtained in the axial plane. With our 64-slice scanner the voxels are isotropic (i.e. 0.625 mm in the X-,Y- and Z-plane), so there is no difference with direct oblique coronal scanning. All reconstructions were performed using filtered back-projection. For comparison, no automated dose-reduction schemes were implemented. With measurements of the CTDIw and the scatter radiation the effective dose (ED) was calculated using the following formula: ED= (CTDIw×WFb&s)+(''scatter to the brain''×WFb)+(''scatter to the torso''×WFt'') Where WFb&s is the weighting factor for bone and skin (0.01), WFb is the weighting factor for the brain (0.01) and WFt is the weighting factor for the torso (0.24). The ICRP 103 weighting factors were used. For WFt we summed the weighting factors for lung (0.12), Liver (0.04), Esophagus (0.04) and Thyroid (0.04). Average ED was compared between the protocols with and without plaster cast by means of an unpaired t-test using SPSS version 2

Figure 1. Study design with phantoms for measurements of radiation in two different settings. Setting A: The CTDI measuring chamber was placed inside the wrist phantom for measurement of the radiation exposure due to the primary beam and the Victoreen 20 cm above the wrist phantom (where the head would be in a clinical situation) for measurement of the scatter to the head.
Setting B: The CTDI measuring chamber was placed inside the wrist phantom for measurement of the radiation exposure due to the primary beam and the Victoreen dosemeter above the head phantom for measurement of the scatter to the rest of the body.

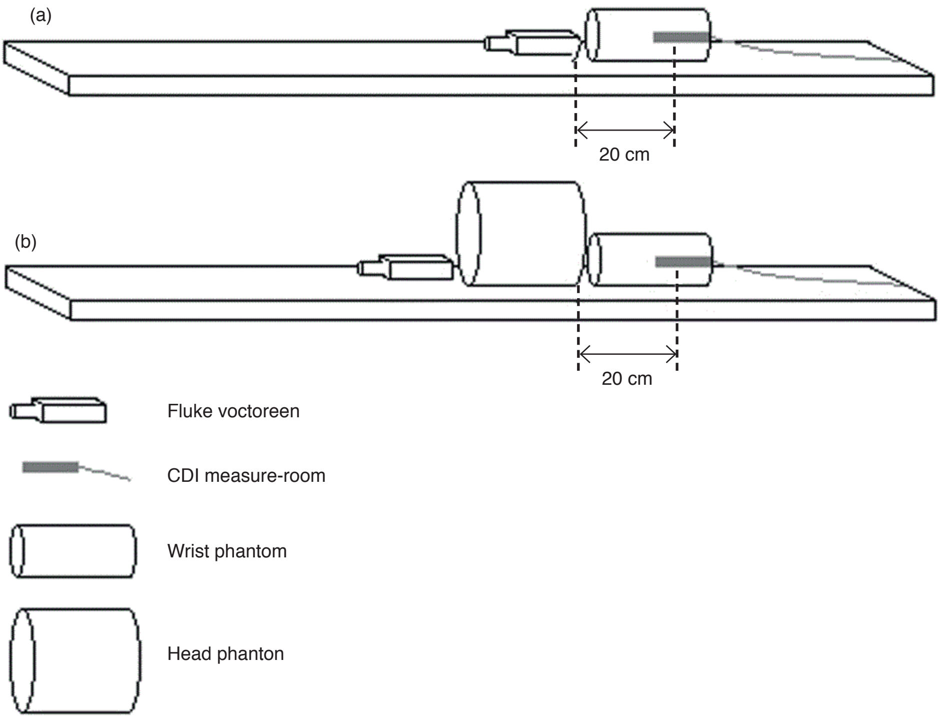

Table 1. CT parameters of five different CT protocols for diagnosing occult scaphoid fractures without and with a plaster cast.

	Without plaster cast		With plaster cast		
CT 64 slice	Protocol 1	Protocol 2	Protocol 3	Protocol 4	Protocol 5
kV	80	80	80	100	100
mA	40	40-150	40-150	80	45
time [s]	4.6	7.8	9	4.6	4.6
collimation	32X0.625	32X0.625	32X0.625	32X0.625	32X0.625
length [mm]	100	185.5	185.5	100	100
rot. time [s]	0.4	0.4	0.4	0.4	0.4
pitch	0.531	0.531	0.531	0.531	0.531

Results

Table 2 presents an overview of the mean results for the five different CT protocols. The average ED for all protocols was 0.02 mSv. The average ED for CT protocols without a plaster cast was 0.017 mS (standard deviation [SD] 0.001) whereas the average ED for CT protocols with a plaster cast was 90% higher (0.032 mSv, SD 0.012). The difference in ED between the protocols with and without plaster cast was not statistically significant (p=0.33).The ED due to the scatter radiation ranged from 0.0003 to 0.0012 mSv, with an average of 0.0008 mSv.

Table 2. Overview of mean (standard deviation (SD)) for measured CTDIw, scatter to the torso, scatter to the brain and calculated ED for five different CT protocols used for diagnosing occult scaphoid fractures without (1,2 and 3) and with (4 and 5) a plaster cast.

Protocol	CTDIw (SD)	Effective Dose CTDIw	Scatter to the brain (SD)	Scatter to the torso (SD)	Effective Dose due to scatter	Effective Dose incl. scatter
	mGy	mSv	mSv	mSv	mSv	mSv
1*	1.5 (0.01)	0.015	0.0045 0.00004)	0.0012 (0.00001)	0.0003	0.015
2#	1.7 (0.01)	0.017	0.0094 (0.00012)	0.0031 (0.00002)	0.0008	0.018
3#	1.6 (0.01)	0.016	0.0080 (0.00017)	0.0022 (0.00002)	0.0006	0.017
Average	1.6	0.016	0.0073	0.0022	0.0006	0.017
4#	3.9 (0.04)	0.039	0.010 (0.00006)	0.0044 (0.00005)	0.0012	0.040
5#	2.2 (0.01)	0.022	0.0076 (0.00009)	0.0028(0.00004)	0.0007	0.023
Average	3.1	0.031	0.0090	0.0036	0.0010	0.032

** CTDIw was measured 6 times. The scatter to the brain and torso was measured 3 times for protocol 1, 4 and 5, (half of total in setting A and half in setting B)*
 # CTDIw was measured 10 times. The scatter to the brain and torso was measured 5 times for protocol 2 and 3 (half of total in setting A and half in setting B)

Discussion

This study provides a quantification of the direct radiation exposure to the wrist when performing a CT of the scaphoid. Moreover, the ED including the scatter radiation to the brain and torso of the patient was quantified. The average ED for all five different CT protocols was 0.02 mSv which is equivalent to approximately 70 hours of background radiation, when assuming a background radiation of around 2.5 mSV a year. Also, this study showed that the ED is almost twice as high when performing a CT of the scaphoid in a plaster cast compared to the situation without a cast. Due to the limited power of the study, however, this difference could not be demonstrated statistically. To our knowledge, one other study investigated the radiation exposure of musculoskeletal CT's and found a radiation exposure of around 0.03 mSv, which is little higher than we found.(9) This might be due to the use of modern scanners with better radiation exposure reduction capabilities. It is difficult, however, to compare our study with this study, as they do not describe the CT protocol they use and in what setting there measurements were done. Moreover these results were mathematically estimated from calculations and may not be reliable and do not account for scatter radiation. Our study used a direct measurement of the radiation exposure and therefore provides more accurate and reliable results. The radiation exposure of a CT of the wrist is relative low and is comparable with a radiograph of the chest (0.04 mSv). The effective dose of other common diagnostic imaging procedures ranges from 0.001 mSv for radiography (X-ray)-Extremity, 0.4 mSv for mammography and 1.5 mSv for radiography (X-ray)-Spine, to 15 mSv for Computed Tomography (CT)-Abdomen and Pelvis. However, controversy exists about the dangers of low-dose radiation exposure in the clinical setting. A radiograph of the chest of a female child between the age of 0 and 9 leads to a lifetime risk of cancer of 1.9×10-6 and a radiograph of the chest between the age of 60 and 69 to a lifetime risk of 0.8×10-6.(10) In the LSS Report 13 on the follow-up the 86,000 survivors of Hiroshima and Nagasaki from 1950-1997, it was concluded that solid cancer rates increased linearly with direct evidence of increased cancer incidence from exposures of 0.5 to 2.0 Sv (500-2,000 mSv), a dose markedly above that of average medical radiation and far more than a CT of the wrist. Further extrapolations of the LSS epidemiological data from low-dose radiation risk of the 65% of survivors exposed to radiation doses <100 mSv, however, did reveal a statistically significant risk of developing solid tumours even at doses <100 mSv in a linear non-threshold model. (5) Cancer risks are estimates from epidemiological studies and are subject to active, ongoing debate. Nonetheless, even in the face of disagreement and uncertainty, patient safety requires the assumption that the risk of radiation exposure is real; and that one should strive to maintain the lowest possible lifetime exposures. According to the ALARA philosophy, the radiation exposure must be kept as low as possible. Therefore, when performing a CT of the scaphoid, the CT protocol with the least radiation exposure should be chosen and that would be the protocol without a plaster cast. Also, the radiologist should consider reducing the scatter radiation by means of radioprotective shields whenever possible.

A limitation of the study was that we only measured the radiation exposure acquired by CT system (General Electric) with five protocols used in our clinic according the technique of Sanders.(8) Both protocol and CT system may differ per hospital. Additionally, in modern CT scanners it is possible to hold the arm more extended with consequently a greater distance between the wrist and the brain, resulting in lower radiation exposure of the brain. Secondly, we measured the radiation exposure for only three anatomical areas of the body (i.e., scatter to the brain, scatter to the torso and radiation exposure of the primary beam). We do however feel that the clinically relevant scatter is limited to the brain and torso and assumed that the scatter to the rest of the body is negligible as scatter is inversely proportional with the distance. A third limitation is that we have measured three protocols six times and two protocols ten times. There was no statistical base for the number of measurements and there was no specific reason for measuring in different numbers. In interpretation of the result the potential under-powering of this study should be taken into account. However, the range of the results were very small. So we believe these result are valid and reproducible. Plastic casts could alter radiation exposure as compared to plaster of Paris. We exclusively measured radiation exposure using a dried plaster cast, which is standard in our clinic in the acute setting of wrist and carpal fractures for the first 10 days. At the first outpatient review, the casts will be changed for a plastic cast. In some clinics, CT might be made at this time point, with a plastic cast. The material of the cast may alter the radiation exposure results. In addition, other CT systems and local protocols obviously also could influence the radiation exposures and the use of a phantom as presented in this study could be very useful to analyse the influence of different clinical settings. Since the wrist is a relatively small object, it in itself does not generate significant scattered radiation. However, the use of different scanning protocols, additional materials (such as casts) could influence the amount of scatter substantially. The scatter components of the CT table are considered a common factor for all CT studies and have therefore been left out of the equation. An evaluation of the table composition and scatter could be a topic of further investigation.

In summary, this study provides insight into the radiation exposure for patients with a CT of the wrist or hand, including the scatter radiation. The CT protocols used for scaphoid analysis immobilised in a plaster cast seem to result in higher radiation exposure and measurable scatter. With respect to the ALARA philosophy, CT's of the wrist should preferably be performed without a plaster cast. A radioprotective shield for the patient leads to less radiation exposure of the torso and could therefore be considered.

Table 3. Mean (SD) for CT measurements recorded by the CT dosimeter for five different CT protocols.

Protocol (number of measurements)	DLP mGycm	CTDi mGy	CTDivol mGy
Without plaster cast			
1 (6)	27.7 (0.16)	1.4 (0.01)	2.8 (0.02)
2 (10)	59.4 0.35)	1.7 (0.01)	3.2 (0.02)
3 (10)	54.4 (0.27)	1.6 (0.01)	2.9 (0.01)
Average	47.2	1.6	3.0
With plaster cast			
4 (6)	73.7 0.68)	3.8 (0.04)	7.4 (0.07)
5 (6)	70.5 (0.40)	2.2 (0.01)	4.2 (0.02)
Average	72.1	3.0	5.8

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Chapter 6

Comparison of MRI, CT and bone scintigraphy for suspected scaphoid fractures

De Zwart AD, Beeres FJP, Rhemrev SJ, Bartlema K, Schipper IB
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Abstract

Objectives The best diagnostic modality for confirmation of the diagnosis of a scaphoid fracture that is not visible on the initial radiograph (occult scaphoid fracture) is still subject of debate. The aim of this study was to compare the accuracy of magnetic resonance imaging (MRI), computed tomography (CT) and bone scintigraphy for the diagnosis of these occult scaphoid fractures.

Methods In a study period of 12 months, 33 consecutive patients with a clinically suspected scaphoid fracture without a fracture on the scaphoid radiographs were evaluated with MRI, CT and bone scintigraphy. In case of a discrepancy between the diagnostic modalities, the final diagnosis was based on standardised follow-up with clinical examination and a repeated radiograph.

Result Three of the 33 patients had a scaphoid fracture. MRI missed one scaphoid fracture and did not over-diagnose. CT missed two scaphoid fractures and did not overdiagnose. Bone scintigraphy missed no scaphoid fractures and over-diagnosed one scaphoid fracture in a patient with a fracture of the trapezium.

Conclusion This study shows that neither MRI, nor CT and bone scintigraphy are 100% accurate in diagnosing occult scaphoid.

Introduction

Fractures of the scaphoid are the second most common fractures of the upper limb after distal radius fractures.(1,2) Rapid and accurate diagnosis is needed, because delayed initiation of therapy increases the risk of complications such as non-union and avascular necrosis and subsequent functional impairment.(3-6) The diagnosis of a scaphoid fracture may however be difficult to establish on a conventional radiograph. Previous research has shown that 10% of scaphoid fractures are missed on primary radiographs.(7-9) Repeated radiographs after 7-10 days seem to have limited value, without additional diagnostics.(10-12) The irregular contour, the 3-dimensional location in the wrist of the scaphoid and the overlap of the carpal bones render interpretation of scaphoid radiographs difficult, especially in the absence of fracture dislocation. Magnetic resonance imaging (MRI), computed tomography (CT) and bone scintigraphy have been shown to have better diagnostic performance than scaphoid radiographs.(13) However, it remains subject of debate which of these three is the most appropriate and accurate modality for the diagnostic work-up of a clinically suspected scaphoid fracture. To our knowledge, no prospective study has been performed comparing diagnostic accuracy of MRI in the acute stage (<72h), CT in the acute stage (<72h) and delayed bone scintigraphy (between three and five days) in one patient series. For this reason we compared MRI, CT and bone scintigraphy in a consecutive series of patients with a clinical suspicion of a scaphoid fracture and a negative radiograph.

Methods and materials

This prospective study was approved by the regional Medical Ethics Committee.

Patients were eligible if there was a clinical suspicion of a scaphoid fracture, a recent hand trauma (within 48 h) and no evidence of a scaphoid fracture on the initial scaphoid radiographs. All consecutive eligible patients that visited the Emergency Department (ED) of our institution were included for extensive diagnostic work-up after both written and oral informed consent. Poly-trauma patients, patients with a history of a carpal fracture, patients younger than 18 years and patients with contra-indications for MRI, CT or bone scintigraphy were excluded.

Physical examination
Included patients underwent a standardised physical examination of both wrists and hands at the ED. Patients were asked to localise the "point of maximal tenderness" for pain. Direct pressure was applied on the anatomic snuffbox, distal radius and other carpal bones. Axial pressure was applied on both the first and second digit. All patients were clinically re-examined at two and six weeks after injury.

Scaphoid radiographs
All radiographs were obtained using a digital technique and a computed radiography system (Siemens Vertex 3D,Erlangen, Germany). Initial scaphoid radiographs were taken in six planes: (1) a postero-anterior view with the hand five degrees of endorotation, (2) a true lateral view with the wrist resting in the ulnar position on the X-ray plate, (3) an oblique view with the radius 30° up, (4) an oblique view with the radius 60° up, (5) an antero-posterior view in ulnar deviation and (6) a postero-anterior view with the thumb in fist. Standard scaphoid radiographs were made within 48h after trauma and repeated after six weeks.

MRI
MRI was performed within 72h after the initial presentation at the ED using a 1.5 T MR scan (GE/ONI MSK Extreme). The patient lay prone on the scanner couch with the injured hand extended forward palm down over the patient's head. The MR imaging protocol included coronal T1-weighted turbo spin-echo images with a TR of 450 ms, a TE of 13 ms, a slice thickness of 2 mm with a distance factor of 10%. The parameters for the coronal, oblique and sagittal fat-suppressed T2-weighted fast spin-echo images were 5220/73 ms (TR/TE). A slice thickness of 2 mm with a distance factor of 10% was used.

CT
The CT scans were obtained within 72h after the initial presentation at the Emergency Department with a Toshiba 64 slice scanner using the technique described by Sanders.(14) Slice thickness was 0.5 mm with reconstructions every 0.3 mm (120 per kV, 60 mA). For multi-planar reformatted images, parameters were 2 mm slice thickness, 2 mm interval. Sagittal and coronal reconstructions were made for all CT scans.

Bone scintigraphy
Bone scintigraphy was performed between three and five days after trauma, using a standard protocol of images of the early static phase, on a SKYLight gamma camera performed between two and a

half and four hours after the intravenous injection of 500 MBq of Tc-99 m-HDP (Technetium-99 m hydroxymethylene diphosphonate) visualising the osteoblastic activity with a planar collimator. Each imaging process took 10 min.

Image analysis

All radiographs were reviewed by the attending resident surgeon in the ED and decided if the patient was suitable for inclusion. A consultant radiologist evaluated the MRI and CT images. A consultant nuclear medicine physician evaluated the bone scintigraphy. The observers were blinded to the results of the other investigations. The presence of a scaphoid fracture, of other fractures, of arthrosis and of other lesions on CT, MRI and bone scintigraphy was scored by the observers on a standard yes/no format form.

Management of injury

If all diagnostic modalities were negative for fracture, no immobilisation therapy was applied. If at least one of the diagnostic modalities showed a scaphoid fracture, the patient was treated with a scaphoid forearm cast for a period of six weeks. If one of the diagnostic modalities showed another type of fracture, the patient was treated according to the specific protocol.

Reference standard

The final diagnosis of presence or absence of a scaphoid fracture was confirmed after follow-up according to the following reference standard.

- If MRI, CT and bone scintigraphy all showed a fracture, the final diagnosis was: fracture.
- If MRI, CT and bone scintigraphy all showed no fracture, the final diagnosis was: no fracture.

In case of discrepancy between MRI, CT and bone scintigraphy, the final diagnosis was established based on specific clinical signs of a fracture after six weeks (tender anatomic snuffbox and pain in the snuffbox when applying axial pressure on the first or second digit) combined with the radiographic evidence of a fracture after six weeks. If these signs were absent and no radiographic evidence, the final diagnosis was: no fracture.

Results

Between May 2010 and May 2011, 43 consecutive patients with a suspected scaphoid fracture visited the Emergency Department. A scaphoid fracture was apparent on initial radiographs of nine patients. The 34 patients with a clinically suspected scaphoid fracture and negative radiographs were included for extensive diagnostic work-up after providing informed consent. One patient was excluded as no CT was made. The remaining study group of 33 patients consisted of 16 men and 17 women, with a mean age of the 39 years (range 18-73). An overview of the diagnosed scaphoid and other fractures by MRI, CT and bone scintigraphy is given in Table 1. In four patients one or more diagnostic modalities showed a scaphoid fracture. According to the reference standard there were three scaphoid fractures. In one patient MRI and CT showed a trapezium fracture whereas bone scintigraphy showed a scaphoid fracture, which we considered as false positive for scaphoid fracture (Table 2). The calculation of sensitivity of the diagnostic modalities for three scaphoid fractures was not considered meaningful. The specificity for diagnosis of occult scaphoid fractures was 100% (95% CI 0.88–1) for MRI, 100% (95% CI 0.88–1) for CT and 97% (95% CI 0.83–1) for bone scintigraphy. In 11 of the 33 patients with clinically suspected scaphoid fractures, other injuries than scaphoid fractures were diagnosed. Eight were distal radius fractures that had been visualized by all three diagnostic modalities. In one patient a distal radius fracture was diagnosed by bone scintigraphy and MRI, but with a negative CT. There was one patient with a triquetrum fracture diagnosed by all three additional diagnostic modalities and one patient had a trapezium fracture as mentioned above (CT and MRI showed a trapezium fracture and bone scintigraphy a scaphoid fracture). Thus, combined with the scaphoid fracture patients, in 14 of the 33 suspected patients, additional immobilisation therapy was instituted based on the findings of MRI, CT and bone scintigraphy.

Table 1. Diagnoses according to MRI, CT and bone scintigraphy (BS) in 33 patients with clinical suspicion of a scaphoid fracture and negative scaphoid radiographs.

Diagnosis	MRI	CT	BS
Scaphoid fracture	2	1	4
Other fracture	11	11	10
No injury	20	21	19

Table 2. Diagnostic results for the patients in whom one or more diagnostic modalities showed a scaphoid fracture including the clinical follow up at six weeks and the repeated radiograph

	MRI	CT	BS*	X-ray*	P.E.#	Final diagnosis
1	no injury	no injury	scaphoid fx	no injury	scaphoid fx	scaphoid fx
2	scaphoid fx	scaphoid fx	scaphoid fx	scaphoid fx	no injury	scaphoid fx
3	scaphoid fx	no injury	scaphoid fx	no injury	scaphoid fx	scaphoid fx
4	trapezium fx	trapezium fx	scaphoid fx	no injury	no injury	trapezium fx

** at 6 weeks after injury*

 # P.E indicates physical examination; BS bone scintigraphy and fx indicates fracture

Discussion

This study is unique, as it is the first clinical study comparing CT, MRI and bone scintigraphy for diagnosis in suspected scaphoid fractures in one patient series. The results show that these sophisticated imaging methods diagnose scaphoid fractures in 10% of patients with negative initial scaphoid radiographs. In addition, in 25% of the patients another fracture in the same anatomical area was revealed. Many studies have separately examined the results of MRI, CT and bone scintigraphy for diagnosing suspected scaphoid fractures. A meta-analysis of diagnostic studies was performed by Yin et al. (2010), in which the pooled sensitivities and specificities of MRI, CT and bone scintigraphy were calculated.(13) Since this study, four additional prospective studies have been published concerning the diagnostic performance of CT and/or MRI and/or bone scintigraphy.(15-18) Table 3 presents an overview of this literature. The wide variation in diagnostic performance of MRI, CT and bone scintigraphy in these different studies is remarkable. The variation in results will be partly due to the use of varying reference standards. Some studies used repeated MRI or CT, while others used repeated radiographs after two weeks or after six weeks and, like we did in the present study, included the clinical follow-up in the reference standard.(13) Another explanation for the diverse result may be found in different imaging protocols used for CT and MRI. As this study is the first to evaluate CT, MRI and bone scintigraphy in one patient series, it is of additional value to the existing evidence despite some shortcomings. As in all studies that attempt to determine sensitivity and specificity, a reference standard is mandatory. The chosen reference standard is however a point of debate. Repeated radiographs alone are often being used as the reference standard. However, Low and Raby showed that repeated radiographs have a sensitivity of around 20% and a specificity of around 85% with poor interobserver agreement.(10) Other studies showed that repeated radiographs only reveal 2% additional scaphoid fractures.(11-13,19) Clinical signs are also shown in the literature to be of poor predictive value when attempting to diagnose a scaphoid fracture.(20) Anatomic Snuff Box tenderness is a sensitive, but non-specific sign.(21) Clinical criteria are unreliable for a diagnosis of acute scaphoid fracture to be made.(22) However, in a more recent study by Duckworth et al., repeated clinical assessment combined with radiographs was also used, with satisfactory results, in order to develop a clinical prediction rule.(23) Moreover, in our study 10% of the included patients with a suspected scaphoid fracture had indeed a scaphoid fracture according to the reference standard, which is conform literature.(13,24,25) And thus substantiates the use of the chosen reference standard. Given the above, the sole use of repeated radiographs after six weeks is not adequate and will still lead to missed scaphoid fractures. The additional value of repeated clinical evaluation is in our opinion crucial. Since all of the reference standards have limitations and none can be considered 100% accurate, final solid results are not available. Moreover, due to the low incidence of true scaphoid fractures, small variations are easily magnified.(23) A recent study by Buijze et al. has introduced a statistical method which could potentially encounter this problem using latent class analysis. They suggest to deal with probabilities rather than certainties for optimisation of the diagnosis and treatment of scaphoid fractures. This method is promising, however no prospective study using this method has been published yet.(15) Another potential weakness of the study is the small sample size. There were 33 patients included and in only three patients an occult scaphoid fracture was revealed. Because of the small sample size the value of the no precise estimation of the diagnostic accuracy of the separate modalities could be given. However, the specific advantages and limitations of the three diagnostic modalities could well be illustrated in our study. According to the literature MRI has the best performance in diagnosing occult scaphoid fractures with reasonable specificity and sensitivity (in this study a 1.5 T MRI scan is used. Modern MRIs may have better diagnostic performance. However there is no literature to support this). Moreover it will also diagnose soft-tissue injuries.(26) A disadvantage of MRI is the time consuming procedure, that is not always readily available and the costs are relatively high. Advantages of CT are its specificity, availability and the costs are relatively low in comparison with MRI and bone scintigraphy. CT is however less sensitive than MRI and bone scintigraphy. Some suggest this is due to the fact that CT does not detect trabecular scaphoid fractures, whereas MRI and bone scintigraphy do.(27) Furthermore a CT scan involves radiation exposure.(28) The main advantage of bone scintigraphy is its sensitivity and some suggest that is why bone scintigraphy is the investigation of choice. On the other hand, bone scintigraphy tends to overdiagnose scaphoid fractures because it provides false positive results in case of bone bruises and other pathology that increases bone turn-over.(18,26) Another limitation of the bone scintigraphy is that the exact location of the lesion may be difficult to determine.(29) Furthermore bone scintigraphy leads to radiation exposure, is invasive and leads to a delay of 3-5 days. The specific advantages and limitations of each of the diagnostic modalities are summarized in Table 4.

This study illustrates the possibilities and shortcomings of MRI, CT and bone scintigraphy in diagnosing scaphoid fractures in this group of patients. The difficulties that can be encountered when attempting to analyse their diagnostic performance in a reliable way, are demonstrated in the following three patients:

1. This patient had a negative MRI and CT. The bone scintigraphy was positive for a scaphoid fracture (Fig. 1). At six weeks there were clear clinical signs of a fracture with obvious pain in the anatomic snuffbox. The radiograph did however not show a fracture. Combining these data with the fact that MRI and CT may miss scaphoid fractures and bone scintigraphy is highly sensitive but may give false positive results, this clearly illustrates the lack of a reliable reference standard and the challenge in decision making. Finally, the clinical signs were decisive for the final diagnosis (fracture).
2. In this patient the MRI and CT showed a trapezium fracture (Fig. 2a, b). The diagnosis of the bone scintigraphy was scaphoid fracture (Fig. 2c). This example illustrates that bone scintigraphy does not always adequately indicate the exact localization of the fracture.
3. In this patient MRI showed a trabecular fracture of the scaphoid (Fig. 3a) and bone scintigraphy was positive for a scaphoid fracture (Fig. 3b), whereas CT showed no fracture. This example illustrates that CT is not adequate in the diagnosis of trabecular fractures.

Despite the common availability of advanced imaging techniques, occult scaphoid fractures remain difficult to diagnose. Bone scintigraphy, CT and MRI all have their shortcomings when used for diagnosing scaphoid fractures. MRI and CT miss fractures and bone scintigraphy tends to over-diagnose. On the other hand, these imaging modalities will account for 10% additionally diagnosed scaphoid fractures and 25% other wrist and carpal fractures. Regardless of which diagnostic modality is chosen, it is important that every patient with a suspected scaphoid fracture should be followed with great care and clinical re-evaluation, since neither MRI, nor CT and bone scintigraphy are 100% accurate in diagnosing occult scaphoid fractures. The specific advantages and limitations of each diagnostic modality should be familiar to the treating physicians and taken into consideration during the diagnostic process.

Table 3. Overview of relevant literature concerning diagnostic performance of CT, MRI and bone scintigraphy (BS) in suspected scaphoid fractures

CT	Study	Number of patients	Sensitivity	Specificity
	NB VCYin et al. (Meta-analysis)	211	93%	99%
	Ilica et al.	54	86%	100%
	Mallee et al.	34	67%	89%
	Rhemrev et al.	100	64%	99%

BS	Study	Number of patients	Sensitivity	Specificity
	Yin et al. (Meta-analysis)	1102	97%	89%
	Rhemrev et al.	100	93%	91%
	Buijze et al.*	78	100%	89%

MRI	Study	Number of patients	Sensitivity	Specificity
	Yin et al. (Meta-analysis)	513	96%	99%
	Mallee et al.	34	67%	96%
	Buijze et al.*	78	75%	100%

**In this study sensitivities and specificities were calculated using latent class analysis and with a conventional reference standard (repeated radiograph). In this table we used the results of conventional reference standard.*

Table 4. Summary of advantages and disadvantages of MRI, CT and bone scintigraphy (BS).

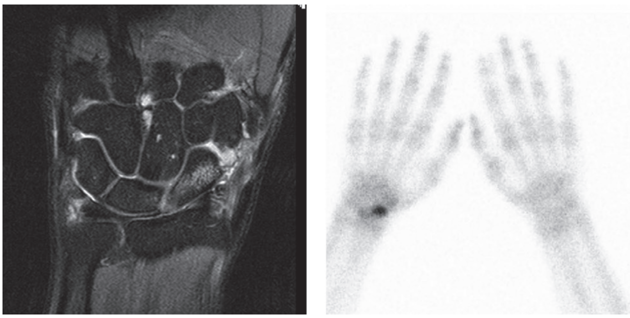
MRI	CT	BS
Advantages	Advantages	Advantages
Specificity Ligamentair injury	Specificity Fast Availability	Sensitivity
Disadvantages	Disadvantages	Disadvantages
Sensitivity Availability Time consuming	Sensitivity Radiation exposure	Specificity Radiation exposure Invasive Time consuming Delay 3 to 5 days

Figure 1. Bone scintigraphy showing activity in the scaphoid area. The nuclear physician reviewed this image as a scaphoid fracture.

Figure 2. (a) T2 image of a MRI showing a trapezium fracture. (b) Image of a CT showing cortex interruption of the trapezium. (c) Bone scintigraphy with activity in the scaphoid area. The nuclear physician reviewed this image as a scaphoid fracture.

(a) (b) (c)

Figure 3. a) T2 MRI image showing bone oedema and interruption of trabecular bone. The radiologists reviewed this as a trabecular scaphoid fracture. (b) Bone scintigraphy showing activity in the scaphoid area, reviewed as a scaphoid fracture



(a) (b)

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Chapter 7

Initial experience of SPECT/CT in the diagnosis of occult scaphoid fracture

De Zwart AD, Beeres FJP, Rietbergen DDD, Krijnen P, Schipper IB
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Abstract

Objectives Bone scintigraphy is often advocated for diagnosing occult scaphoid fractures. Bone scintigraphy is a sensitive diagnostic modality, but lacks specificity, which may result in over-diagnosis. Purpose: To examine, in a pilot study, the potential additional value of single photon emission computed tomography (SPECT) combined with low dose computed tomography (CT) for the diagnosis of an occult scaphoid fracture.

Methods Ten patients that underwent combined bone scintigraphy and SPECT/CT for a clinically suspected scaphoid fracture, where radiographs could not detect a fracture, were included in this pilot study. The bone scintigraphy and SPECT/CT results were independently and separately evaluated by a nuclear physician for scaphoid fractures and other injuries.

Results Bone scintigraphy was positive for a scaphoid fracture in four patients and diagnosed three other fractures. SPECT/CT showed five scaphoid fractures and one other fracture. SPECT/CT – bone scintigraphy had discrepant results in three patients. In two patients bone scintigraphy diagnosed a trapezoid fracture where SPECT/CT showed a scaphoid fracture. The other patient was diagnosed with a scaphoid fracture on bone scintigraphy, whereas SPECT/CT showed bone bruise of other carpal bones.

Conclusion SPECT/CT has the potential to be more accurate than bone scintigraphy as it uses anatomical information of the CT to discriminate between the scaphoid, other carpal bones and bone bruises. Larger studies with an independent reference standard are needed for confirmation of these preliminary data.

Introduction

Magnetic resonance imaging (MRI), computed tomography (CT), or bone scintigraphy are performed to detect an occult scaphoid fracture if scaphoid radiographs show no fracture. The value of these diagnostic tools have been widely investigated and still no consensus exists on the preferred workup of a patient with a clinically suspected scaphoid fracture and with a normal conventional radiograph.(1) The American College of Radiology recommends scaphoid radiographs as the first line of investigation in patients with a suspected scaphoid fracture.(2) If these do not show a fracture, a second line of investigation such as MRI or CT is proposed. Bone scintigraphy can also be used as second line investigation; however, it is usually not appropriate. It is important to diagnose an occult scaphoid fracture early because, if left untreated, it may give rise to serious complications such as osteonecrosis, non-union, carpal instability and functional impairment.(3-8) Among the advanced diagnostic modalities for this specific patient group, bone scintigraphy is favoured for its high sensitivity in confirmation of scaphoid fractures. The disadvantage of bone scintigraphy, however, is its lower specificity compared to MRI and CT.(9-12) Bone scintigraphy uses a radiopharmaceutical, technetium-99 m hydroxymethylene diphosphonate (99mTc HDP), which accumulates on the surface of the by osteoblasts induced growing hydroxyapatite crystal. After trauma, osteoblasts at the fracture site are activated and the HDP will accumulate at the activated osteoblasts. The bone scintigraphy will show increased uptake. However, not only fractures will show increased activity; there will also be accumulation of the radiopharmaceutical in activated osteoblasts at the site of osteoarthritis and extensive bone bruise. Also infections or other inflammation lead to increased activity.(13) A concern related to bone scintigraphy is the determination of the exact localization of the fracture. Especially when there is a fracture of one of the bones articulating with the scaphoid, a false positive diagnosis of a scaphoid fracture may result.(10,14) Single photon emission computed tomography (SPECT) can improve the diagnostic performance of bone functional imaging.(15) The hybrid SPECT/CT systems combine SPECT with CT and have proven to result in a more accurate localization and characterization of other than carpal skeletal lesions.(16,17) The aim of the current pilot study was to investigate if SPECT/CT is of additional value, in comparison with bone scintigraphy, in the diagnostic workup for suspected scaphoid fractures.

Material and Methods

The study proposal was approved by the institutional Ethics Committee and financial and logistic resources were organized for 10 patients. Between May 2010 and May 2011, in patients who visited the Emergency Department (ED) with a clinically suspected scaphoid fracture and negative scaphoid radiographs, an additional bone scintigraphy was made. The attending nuclear physician evaluated the bone scintigraphy. If there was any activity on the bone scintigraphy an additional SPECT/CT was made. Inclusion was stopped after the first 10 patients had agreed to participate.

Study protocol

A clinically suspected scaphoid fracture with negative scaphoid radiographs was defined as pain in the anatomic snuffbox when applying axial pressure on the first or second digit,(18) after a recent trauma (within 48 h) and no evidence of a fracture on conventional scaphoid radiographs (PA, lateral and 2–4 specific views). If a patient was suitable for inclusion, a SPECT/CT was performed after informed consent. Poly-trauma patients, patients aged less than 18 years and those with contraindications for bone scintigraphy were excluded. The bone scintigraphy was made 3–5 days after injury. A three phase bone scintigraphy was performed immediately after intravenous injection of 550 MBq 99mTc-HDP. Dynamic images were acquired during 2 min on a single or two-headed gamma camera (Symbia T6, Siemens, Erlangen, Germany or Toshiba GCA- 7200 pi/7200di/7100ui, Toshiba, Tokyo, Japan), displayed on a 128 128 matrix, zoom factor 1.0, with the hands on the camera head in palmar projection. Five hours after tracer injection planar images of the hands were made for osteoblast activity analysis. The same study protocol and position as the dynamic images were applied, but now displayed on a 256 256 matrix, zoom factor 1.5. The SPECT/CT was performed on the two-headed gamma camera (Symbia T6, Siemens, Erlangen, Germany, with 6-slice CT), using a low-energy high-resolution collimator. Images were acquired for 15 s in each camera position. A total of 64 views were taken to cover 360. The energy window was set to 140 keV with a 20% window. The images were acquired in a 128 128 matrix with a zoom factor of 1.23. Reconstruction was performed using iterative reconstruction OSEM (ordered subset expectation maximization). We used a low dose CT, step and shoot protocol (25 mA, 130 kV, FOV 300 mm) with 2.0 mm slice thickness. Images were reconstructed in the axial, coronal and sagittal planes. SPECT and low dose CT were fused on a dedicated nuclear medicine workstation using the MedView (MedImage Inc., Ann Arbor, MI, USA) software package.

Image analysis

The images were analyzed by one nuclear physician with four years of experience as a specialist. The bone scintigraphy results and additional SPECT/CT images were evaluated independently and separately. Clinical information and data were anonymized. The age of the patient was not blinded as the information is needed to evaluate a bone scintigraphy for osteoarthritic changes. The images were evaluated in random order by a nuclear physician for scaphoid fractures, other fractures, bone bruise and other diagnoses. The bone scintigraphy and SPECT/CT images were evaluated separately but because of the small number of scans the observer could recognize a bone scintigraphy and SPECT/CT of the same patient.

Results

10 patients were included (five men, five women; mean age, 40.4 years; age range, 19–72 years). Table 1 summarizes the results for the bone scintigraphy and SPECT/CT. In seven patients bone scintigraphy and SPECT/CT had corresponding outcomes: In three patients the images showed a scaphoid fracture, in one patient a distal radius fracture and in one patient a bone bruise. Two patients had some atypical activity on bone scintigraphy with however a final diagnosis of ‘‘no fracture nor bone bruise’’ on bone scintigraphy and SPECT/CT. The three discrepant between SPECT/CT and bone scintigraphy, concerned two patients that were diagnosed with a trapezoid fracture with bone scintigraphy and a scaphoid fracture with SPECT/CT. The third patient was diagnosed with a scaphoid fracture on bone scintigraphy, whereas SPECT/CT showed bone bruises of other carpal bones. Figures 1 and 2 illustrate the discrepancies between bone scintigraphy and SPECT/CT. Figure 3 clearly demonstrates the increased exactness of SPECT/CT for anatomical localization, as compared with bone scintigraphy.

Table 1. Final diagnosis of bone scintigraphy and SPECT/CT – in the last column the congruence or incongruence between bone scintigraphy and SPECT/CT are indicate.

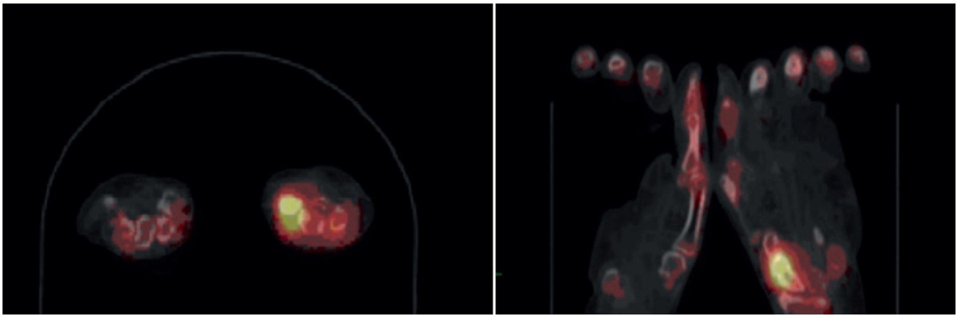
Patient	Diagnosis on BS#	Diagnosis on SPECT/CT	Congruent +/ Incongruent (-)
1	Distal radius fracture	Distal radius fracture	+
2	Scaphoid fracture	Scaphoid fracture	+
3	Trapezium fracture	Scaphoid fracture	-
4	Scaphoid fracture	Scaphoid fracture	+
5	Scaphoid fracture	Bone bruise carpus*	-
6	Trapezoid fracture	Scaphoid fracture	-
7	No fracture	No fracture	+
8	Scaphoid fracture	Scaphoid fracture	+
9	No fracture	No fracture	+
10	Bone bruise scaphoid	Bone bruise trapezium	+

 # Bone scintigraphy

**In this patient MCP-1, CMC-1, scaphoid, trapezium, triquetrum and hamatum showed increased activity*

Figure 1. Patient 3 in Table 1. (a) Bone scintigraphy revealed increase bone activity in a radial carpal bone, probably trapezium. (b) The fusion image of the SPECT/CT shows the more circumscript area of the tracer uptake to be centred slightly more proximal, very suspect for (distal) scaphoid fracture.

(a)



(b)

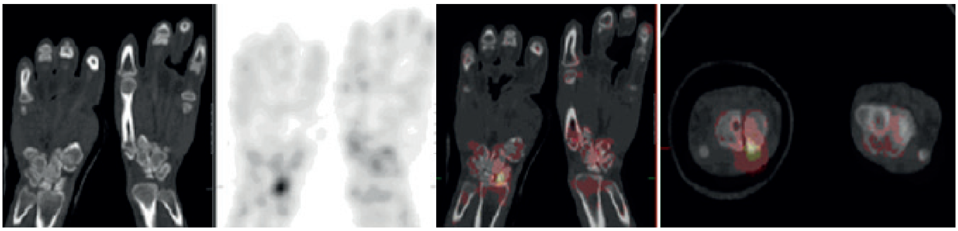
Figure 2. Patient 5 in Table 1. (a) Bone scintigraphy was suspect for a scaphoid fracture. (b) SPECT/CT axial and coronal view of the same patient showed no activity around the scaphoid but in the intercarpal region. This scan was evaluated as bone bruise of other carpal bones.

(a)

(b)

Figure 3. Patient 4 in Table 1. (a) Bone scintigraphy was positive for scaphoid fracture. (b) SPECT/CT illustrates that the exact localization of the fracture concerns the proximal pole of the scaphoid and that it concerns a small fracture fragment.

(a)



(b)

Discussion

This pilot study investigated the potential additional value of SPECT/CT in the diagnostic workup for suspected scaphoid fractures as compared with bone scintigraphy. Within the limitations of a small pilot study we found that SPECT/CT seems to adequately localize fractures in the carpus and therefore may be more specific and even more sensitive than bone scintigraphy in diagnosing scaphoid fractures, according to anatomical location; the SPECT/CT clearly showed two scaphoid fractures in patients for which the bone scintigraphy was negative regarding scaphoid fractures. The more exact anatomical information helps to discriminate between scaphoid fracture and fractures of other carpal bones. It also serves to specifically depict the fracture site in the scaphoid bone and whether it is localized proximally or distally in the scaphoid bone. This specification has distinct treatment consequences and is thus a clinically relevant addition in the diagnostic process.(19) Moreover, a fracture line visible on CT can distinguish a bone bruise from a fracture. The definite diagnosis of a scaphoid fracture is still being recognized as a challenge. There is no consensus about the best diagnostic strategy for a patient with a clinically suspected scaphoid fracture with a negative scaphoid specific radiograph.(1,20,21) CT, MRI and bone scintigraphy all have been widely investigated for their diagnostic performance. A recent meta-analysis of Yin et al. favours MRI, because follow-up radiographs and CT are less sensitive and bone scintigraphy is less specific.(22) The American College of Radiology (ACR) recommends performing MRI in case of a suspected scaphoid fracture with a negative scaphoid radiograph. However, cast immobilization with repeated radiographs after two weeks and CT are also appropriate. The ACR does not specifically recommend bone scintigraphy but states that bone scintigraphy may be useful when combined with SPECT/CT.(2) With MRI as upcoming diagnostic modality bone scintigraphy is being used less for diagnosing scaphoid fractures. However bone scintigraphy is still the most sensitive modality.(9,22) Moreover, by combining it with SPECT/CT it may be as specific as MRI. A disadvantage of SPECT/CT is the higher radiation exposure compared with MRI and CT (SPECT/CT 4 mSv, CT 0.03 mSv, MRI no radiation exposure, background radiation 2.5 mSv a year).(10,23) To our knowledge two similar studies recently investigated the clinical value of SPECT/CT in the diagnosis of radiological occult scaphoid fractures. Alainmat et al. illustrated that SPECT/CT showed bone disruptions as well as carpal-associated lesions and differentiated chronic arthritis or ligament lesions in five patients.(24) Querellou et al. evaluated 57 patients with a clinically suspected scaphoid fracture and a negative conventional radiograph, using SPECT/CT and MRI.(17) They concluded that SPECT/CT is more sensitive for a fracture in the carpal area, as it detected 10 more carpal fractures than MRI. However, in this study relatively high numbers of bone bruises were diagnosed on MRI. Moreover the discriminative value of the MRI for fractures and bone bruises remains topic of debate. Also the clinical implications of a bone bruise remains disputed.(25,26) Studies on different anatomical areas underline the additional value of SPECT and the potential benefits of combined SPECT/CT in orthopedics and trauma.(16,27-30) The major advantage of SPECT/CT is the combination of the high sensitivity of SPECT with the specificity of CT. This may result in a higher diagnostic accuracy. This increased diagnostic accuracy will be of major benefit, especially for a small and complex anatomic area as the carpal region including the scaphoid bone. As in many pilot studies, this study presents itself with the inherent limitations of a small pilot study. No statistical significance could be tested. In addition, the lack of a generally accepted reference standard to compare SPECT/CT to, presented a challenge to this study. However, this problem is inherent to the fact that there are no alternative diagnostics that are more reliable by means of both high sensitivity and specificity for occults scaphoid fractures.

Another limitation is that we only made a SPECT/CT of patients with activity on bone scintigraphy. However as both diagnostic modalities use the same substrate, i.e. the uptake of 99mTc HDP, we believe that if bone scintigraphy showed no activity, SPECT/CT also would not.

In conclusion, SPECT/CT facilitates the detection of occult fractures and presents additional information about the injury site and localization of the fracture. SPECT/CT could potentially serve as a future reference standard for studies concerning the scaphoid fracture, but additional research with an independent reference standard is needed to confirm these preliminary suggestions.

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Chapter 8

Discussion and future perspectives

This thesis is about a patient who fell on an outstretched hand and sustained a scaphoid fracture that did not show on conventional radiographs. The question that arises is what the best diagnostic work-up will be for this patient. Although an enormous amount of research exists, we still do not have an evidence based answer to this question and hospitals use different protocols both nationally and internationally.(1-3) Due to inconsistent results published in literature, an ideal protocol could not be developed.
The aim of this thesis is to add valid and relevant data in the quest for the optimal protocol detecting scaphoid fractures that are not visible on conventional radiographs, the so-called occult scaphoid fractures.

In this thesis the diagnostic value of CT, MRI, bone scintigraphy and Tc-99m-HDP single photon emission computed tomography combined with low dose computed tomography (SPECT/CT) in occult scaphoid fractures is investigated.

We found the specificity of MRI to be less than reported in literature. We believe our study method, using healthy volunteers is more reliable compared to the studies that used different and imperfect reference standards and reported higher specificity.(4)
CT is specific, but has a lower sensitivity. Also observer variability is moderate. The clinical consequences of the missed fractures with CT are unknown. The radiation exposure of CT scan of the wrist is low. As it needs to be kept as low as possible, we advise to scan without a plaster cast.
Bone scintigraphy is a sensitive tool, but its specificity is lower which may result in overtreatment. Moreover, it is an invasive procedure, leads to radiation exposure and is time consuming.
SPECT/CT has similar objections. The diagnostic performance, however, seems promising. In our pilot study SPECT/CT has the potential to be more accurate than bone scintigraphy, as the diagnosis changed in three out of 10 patients using the anatomical information of the CT to discriminate between the scaphoid, other carpal bones and bone bruises. In future research it could serve as a superior reference standard.

Diagnostic challenges to overcome

If there is a clinically suspected scaphoid fracture (pain in the anatomic snuff box and/or pain on axial compression of the thumb and/or pain of the scaphoid tubercle), after a fall on an outstretched hand, there is a chance of 10 to 20 percent that an occult scaphoid fracture is present.(5-7) Therefore, advanced diagnostic methods such as CT, MRI and bone scintigraphy are used to rule out an occult fracture.

There are several issues in diagnosing occult fractures and the use of the different diagnostic modalities:

- It is unknown how many untreated occult fractures result in a symptomatic non-union.
- There is continuing inconsistency about if and how scaphoid fractures should be immobilised. Twenty years ago an above elbow cast is applied for 12 weeks, now some studies suggest a 4 weeks below elbow cast, without thump immobilisation.(8)
- Patients nowadays can be more demanding and litigation is infiltrating our decision models fast.(9) This potentially results in defensive medicine. However to what costs and to what extent of overtreatment?
- The main diagnostic challenge is that there is no 100% reliable reference standard available, which makes it difficult to conclude whether an outcome of a diagnostic modality is true or false.
- The low prevalence of occult fractures (10-20%) renders it relatively difficult to detect all fractures without overtreating multiple patients. Small percentages of false positive outcomes are magnified.(10)
- Diagnostic modalities are constantly evolving. MRI and CT imaging nowadays cannot be compared with several years ago as resolutions have improved dramatically. Comparison of diagnostic modality research results is there for complex and not always valid over time.

Pro's and cons of diagnostic solutions in this thesis

MRI

Literature reports that MRI has a specificity of 98-100% for ruling out scaphoid fractures (table 1). Sensitivity ranges between 88-98% (table 1). In this thesis the specificity of MRI is determined using healthy volunteers. As no 100% reliable reference standard is available we have turned it around and made sure we knew the diagnosis beforehand (no fracture). This resulted in a surprising high number of false positive outcomes and a specificity of 96%. The 96% may even be an overestimation as patients may have more abnormal signals on MRI after a fall on outstretched hand, which can be interpreted as a fracture. MRI is often used as a reference standard in many studies. In the light of the above findings, results of these studies also have to be interpreted with care.

We did not assess the sensitivity of MRI in this thesis. There are many studies evaluating the diagnostic performance of MRI and often report very high sensitivities (88-98%, table 1), but still without a valid reference standard. There may be room for a future study with optimized methodology to investigate the sensitivity of MRI, bearing in mind that adding value without a true reference standard will be difficult. Also, the ever improving quality of MRI's over time should then be taken into account.

CT

Studies concerning the diagnostic value of CT for diagnosing occult scaphoid fractures with sufficient power are scarce. In this thesis the diagnostic value of CT is investigated in a large patient population with clinically suspected occult scaphoid fractures. As a reference standard bone scintigraphy in combination with persistent clinical signs and radiograph follow up (6 weeks) was chosen. In our study, sensitivity of CT for diagnoses of an occult scaphoid fracture was 70% and specificity 99%. We hypothesize that the missed fractures had minimal dislocation as CT has high resolution and is superior in detecting dislocation of a fracture.(11) Accordingly, the fractures visible on follow up radiograph were all mid-waist scaphoid fractures without dislocation. If future studies can prove that these fractures will heal without a specific period of cast immobilisation, CT could be a very suitable diagnostic modality. Since CT is very specific it could save a lot of overtreatment when compared to repeated radiographs, bone scintigraphy and even MRI.

The interobserver agreement of CT for diagnosis of occult scaphoid fractures in the same patient population was moderate, which is quite disappointing. A different protocol with thinner CT slices may help improve this. It has to be taken into account that the interobserver agreement was determined in a population with clinical signs of a scaphoid fracture with ''no'' fracture on conventional radiographs, suggesting that if present at all, the fracture would not show much dislocation.

Another CT-related drawback is the use of radiation. Although radiation exposure of a CT of the wrist is low (0.02-0.03 mSv), patients need to know to what amount of radiation they are subjected too and ethically we need to keep the dosage As Low As Reasonably Achievable (ALARA). Scanning with a plaster cast results in an increased radiation exposure, as shown in this thesis. Therefore, we strongly advise to always make a CT without a plaster cast; it reduced radiation exposure by 90%. For comparison, bone scintigraphy of the wrist leads to a radiation exposure of 4 mSv and MRI none.

MRI, CT and bone scintigraphy in one patient population

For the first time in literature CT, MRI and bone scintigraphy were compared in the same patient population. Surprisingly there was only consistency in the negative results (all three scans showed no fracture). In the other patients the diagnostic modalities showed different results, consequently one or two had false outcomes in these patients. This illustrates the difficulty to investigate these diagnostic modalities without a true reference standard. None of these advanced diagnostic modalities meet the requirements to be the reference standard.

SPECT/CT

Finally, we have done a pilot study with SPECT/CT for diagnosing occult scaphoid fractures. In this pilot study the sample size was small (10 patients) and only one observer evaluated the SPECT/CT's. Bone scintigraphy was used for comparison. As location of the uptake of technetium-99 m hydroxymethylene diphosphonate was determined more accurate with SPECT/CT than with bone scintigraphy, SPECT/CT lead to different diagnoses in three out of the ten patients. SPECT/CT combines the high sensitivity of bone scintigraphy with the high specificity of CT and may in the end proof to be the most adequate for diagnosing occult scaphoid fractures. There are however considerable clinical and organizational disadvantages related to the SPECT/CT. It uses radiation and is time-consuming which makes it not very appropriate in daily practice. Still, it may be very suitable as a reference standard in further clinical research. Therefore more research is needed to determine the diagnostic value of SPECT/CT in a larger patient population.

Table 1. Pooled estimated results of the included reviews and meta-analyses.

	type	CT sensitivity	CT specificity	MRI sensitivity	MRI specificity	BS sensitivity	BS specificity
Mallee, 2015	Cochrane review	72	99	88	100	99	86
Yin, 2010	meta-analysis	93	99	96	99	97	89
Yin, 2012	meta-analyse*	85	100	98	100	98	84
Gemme, 2015	systematic review	83	97	96	98		
Carpenter, 2014	meta-analyse	83	97	95	98	90	81

** Including latent class analysis*

Review of literature

Many studies have been published concerning the subject of this thesis. We have performed a systematic review of reviews to give an overview of the knowledge nowadays, concerning diagnosis of scaphoid fractures (search strategy, figure 1). We chose to include reviews from 2010 as reviews concerning this subject are abundant. Moreover resolutions of CT and MRI have been improved, which makes it important that recent literature is included in the reviews. We have included and compared one Cochrane review, three meta-analysis and one systematic review. (exclusion chart, figure 2). The overall specificity and sensitivity results per modality, deducted from these reviews, are presented in table 1.

Mallee et al. (2015) have performed a Cochrane review for CT, MRI and bone scintigraphy.(5) They have included 11 studies of moderate to good quality. The pooled sensitivities and specificities are in Table 1. They found high heterogeneity in results between the studies as different reference standards were used. They concluded that statistically bone scintigraphy has the best diagnostic accuracy for detecting occult scaphoid fractures. However, due to a lower specificity it will lead to a relatively high rate of overtreatment.

Carpenter et al. (2014) have performed a meta-analysis for CT, MRI, bone scintigraphy, ultrasound, physical exam and patient history in relation to detecting occult scaphoid fractures.(12) They included 39 studies of low to moderate quality, concerning CT, MRI and bone scintigraphy. The pooled sensitivity

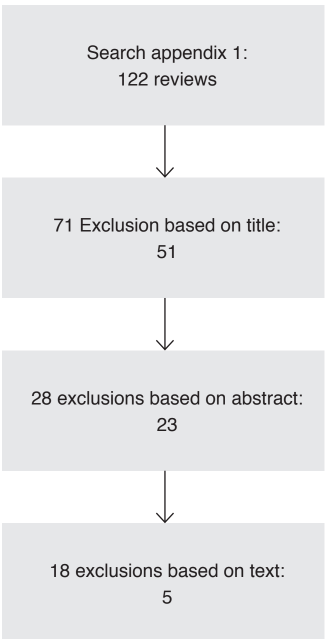
Figure 1. Search strategy

We searched Pubmed, Web of Science, Embase and Cochrane with the following search strategy:

("scaphoid bone fracture"[all fields] OR "scaphoid bone fractures"[all fields] OR "scaphoid bone injuries"[all fields] OR "scaphoid fracture"[all fields] OR "scaphoid fractures"[all fields] OR "scaphoid injuries"[all fields] OR "scaphoid injury"[all fields] OR "scaphoid stress fracture"[all fields] OR "scaphoid waist fracture"[all fields] OR "scaphoid waist fractures"[all fields] OR "scaphocapitate fracture syndrome"[all fields] OR "scaphocapitate fractures"[all fields] OR (("navicular body fracture"[all fields] OR "navicular body fractures"[all fields] OR "navicular bone fracture"[all fields] OR "navicular fracture"[all fields] OR "navicular fractures"[all fields] OR "navicular stress fracture"[all fields] OR "navicular stress fractures"[all fields] OR "navicular stress injuries"[all fields] OR "navicular stress injury"[all fields]) AND ("Hand"[mesh] OR "hand"[tw] OR "hands"[tw] OR "metacarpus"[tw] OR "metacarpal"[tw])) OR (("Scaphoid Bone"[mesh] OR "scaphoid"[ti] OR scaphoid*[ti] OR "scaphocapitate"[ti] OR ("navicular"[ti] AND ("Hand"[mesh] OR "hand"[tw] OR "hands"[tw] OR "metacarpus"[tw] OR "metacarpal"[tw]))) AND ("Fractures, Bone"[Mesh] OR "fracture"[ti] OR "fractures"[ti] OR "trauma"[ti] OR "injury"[ti] OR "injuries"[ti]))) AND ("Diagnosis"[Mesh:NoExp] OR "Diagnosis, Differential"[Mesh] OR "Diagnostic Imaging"[mesh:noexp] OR "Image Interpretation, Computer-Assisted"[mesh] OR "Magnetic Resonance Imaging"[mesh] OR "Multimodal Imaging"[mesh] OR "Radiography"[mesh] OR "Radionuclide Imaging"[mesh] OR "Tomography"[mesh] OR "Ultrasonography"[mesh] OR "diagnosis"[tiab] OR "diagnostic"[tiab] OR "diagnosis"[Subheading:NoExp] OR "radiography"[Subheading] OR "radionuclide imaging"[Subheading] OR "ultrasonography"[Subheading] OR "X-rays"[tw] OR "radiography"[tw] OR "radiology"[tw] OR "imaging"[tw] OR "computed tomography"[tw] OR "computer tomography"[tw] OR "computed assisted tomography"[tw] OR "computer assisted tomography"[tw] OR "CT-scan"[tw] OR "CAT-scan"[tw] OR "CT-scans"[tw] OR "CAT-scans"[tw] OR "magnetic resonance imaging"[tw] OR"MRI"[tw] OR "MR imaging"[tw] OR "scintigraphy"[tw] OR "SPECT"[tw] OR "SPECT-CT"[tw] OR "SPECTCT"[tw] OR "sonograms"[tw] OR "sonogram"[tw] OR "sonography"[tw] OR "sonographic"[tw] OR "ultrasound"[tw] OR "ultrasonography"[tw] OR "echography"[tw] OR "predictive value of tests"[mesh] OR "False Negative Reactions"[mesh] OR "False Positive Reactions"[mesh] OR "false negative"[all fields] OR "false positive"[all fields] OR "predictive value"[all fields] OR "Sensitivity and Specificity"[Mesh] OR "detection"[all fields] OR "detected"[all fields] OR "interobserver variability"[all fields] OR "inter-observer variability"[all fields] OR "intraobserver variability"[all fields] OR "intra-observer variability"[all fields] OR "clinical prediction"[tw] OR "sensitivity"[tw] OR "specificity"[tw]) AND (english[la] OR dutch[la]) NOT ("Animals"[mesh] NOT "Humans"[mesh]) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT]) AND (systematic[sb] OR "review"[ptyp] OR "Meta-Analysis"[Publication Type] OR meta-analy*[tw] OR metaanaly*[tw] OR review*[ti]) and specificity for CT, MRI and bone scintigraphy are in Table 1. They concluded high heterogeneity between the studies. Also the majority of the studies investigated the value of MRI, which could have led to diagnostic research bias. They also discussed that there was no standardised inclusion criteria and different reference standards were used. They concluded MRI was the most accurate diagnostic tool; bone scintigraphy is only suitable for ruling out and CT only for ruling in scaphoid fractures.

Yin et al. (2010) performed a systematic review and meta-analysis for diagnostic accuracy of imaging modalities for suspected scaphoid fractures.(4) They investigated follow -up radiographs, CT, MRI and bone scintigraphy (search 1966-2008) and included 26 (24 concerning CT, MRI and bone scintigraphy) studies. Major conclusions were heterogeneity in methods, patient populations and different diagnostic protocols, between the included studies and lack of a true reference standard. They also marked possible confounders as these analyses are indirect (MRI, CT and bone scintigraphy were not tested in the same patient population). They concluded that MRI was the most accurate test; follow-up radiographs and CT may be less sensitive and bone scintigraphy is less specific. Yin et al. have repeated their search to 2011 and included six more studies and performed a latent class analysis.(6) The results of the pooled sensitivities and specificities of the meta-analysis (2010) and meta-analysis combined with latent class analysis (2012) are in Table 1. The latent class analysis and the inclusions of more recent literature did not change the results significantly. However, the latent class analysis was suboptimal as there was a lot of missing data.

Figure 2. Exclusion chart



Gemme et al. (2015) performed a systematic review for diagnosing scaphoid fractures.(13) They investigated the value of snuffbox tenderness, thumb compression, radiograph fat pad, radiographs 10-14 days later, CT and MRI. They included 75 studies of low to moderate quality. The results for CT and MRI are in Table 1. They concluded a significant level of heterogeneity, likely because there were no standardised inclusion criteria. Furthermore, there was a significant incorporation bias, double criteria standard and temporal bias. They concluded that MRI is the investigation of choice. However, in 3% of the emergency departments in the UK, MRI is available. As follow-up radiographs and physical exams are not sufficient to exclude a scaphoid fracture, advanced diagnostic follow up should be conducted.

Comparing our results to literature

Literature reports a specificity of 99% or higher for MRI.(5) Our MRI study, using healthy volunteers without a fracture or complaints, resulted in a specificity of 96%. The study design with healthy volunteers has advantages since no reference standard is needed. A potential explanation for the relatively low specificity might be the differences in reference standard. As other studies use imperfect reference standards it is possible that the false positive MRI's also had a false positive reference standard. Most studies used a combination of clinical findings and follow up radiography. It is known that clinical findings are not specific.(13,14) Contusions of the scaphoid may have had a positive MRI and positive clinical findings without a present fracture. On the other hand, since only non-fractured wrists are reviewed a spectrum bias may have been introduced in our study.

The results of the comparison of CT scan with bone scintigraphy for detection of occult scaphoid fractures are consistent with those of previous publications.(15,16) CT is specific, however not a very sensitive diagnostic modality. We also found a moderate interobserver agreement. One other study investigated the interobserver agreement in this patient population and they found substantial agreement.(7) The difference might be the result of a different CT protocol with thinner slices.

Since it is important not to miss any fractures, CT does not seem to be the investigation of choice. However, CT has numeral advantages. Its availability is better than that of MRI and bone scintigraphy and it is less time-consuming. Also, since specificity is high, there is little overtreatment. An important question is to what extent the missed fractures with CT will lead to an adverse outcome. Displacement on scaphoid radiographs is associated with a higher rate of non-unions.(11) Unfortunately no study has been performed assessing the rate of non-unions with different fracture patterns on CT. Moreover there is no study evaluating the rate of non-unions in patients with a clinically suspected scaphoid fractures, a negative radiograph and negative CT, which received no treatment.

Bone scintigraphy is a sensitive tool, however it has a lower specificity compared to MRI and CT. Our results are comparable to the reviews published prior to our study. Bone scintigraphy is less favorable because it is time-consuming, invasive, expensive and it leads to radiation exposure. If we add the disadvantage of its lower specificity, it is not the most suitable diagnostic tool, despite its high sensitivity. It could serve as a reference standard in future studies, especially when combined with SPECT/CT as we showed in our pilot study. Only one recent study of Querellou et al. evaluated 57 patients with a clinically suspected scaphoid fracture and a negative conventional radiograph, using

SPECT/CT and MRI.(17) They concluded that SPECT/CT is more sensitive for a fracture in the carpal area, as it detected 10 more carpal fractures than MRI.

In this thesis we compared CT, MRI and bone scintigraphy on the same population, which is unique. There were no consistent outcomes between the three diagnostic modalities, which illustrates the shortcomings of every diagnostic modality.

Repeated radiographs have not been investigated in this thesis although many clinics still use these repeated radiographs for assessing patients with a clinically suspected scaphoid fracture.(1-3) Ultrasound is an alternative diagnostic modality which we did not investigate. However, there is sufficient literature that demonstrates ultrasound and repeated radiographs to be inadequate for ruling out scaphoid fractures. Yin et al. assessed the value of repeated radiographs in their meta-analysis combined with the latent class analysis.(6) Sensitivity was not sufficient especially when MRI was used as a reference standard. In 2016 this was underlined with an observer study were 81 orthopedic surgeons assessed repeated radiographs. They found a low agreement and concluded repeated radiographs are not adequate.(18) The value of ultrasound has been assessed in a review. Four studies had very small sample sizes. Only one study included 58 patients and used repeated radiographs at 10-14 days as a reference standard. Sensitivity was only 50%. They concluded ultrasound is not sensitive enough to rule out scaphoid fractures. Of course there may be room for ultrasound in the absence of other diagnostics such as MRI, CT or bone scintigraphy.(19)

Future perspectives

Obviously, the major problem in investigating advanced imaging techniques for detecting occult scaphoid fractures is the absence of a true reference standard and the low prevalence of true fractures. Statistical compensation for this lack of standard may proof helpful.

Latent class analysis may provide a more accurate estimation of the diagnostic characteristics in these advanced imaging techniques without a true reference standard. However, for an adequate analysis, study methods still need to be optimized and more patient variables (age, sports, outcome etc) are needed for a proper latent class analysis.(6)

As for the low prevalence of true fractures, the pre-test probability of a fracture can be influenced by incorporating a clinical prediction rule.(14,20)

Furthermore, the value of SPECT/CT is promising. Although SPECT/CT has considerable disadvantages (costs, time-consuming, radiation exposure), it may have a function as a reference standard in studies.

In future studies we need to combine the best possible reference standard, a clinical prediction rule and results interpreted with latent class analysis. Only then we may obtain more comparable and more reliable results.

Moreover we need to interpret the results in clinical perspective.Radiographically unstable and proximal pole fractures are associated with a higher rate of non-union. (21-25) Non-displaced fractures on conventional radiographs will heal with conservative treatment in 90-100%.(21,23) However, the occult fracture seems a different entity and it is not known how important treatment of an occult scaphoid fracture is. In perspective of this thesis, the importance of the treatment of potentially missed fractures on CT, MRI and bone scintigraphy is not known. It can be hypothesized that fractures missed with CT will probably be minimal dislocated and will have a good healing tendency anyway. The ultimate goal remains uncomplicated fracture healing and prevention of non-unions. Although CT misses between 20 to 30% of the occult scaphoid fractures compared to MRI and bone scintigraphy, the clinical consequences may be far less impressive than these percentages.

In this context it is interesting to look at the retrospective study of Reigstad et al., ''Scaphoid non-unions, where do they come from? The epidemiology and initial presentation of 270 scaphoid non-unions''. (26) In this study 270 patients with scaphoid non-unions were evaluated for their clinical presentation. Surprisingly only 148 (55%) patients with a non-union had initially visited a doctor. In 60 patients (22%) the diagnosis was missed on initial radiography and instead the patients were diagnosed with a sprain. These 60 patients with an occult scaphoid fracture could have been diagnosed with a scaphoid fracture if additional imaging had been performed, however, probably without consequences for their final outcome. The incidence of non-unions is 2,5 per 100.000 persons.(26) Therefore, 0,5 per 100.000 scaphoid non-unions were at initial presentation occult (assuming the 22% occult fractures of the study above). The incidence of scaphoid fractures is approximately 30 per 100.000.(27) As 25% of clinical suspected scaphoid fractures have a fracture, the incidence of suspected scaphoid fractures is 120 per 100.000. Therefore, 0,42% (0,5/120) of patients with a suspected scaphoid fracture can have benefit of additional imaging. The difference between the sensitivity of CT and MRI is around 20-30%, consequently in 0,1% of patients with a suspected scaphoid fracture, that can be missed with CT compared to MRI, has potentially a fracture that can lead to a non-union. Moreover there is the possibility that CT only misses the fractures with minimal dislocation and good healing tendency and will detect the fractures with the potential of becoming a non-union.

Clinical implications for the diagnosis of a scaphoid fracture

- When using CT there is a chance that fractures are missed.
- CT is less sensitive than MRI and bone scintigraphy and has moderate observer agreement. The clinical implications of this are currently unknown.
- If a CT scan is indicated, it is advised to make a CT of the wrist without a plaster cast in order to keep radiation exposure as low as possible.
- When using MRI there is a chance that fractures are missed.
- The specificity of MRI may be overestimated in literature.
- Bone scintigraphy is sensitive but less specific. When using bone scintigraphy there is a relatively high chance of overtreatment.
- Also, bone scintigraphy is time-consuming, invasive and radiation exposure is a disadvantage.

As no true reference standard is available and results can be magnified due to a low prevalence of true fractures, care has to be taken into account when interpreting results of any study concerning this topic. Future research has to focus on latent class analysis and study methods should be optimized. In order to obtain comparable data a prospective study for SPECT/CT is suggested as this could serve as a reference standard. Future research has to focus on the risk factors for developing non-union after occult scaphoid fractures, before we can develop an ultimate protocol.

Conclusion

In conclusion, in case of an clinically suspected radiographic occult scaphoid fracture, bone scintigraphy is very suitable diagnostic modality for detecting occult scaphoid fractures, however its radiation exposure is relatively high and the lesser specificity will lead to overtreatment. The most practical radiologic workup in the light of the present research would be MRI or CT. The chance of undertreatment should however be taken into account.

Therefore, clinical presentation, individual patient characteristics and fracture patterns will co-determinate the injury management. The treating physician holds final responsibility for the individualised further diagnostic follow-up and treatment strategy, as MRI, CT and bone scintigrapy individually are not 100% conclusive.

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Chapter 9

Summary

In **chapter 1** the aim of this thesis is introduced. The most appropriate diagnostic modality for detecting a scaphoid fracture that is not visible on conventional radiography (occult fracture) is still a subject of debate. An often encountered problem in literature is the lack of a reference standard and the low prevalence of true scaphoid fractures among the clinically suspected fractures.(1,2)
The aim of this thesis is to add valuable data concerning the features of different diagnostic modalities for diagnosing occult scaphoid fractures.

MRI has been suggested as the best reference standard for an occult scaphoid fracture among patients with a suspected scaphoid fracture.(2-7) In **chapter 2** we determined the rate of false-positive diagnosis of a scaphoid fracture for MRI in a cohort of 31 healthy volunteers of which both wrist were scanned and of two healthy volunteers one wrist was scanned. To simulate the usual clinical context the 64 scans of healthy volunteers were mixed with 60 MRI scans of clinically suspected scaphoid fractures and normal scaphoid radiographs. These 124 MRI scans were blinded and randomly ordered. Five radiologists evaluated the MRI scans independently for the presence or absence of a scaphoid fracture and other injuries according to a standard protocol. The radiologists diagnosed a total of 13 scaphoid fractures among the healthy volunteers; therefore, specificity for diagnosis of scaphoid fracture was 96% (95% confidence interval: range 94–98%). The five observers had a ''moderate interobserver agreement'' regarding diagnosis of scaphoid fracture in healthy volunteers according kappa statistics (multirater kappa 50.44; p, 0.001).(8)
We concluded that specificity of MRI for scaphoid fractures is high (96%), but false-positives do occur. Radiologists only have a ''moderate agreement'' when interpreting MRI scans from healthy volunteers. MRI is not the ideal reference standard for occult scaphoid fracture.

Since there is a low prevalence of true scaphoid fractures among clinically suspected scaphoid fractures, prospective studies need a relatively large number of patients in order to get significant results. In **chapter 3** we examined if the CT is superior to bone scintigraphy for diagnosis of an occult scaphoid fracture in a large prospective study. In a period of 39 months, a total number of 159 consecutive patients with a clinically suspected scaphoid fracture and no fracture on scaphoid radiographs, were evaluated with CT and bone scintigraphy. The reference standard for a true (radiographic occult) scaphoid fracture was either 1) diagnosis of fracture on both CT and bone scintigraphy, or 2) in case of discrepancy, persistent clinical signs after two weeks and/or evidence of a fracture on the repeated radiograph at six weeks.
CT showed 15 scaphoid and 35 other carpal fractures. Bone scintigraphy showed 28 scaphoid and 57 other carpal fractures. According to the reference standard there were 20 scaphoid fractures. CT had a sensitivity of 70%, specificity of 99%, accuracy of 96%, a positive predictive value (PPV) of 93% and a negative predictive value (NPV) of 96%. Bone scintigraphy had a sensitivity of 95%, specificity of 94%, accuracy of 94%, a PPV of 68% and a NPV of 99%. The percentages of sensitivity, specificity and correct predictions between the two diagnostic methods were compared with a McNemar test. A p-value < 0.05 was considered significant. The percentages of sensitivities and accuracies did not differ significantly between CT and bone scintigraphy (respectively p=0.125 and p=0.629) however sensitivity of CT appears to be less (70%) than bone scintigraphy (95%). The specificity of CT is significantly better than that of bone scintigraphy (p=0.022). Therefore CT is the investigation of choice for ruling in a scaphoid fracture- bone scintigraphy the modality of choice to rule out a scaphoid fracture in clinically suspected patients. In conclusion, early CT imaging is not superior to bone scintigraphy for suspected scaphoid fractures.

Additionally, to sensitivity and specificity, should the observer agreement be analysed in order to evaluate the performance of a diagnostic modality. The advantage of observer agreement is no reference standard is needed. In **chapter 4** the interobserver agreement of CT among four specialized musculoskeletal radiologists is calculated. The radiologists evaluated CT scans of 150 consecutive patients who were clinically suspected of having sustained a scaphoid fracture but whose scaphoid radiographs were normal. The radiologists were asked to determine the presence or absence of a scaphoid fracture and to localize the fracture (distal, waist, proximal). Interobserver agreement was calculated using the kappa statistic.(8) The radiologists diagnosed between 11 (7%) and 22 (15%) scaphoid fractures. Concerning scaphoid fractures, the kappa value was 0.51. Observer agreement on the presence of a scaphoid fracture and its location on a CT scan was moderate among the 4 radiologists. This finding raises the question as to whether scaphoid fractures could be under- or overdiagnosed in daily practice when CT is used to exclude or confirm a fracture. This should be kept in mind when interpreting radiological results in patients with suspected scaphoid fractures.

A disadvantage of CT is the radiation exposure. This is the first study evaluating radiation exposure of CT of the wrist using direct measurements**.** In **chapter 5** the radiation exposure including scatter radiation is measured, resulting from CT of the scaphoid in different settings as used in daily practice and to calculate the effective dose (ED) using a wrist phantom. The radiation exposure was quantified for five different CT protocols, all used in daily practice for the scaphoid fractures. Two protocols concerned a CT of the scaphoid with a plaster cast of the hand and three protocols without. For all protocols the Computed Tomographic Dose Index weighted (CTDIw), the scatter dose to the brain and scatter dose to the torso were derived from the CT and measured externally with the Piranha dose meter. The average CTDIw was 2.18 mGy. The average scatter to the brain and torso was 0.011 mSv. The average estimated ED was 0.02 mSv (range 0.02 to 0.04) of which 0.0008 mSv (range 0.0003 to 0.0012) was due to the scatter radiation. The two CT protocols of the scaphoid performed with a plaster cast resulted in a 90% higher ED, although the power of the study was too low to demonstrate this as statistically significant. However as we have to keep radiation exposure As Low As Reasonable Achievable (ALARA), it is therefore recommended that, if possible, a CT should be performed without a plaster cast.

In the literature diagnostic modalities are compared frequently. However MRI, CT and bone scintigraphy were not combined together in the same patient group with a suspected scaphoid fracture but negative radiographs. In **chapter 6** MRI, CT and bone scintigraphy were compared for the diagnosis of occult scaphoid fractures. 33 consecutive patients with a clinically suspected scaphoid fracture without a fracture on the scaphoid radiographs were evaluated with MRI, CT and bone scintigraphy. In case of a discrepancy between the diagnostic modalities, the final diagnosis was based on standardised follow-up with clinical examination and a repeated radiograph.

Three of the 33 patients had a scaphoid fracture. MRI missed one scaphoid fracture and did not over-diagnose. CT missed two scaphoid fractures and did not over-diagnose. Bone scintigraphy missed no scaphoid fractures and over-diagnosed one scaphoid fracture in a patient with a fracture of the trapezium.

This study shows that neither MRI, nor CT or bone scintigraphy are 100% accurate in diagnosing occult scaphoid fractures. MRI and CT miss fractures and bone scintigraphy tends to over-diagnose. The specific advantages and limitations of each diagnostic modality should be familiar to the treating physicians and taken into consideration during the diagnostic evaluation of suspected scaphoid fractures.

Bone scintigraphy has often been advocated for diagnosing occult scaphoid fractures.(5,9,10) Bone scintigraphy is a sensitive diagnostic modality, but lacks specificity, which may result in over-diagnosis. **Chapter 7** is a pilot study investigating the SPECT combined with low dose CT for the diagnosis of an occult scaphoid fracture. Ten patients that underwent combined bone scintigraphy and SPECT/CT for a clinically suspected scaphoid fracture, where radiographs could not detect a fracture were analysed. The bone scintigraphy and SPECT/CT results were independently and separately evaluated by a nuclear physician for scaphoid fractures and other injuries.

Bone scintigraphy was positive for a scaphoid fracture in four patients and diagnosed three other carpal fractures. SPECT/CT showed five scaphoid fractures and one other carpal fracture. SPECT/CT - bone scintigraphy had discrepant results in three patients. In two patients bone scintigraphy diagnosed a trapezoid fracture where SPECT/CT showed a scaphoid fracture. The other patient was diagnosed with a scaphoid fracture on bone scintigraphy, whereas SPECT/CT showed bone bruise of other carpal bones.

We concluded that SPECT/CT has the potential to be more accurate than bone scintigraphy as it uses anatomical information of the CT to discriminate between the scaphoid, other carpal bones and bone bruises. Larger studies with an independent reference standard are needed for a confirmation of this preliminary data.

Chapter 8 is the general discussion. It reflects on our results and compares them with literature. Specificity of MRI is lower than reported in literature and this has implications for all studies using MRI as a reference standard. CT may be a very practical diagnostic modality in the diagnostic workup for patients with a suspected scaphoid fractures. The fractures missed with CT and the moderate observer agreement are a problem. However, missed fracture with CT are possibly the fractures that have a very good prognosis. Observer agreement may improve if thinner slices are used. The radiation exposure of CT is low, especially when the scan is made without a plaster cast. For the diagnosis of the occult scaphoid fracture, MRI and bone scintigraphy can be used as well, however they also have limitations. Literature is not very consistent in results of MRI and sensitivity and specificity may be overestimated due to publication bias, no true reference standard and low prevalence of true fractures.(11-15) Bone scintigraphy lacks specificity, however combined with CT (SPECT/CT) it could be the most reliable method. There are some practical problems (availability, costs, radiation exposure, invasive and time-consuming), therefore it may only be useful in studies as a reference standard.

Future studies have to focus on methods to obtain comparable results and collect sufficient data for latent class analysis.(1,13) A clinical prediction rule may be a solution for the low prevalence of true fractures.(16,17) Finally, the value of SPECT/CT has to be investigated whether this could serve as the new reference standard.

Since there have been a lot of publications, there is a summary of all the reviews of the last 5 years in order to get a good overview of current knowledge.(11-15)

Chapter 9 includes a summary of this thesis and **chapter 10** contains the Dutch translation.

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Chapter 10

Samenvatting

In **hoofdstuk 1** wordt het doel van dit proefschrift behandeld. Het is niet duidelijk wat het meest geschikte diagnosticum is voor een scaphoid fractuur die niet op een röntgenfoto is te zien (occulte fractuur). Twee grote problemen in het onderzoek hiernaar, zijn het gebrek aan een betrouwbare referentie standaard en de lage prevalentie van werkelijke scaphoid fracturen onder de klinisch verdachte fracturen.(1,2)
Het doel van dit proefschrift is het leveren van aanvullende argumenten voor en tegen het gebruik van de verschillende diagnostische modaliteiten die ingezet kunnen worden om een occulte scaphoid fractuur aan te tonen.

De resultaten in de literatuur suggereren dat MRI de beste referentie standaard is voor het vaststellen van een scaphoid fractuur die niet te zien is op de röntgenfoto.(2-7) In **hoofdstuk 2** hebben we het aantal vals positieve uitslagen voor MRI bepaald in een cohort van 33 gezonde vrijwilligers. Bij 31 van deze vrijwilligers zijn beide polsen gescand en bij twee van deze vrijwilligers is één pols gescand. Om de werkelijkheid te benaderen hebben we MRI scans van 60 patiënten met een klinische verdenking op een scaphoid fractuur en een negatieve röntgenfoto, toegevoegd aan de scans van de gezonde vrijwilligers. Deze 124 MRI scans werden geblindeerd en gerandomiseerd. Vijf radiologen hebben alle MRI scans beoordeeld op de aan- en afwezigheid van een scaphoid fractuur en andere fracturen volgens een standaard protocol. De radiologen hebben in totaal 13 scaphoid fracturen gediagnosticeerd bij de gezonde vrijwilligers; de specificiteit van MRI voor de diagnose scaphoid fractuur was 96% (95% betrouwbaarheids interval: range 94-98%). De vijf observanten hadden een ''moderate observer agreement'' voor de diagnose scaphoid fractuur volgens kappa statistiek (multirater kappa 50.44; p,0.001).(8)
De conclusie is dat MRI een aanzienlijke specificiteit kent (96%), maar dat vals positieve MRI scans wel voorkomen. Radiologen hebben een ''moderate observer agreement'' als ze MRI scans van gezonde vrijwilligers beoordelen. De MRI is daarmee niet ideaal om te gebruiken als referentie standaard voor occulte scaphoid fracturen.

Gezien de lage prevalentie van werkelijke scaphoid fracturen onder de klinisch verdachte fracturen in prospectieve studies, is een relatief groot aantal patiënten nodig voor significante resultaten. In **hoofdstuk 3** is onderzocht of CT superieur is aan de botscintigrafie voor het diagnosticeren van occulte scaphoid fracturen in een grote prospectieve studie. In een periode van 39 maanden zijn van 159 opeenvolgende patiënten met een klinische verdenking op een scaphoid fractuur en geen fractuur op de röntgenfoto een CT en botscintigrafie gemaakt. De referentie standaard voor een werkelijke scaphoid fractuur (op de röntgenfoto occult) was, of 1) CT en botscintigrafie positief voor fractuur, of 2) in geval van discrepantie tussen CT en botscintigrafie, persisterende kliniek en/of een fractuur zichtbaar op de herhaalde röntgenfoto na 6 weken.
CT liet 15 scaphoid fracturen en 35 andere carpale fracturen zien. Botscintigrafie liet 28 scaphoid en 57 andere carpale fracturen zien. Volgens de referentie standaard waren er 20 scaphoid fracturen. CT had een sensitiviteit van 70%, een specificiteit van 99%, een accuraatheid van 96%, een positief voorspellende waarde (PPV) van 93% en een negatief voorspellende waarde (NPV) van 96%. Botscintigrafie had een sensitiviteit van 95%, een specificiteit van 94%, een accuraatheid van 94%, een PPV van 68% en een NPV van 99%. De percentages van sensitiviteit en accuraatheid verschilden niet significant tussen CT en botscintigrafie (respectievelijk p=0.125 en p=0.629), daarentegen lijkt de sensitiviteit van CT minder (70%) dan de sensitiviteit van botscintigrafie (95%). De specificiteit van

CT is significant beter dan van botscintigrafie (p=0.022). CT is het aangewezen onderzoek om een fractuur aan te tonen – botscintigrafie om een fractuur uit te sluiten bij een klinisch verdachte scaphoid fractuur. Concluderend, acute CT is niet superieur aan botscintigrafie bij klinisch verdachte scaphoid fracturen.

Naast de sensitiviteit en specificiteit, moet de observer agreement bepaald worden om de waarde van een diagnostische modaliteit te evalueren. Voordeel hierbij is dat er geen referentie standaard nodig is. In **hoofdstuk 4** is de interobserver agreement van CT tussen vier gespecialiseerde radiologen berekend. De radiologen hebben CT scans van 150 opeenvolgende patiënten, die een klinische verdenking op een scaphoid fractuur hadden en normale röntgen foto's, bekeken. De radiologen is gevraagd of er sprake was van een scaphoid fractuur en waar deze precies zat (distaal, centraal, proximaal). Interobserver agreement werd berekend volgens kappa statistiek.(8) De radiologen diagnosticeerde tussen de 11 (7%) en de 22 (15%) scaphoid fracturen. Betreffende de scaphoid fracturen was de kappa waarde 0,51. De observer agreement betreft de locatie van de fractuur was ''moderate'' tussen de vier radiologen. Deze bevinding werpt de vraag op of scaphoid fracturen in de dagelijkse praktijk worden over- of onder gediagnosticeerd, als CT wordt gebruikt om een scaphoid fractuur aan te tonen dan wel uit te sluiten. Dit is belangrijk om rekening mee te houden als de radiologische gegevens worden geïnterpreteerd bij patiënten met een klinische verdenking op een scaphoid fractuur.

Een nadeel van CT is stralingsbelasting. Dit is de eerste studie die de mate van stralingsbelasting evalueert van een CT van de pols, gebruik makend van directe metingen. In **hoofdstuk 5** is de blootstelling aan straling gemeten, inclusief de scatter straling, door middel van een fantoom, om de effectieve dosis stralingsbelasting (ED) van een CT van de scaphoid te meten. Dit werd gedaan voor vijf verschillende protocollen die klinisch gangbaar zijn. Twee protocollen waren voor een CT van de scaphoid in gips en drie voor een CT van het scaphoid zonder gips. Voor alle protocollen de Computed Dose Index weighted (CTDIw), de scatter dosis naar het brein en naar de torso werden gemeten door de CT en extern gemeten door een Piranha dosis meter. De gemiddelde CTDIw was 2,18 mGy. De gemiddelde scatter dosis naar het brein en de torso was 0,011 mSv. De gemiddelde ED was 0,02 mSv (spreiding 0,02 tot 0,04) van welke 0,0008 mSv (spreiding 0,0003 tot 0,0012) kwam van de scatter. De twee protocollen voor CT van de scaphoid met gips resulteerden in een 90% hogere ED, al was dit niet een significant verschil. Gezien we de stralingsbelasting As Low As Reasonable Achievable (ALARA) moeten houden, kunnen we aanbevelen om, wanneer mogelijk, een CT te maken zonder gips.

In de literatuur worden diagnostische modaliteiten vaak met elkaar vergeleken. Daarentegen zijn MRI, CT en botscintigrafie nooit met elkaar vergeleken in dezelfde patiëntengroep met een klinische verdenking op een scaphoid fractuur zonder afwijkingen op de röntgenfoto. In **hoofdstuk 6** worden MRI, CT en botscintigrafie met elkaar vergeleken voor de diagnose van een occult scaphoid fractuur. 33 opeenvolgende patiënten met een klinische verdenking op een scaphoid fractuur zonder een fractuur op de röntgenfoto, werden beoordeeld met MRI, CT en botscintigrafie. In geval van discrepantie tussen de diagnostische modaliteiten werd de uiteindelijke diagnose gesteld op basis van herhaald klinisch onderzoek en herhaalde röntgenfoto's.
Drie van de 33 patiënten hadden een scaphoid fractuur. MRI miste één scaphoid fractuur en over-diagnosticeerde geen patiënten. CT miste twee fracturen en over-diagnosticeerde geen patiënten.

Botscintigrafie miste geen scaphoid fracturen en over-diagnosticeerde één scaphoid fractuur bij een patiënt met een trapezium fractuur.
Deze studie laat zien dat zowel MRI als CT de neiging heeft om vals negatief te zijn en dat botscintigrafie de neiging heeft vals positief te zijn. De specifieke voor- en nadelen van elke diagnostische modaliteit moeten bekend zijn bij clinici die er gebruik van maken en tijdens het diagnostische proces van klinisch verdachte scaphoid fracturen moet met de beperkingen rekening worden gehouden.

Botscintigrafie wordt vaak genoemd als geschikte diagnostische modaliteit om een occulte scaphoid fractuur te diagnosticeren.(5,9,10) Botscintigrafie is sensitief maar mist specificiteit, wat kan resulteren in over-diagnose. **Hoofdstuk 7** is een pilot studie die kijkt naar de SPECT gecombineerd met CT voor de diagnose van occulte scaphoid fracturen.
Van tien patiënten met een klinische verdenking op een scaphoid fractuur en een negatieve röntgenfoto werd een SPECT/CT en een botscintigrafie gemaakt en geanalyseerd. De scans werden onafhankelijk en apart van elkaar bekeken door een nucleair geneeskundige en beoordeeld voor scaphoid fractuur en andere afwijkingen.
De botscintigrafie was positief voor een scaphoid fractuur bij vier patiënten en er werden nog drie andere carpale fracturen gezien. SPECT/CT liet vijf scaphoid fracturen en één andere carpale fractuur zien. SPECT/CT- botscintigrafie hadden discrepante resultaten bij drie patiënten. Bij twee patiënten werd botscintigrafie verslagen als trapezoid fractuur waarbij de SPECT/CT een scaphoid fractuur liet zien. Bij de andere patiënt was de botscintigrafie positief voor een scaphoid fractuur, terwijl de SPECT/CT een bone bruise van andere carpalia liet zien.
Concluderend heeft de SPECT/CT de potentie om meer accuraat te zijn dan botscintigrafie, omdat het gebruik maakt van anatomische informatie van de CT om onderscheid te maken tussen de scaphoid, andere carpalia en bone bruises. Grotere studies met een onafhankelijke referentie standaard zijn nodig om deze voorlopige resultaten te bevestigen.

Hoofdstuk 8 is de algemene discussie. De resultaten van alle onderzoeken worden nader besproken en vergeleken met de literatuur. De specificiteit van MRI is lager dan wordt gerapporteerd in de literatuur en dit heeft implicaties voor al het onderzoek dat is gedaan met de MRI als referentie standaard. CT is een zeer praktische diagnostische modaliteit om te gebruiken als aanvullend onderzoek, als de röntgenfoto negatief is bij een patiënt met een klinische verdenking op een scaphoid fractuur. Dat CT fracturen mist en de ''moderate observer agreement'' zijn een probleem, hoewel de fracturen die gemist worden mogelijk een goede prognose hebben. Als er dunnere slices worden gebruikt kan de observer agreement verbeterd worden. De stralingsbelasting is erg laag, met name als er zonder gips gescand wordt. Om de occulte fractuur te diagnosticeren, kunnen de MRI en de botscintigrafie ook gebruikt worden, maar ook dezen hebben beperkingen. De literatuur is niet heel eenduidig over de resultaten van de sensitiviteit en specificiteit van MRI. De sensitiviteit en specificiteit zijn mogelijk overschat door publicatie bias, een gebrek aan betrouwbare referentie standaard en de lage prevalentie van werkelijke scaphoid fracturen.(11-15) Botscintigrafie is niet specifiek, maar gecombineerd met CT (SPECT/CT) is het mogelijk het meest betrouwbare onderzoek. Er zijn wel een aantal praktische bezwaren (beschikbaarheid, kosten, stralingsbelasting, invasief en tijdrovend), waardoor het wellicht alleen in onderzoekverband als referentie standaard geschikt is. Toekomstige studies moeten met name kijken hoe ze vergelijkbare resultaten kunnen krijgen en zorgen voor voldoende data om een latent class analyse te kunnen doen.(1,13) Een ''clinical prediction rule'' kan

de oplossing zijn voor de lage prevalentie van werkelijke fracturen. (16,17) Daarnaast moet de waarde van SPECT/CT onderzocht worden en er moet bepaald worden of dit een mogelijke nieuwe referentie standaard kan zijn.
Gezien de vele publicaties over dit onderwerp is er een samenvatting bijgevoegd van alle reviews van de laatste vijf jaren als overzicht van de huidige kennis.(11-15)

Hoofdstuk 9 bevat de samenvatting van het proefschrift en **hoofdstuk 10** geeft de samenvatting weer in het Nederlands.

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Curriculum vitae

Andele Dirk de Zwart was born on April 7th 1982 in Sneek, the Netherlands. He graduated from High School in 2001.

After one year of studying Biomedical Sciences at the Vrije Universiteit (VU) of Amsterdam, Andele started studying for his medical degree at the VU Medical Center of Amsterdam in 2003. During his internships he started a prospective study with Dr. F.J.P. Beeres and Dr. S.J. Rhemrev in the Medical Center of Haaglanden, comparing CT and Bone scintigraphy for diagnosing occult scaphoid fractures.

After completion of his medical study in 2010, he worked as a resident at Leiden University Medical Center. During this residency Andele continued his study on scaphoid fractures, under supervision of Prof. Dr. I.B. Schipper.

In 2012 he started as orthopaedic surgery resident at the Academic Medical Center of Groningen, led by Prof. Dr. S.K. Bulstra.

At this moment he works as a resident in Martini Hospital, led by Dr. J.J.A.M van Raay. He will complete this residency in May 2019.