A literature review of the cost-effectiveness of nuclear MEDICINE

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ABBREVIATIONS

ACT	anticoagulant therapy
AIDS	autoimmune deficiency syndrome
APE	aerosol production system nebuliser
CA	coronary angiography
CAD	coronary artery disease
CBF	cerebral blood
CT	computed tomography
CVD	cerebrovascular disease
DMSA	Technetium-99m-dimercapto-succinic acid
DSA	digital subtraction angiography
DTPA	Technetium-99m-diethylene-triamine-penta-acetic acid
DV	dual vessel disease
ECD	ethyl cysteinate dimer
ECG	electrocardiogram
efficacy-D	diagnostic efficacy
efficacy-M	management efficacy
efficacy-O	outcome efficacy
FNAB	fine-needle aspiration biopsy
HMPAO	Technetium-99m-hexamethyl-propylene-amine oxide
IBD	inflammatory bowel disease
IHD	ischaemic heart disease
ILS	Indium-111 leucocyte scintigraphy
IMP	Iodine-123-isopropyl-iodoamphetamine
MAG_3	Technetium-99m-mercapto-acetyl-triglycine
MI	myocardial infarction
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MS	multiple sclerosis
MV	multi vessel disease
OIH	Iodine-131-ortho-iodohippurate
P	perfusion lung scan
PA	pulmonary angiography

PE	pulmonary embolism
PET	positron emission tomography
QUALY	quality-adjusted life year
RBS	radionuclide brain scanning
rCBF	regional cerebral blood flow
ROC	receiver operating characteristic
SPECT	single positron emission computed tomography
SV	single vessel disease
TSH	thyroid stimulating hormone
UTI	urinary tract infection
V	ventilation lung scan
V/Q	ventilation/perfusion lung scan
WBC	white blood cell

EXECUTIVE SUMMARY

Client, sponsor and principal researcher

The British Nuclear Medicine Society (BNMS) was the client for the study. The costs of the six-month project were met by Amersham International. In order to achieve an objective assessment, a principal researcher, Dr Jan Carter, was identified. Dr Carter has a scientific and medical research background without any previous nuclear medicine experience. She holds a master's degree in management studies.

A steering group with inputs from the different disciplines of nuclear medicine, cardiology, public health and health economics guided all aspects of the work and approved this paper.

The Steering Group comprises:

Susan Clarke Chair	Consultant Physician, Dept of Nuclear Medicine, Guy's & St Thomas's Hospital Trust, Senior Lecturer, Radiological Sciences, UMDS, University of London, President of BNMS
Robert J Maxwell	Chief Executive, The King's Fund
Christine Farrell	Director of Clinical Change, King's Fund Centre
Roberto Rona	Reader in Public Health Medicine, UMDS, University of London
Martin Buxton	Professor, Health Economics Research Group, Brunel University

Richard Underwood Senior Lecturer in Cardiac Imaging, Royal Brompton Hospital

Jan Carter Principal Researcher, Senior Management Consultant (contactable on 0865-62824)

David Perry Project Manager, Chief Executive, Sales & Marketing Associates.

Aims

The aim of this study has been to review published research to establish:

- what is known with regard to the cost-effectiveness of nuclear medicine procedures,
- from this knowledge, which procedures have high, medium and low probabilities of being proven to be cost-effective,
- from this research, which areas are likely to be the best for future work on efficacy and cost-effectiveness.

Methodology

The Steering Group approved the methodology which centred around a worldwide literature search and review in the following disease areas: heart, kidney, lung, bone, brain, bowel, thyroid.

In all, some 454 published papers were accessed through *Index Medicus* and Medline, Biosis and Healthplan databases. Of these, 328 were reviewed for this study. Key words centred around: imaging techniques for the disease categories, efficacy, comparison, costs, cost-effectiveness and management. The amount of published work using real cost-effectiveness analyses in nuclear medicine is small compared with the number of papers available on clinical issues. Only five papers were found for nuclear cardiology, three for renal disease and two for pulmonary embolism and thyroid nodules. Many papers talked about costs and related them to cost-effectiveness without real analysis.

Conclusions

The table below shows the general conclusions which have been drawn from the literature researched about the cost-effectiveness of nuclear medicine techniques used in diagnosis and management of the diseases studied in this report.

Disease		Cost-effectiveness score*
Heart	– coronary artery disease – diagnosis	Medium
	– management	High
Kidney	– hypertension, transplant, urinary tract infection	Medium–High
Lung	– pulmonary embolism	High
Brain	– still in the research phase	Low
Bone	– metastases – primary diagnosis,	High
	– follow-up	Low
Bowel	– inflammatory bowel disease	High
Thyroid	– nodule	Low
	– follow up	High+

* This subjective cost-effectiveness 'score' does not relate to all techniques used for assessing a disease but to specific procedures as detailed in the main report.

High+ – nuclear medicine technique accepted as cost-effective.
High – literature provides enough information to warrant further studies of cost-effectiveness.
Medium – literature provides some evidence to suggest that further studies of cost-effectiveness may be warranted
Low – nuclear medicine techniques accepted as not being cost-effective or still in the research phase.

This review of the literature points towards the potentially most rewarding areas for immediate work on cost-effectiveness as being:

- myocardial perfusion imaging in ischaemic heart disease,
- leucocyte scintigraphy in inflammatory bowel disease,
- renal scintigraphy.

INTRODUCTION

The continuing escalation of the cost of medical care is a major problem for today's society. It is generally recognised that there are wasteful practices in health care which contribute significantly to the problem. Although few would argue with the proposition that medical care should be as cost-effective as possible, there is usually insufficient reliable information to help identify ineffective practices. Assessing the cost-effectiveness of a medical practice is a complex problem that requires precise evaluation of costs and benefits as well as evaluation of traditional physiological and pathological parameters.

The changes in the National Health Services (NHS) over the past ten years, including the introduction of the White Paper *Working with Patients* in 1989, have been in part responsible for the more critical approach to clinical management that now exists within the NHS. There is a new emphasis placed on accountability, costing of medical activity and budget control. The need for clinical investigations is being challenged and evidence of cost-effectiveness is being sought by both purchasers and managers, clinical and non-clinical, within provider units. In an attempt to standardise packages of care, with the aim of improving both the quality and the cost-effectiveness of care, guidelines are being created by the Royal Colleges, specialist societies and the Department of Health. For these guidelines to be successfully applied it is vital that practitioners are convinced that the management guidelines are based on good evidence of scientific and clinical efficacy.

The utilisation of nuclear medicine investigations in the UK is far less than in many other countries in Europe. Nuclear medicine investigations in other countries play a significant role in the management of patients with common medical problems, including coronary artery disease, renal disorders and thyroid disease. The reason for the underutilisation of nuclear medicine techniques in the UK is complex, but the British Nuclear Medicine Society recognises that if clinicians are to use nuclear medicine techniques in an appropriate way, they need to be convinced of the sensitivity and specificity of these techniques, and also their cost-effectiveness. It was to gather evidence on cost-effectiveness that in 1993 the British Nuclear Medicine Society initiated this independent study.

Aims of the report

- To review major current and emerging applications of nuclear medicine through a literature search. (Phase I)
- To identify applications for which there is good evidence of clinical effectiveness. (Phase I)
- To consider which of the applications might offer considerable economic benefit, which are entirely uncertain and which are not likely to be beneficial. (Phase I)
- To determine priorities for prospective economic evaluation of applications and to identify key parameters for subsequent analysis. (Phase II)

Organisation of the report

Chapter 1 gives a brief history of nuclear medicine and discusses whether nuclear medicine is underused in the UK. Chapter 2 presents a general overview of efficacy and cost-effectiveness with the aim of providing a background to the concepts.

Each disease is then reported separately (Chapters 3–9). Cardiac disease is examined in more detail than other disease categories because of its clinical significance. These chapters provide information on the background, clinical utility and limitations of the various techniques used in the diagnosis and prognosis of the different diseases. The cost-effectiveness of procedures is discussed on the basis of current available evidence from the literature.

Finally, Chapter 10 presents the general conclusions of Phase I with suggestions for future work.

Papers in the Bibliography are listed in general categories and disease categories. The Bibliography appears at the end of the book.

Methods

In order to obtain an objective approach to this study, a principal researcher with a background in scientific and medical research but no previous experience of nuclear medicine, was appointed.

A steering group consisting of experts in nuclear medicine, public health, health economics and project management was established to identify the questions to be addressed and to assist in assessing the literature. This group met approximately once a month over the six months of Phase I. The disease categories to be included in the study were determined by the Steering Committee (Table 1), as well as the nuclear medicine procedures (Table 2).

Relevant studies were collected back to 1980 from *Index Medicus* and Medline, Biosis and Healthplan databases. Keywords used in the searches included: nuclear medicine; magnetic resonance imaging; radiology; heart imaging; renal imaging; lung imaging; brain imaging; bone imaging; bowel imaging; thyroid imaging; costs; economics; cost-effectiveness; management; efficacy; diagnostic tests.

All references were entered in a reference manager database. The number of papers identified for each disease are documented in Table 3. The references for each disease were reviewed for efficacy, costs and cost-effectiveness.

References in the Bibliography are categorised under the following headings: nuclear medicine; costs/cost-effectiveness; methodology; magnetic resonance imaging; heart; renal; pulmonary embolism; brain; bone; inflammatory bowel disease; thyroid. The number of references used for each disease are given at the beginning of the chapter. Specific references quoted in the text are listed at the end of each chapter.

Table 1 Disease categories

HEART	Ischaemic heart disease
KIDNEY	Urinary tract infection Hypertension Transplant
LUNG	Pulmonary embolism
BRAIN	Dementia Confusion Depression Focal neurology
BONE	Neoplasia
BOWEL	Inflammatory bowel disease
THYROID	Thyroid nodule Thyrotoxicosis

Table 2 Nuclear medicine procedures

HEART	perfusion planar/SPECT	^{201}Tl	
		^{99m}Tc	cardiolite myoview
RENAL	static	^{99m}Tc	DMSA
	dynamic	^{99m}Tc	DPTA
		^{99m}Tc	MAG_3
LUNG	perfusion	^{99m}Tc	microspheres aggregates
	ventilation	^{127}Xe, ^{133}Xe, ^{81m}Kr gases	
		^{99m}Tc	DPTA aerosol colloids
BRAIN	perfusion	^{99m}Tc	HMPAO
BONE	dynamic/ static	^{99m}Tc	diphosphonates
BOWEL	static	^{111}In ^{99m}Tc HMPAO	WBC
THYROID	static	^{99m}Tc, ^{123}I, ^{201}Tl	

Table 3 Number of papers in each category

Category	No.
General/Nuclear Medicine	25
Costs/Cost-effectiveness	37
Methodology	15
Magnetic Resonance Imaging	21
Radiology	15
Radionuclide Imaging	
Heart	113
Kidney	19
Lung	11
Brain	28
Bone	23
Bowel	8
Thyroid	13
Total references reviewed	328

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BACKGROUND TO THE STUDY

The history of nuclear medicine

The development of nuclear medicine began in the late 1940s. At that time, scientists in the USA and UK used radioactive iodine to assess how much iodine localised in the thyroid by means of a Geiger-Müller counter measuring the amount of radiation coming from the thyroid. In 1947–8, US and German scientists discovered that gamma rays could be detected effectively by a scintillation crystal and photomultiplier tube combination enabling automated measurement. By 1951, instrumentation had been developed which allowed the thyroid gland to be mapped on a 400-point grid over approximately one and a half hours. Simultaneously, during the 1950s, radioactive pharmaceuticals were developed to allow the study of other organs (including heart, liver, brain, kidneys and bone), together with new instrumentation which allowed more accurate detection of gamma rays. From the 1960s to the 1970s, newly developed radioactive nuclides such as Technetium-99m changed the practice of nuclear medicine dramatically. The 1970s and 1980s saw the advent of computers which allowed quantitation of an increasing number of procedures.

Despite competition from other imaging modalities in the 1980s, in the USA, the market for radionuclide imaging equipment expanded rapidly. In 1987 and 1991, the market was worth \$223.7m and \$436.4m, respectively. The projected value for 1996 is \$650m. The reasons for this increment lie in the increased performance of nuclear cardiology procedures, new radio-pharmaceuticals, an understanding of the advantages of functional imaging as a complement to, rather than as an alternative for, precise anatomical imaging, and new, high performance, multi-detector single photon emission computed tomography (SPECT) systems. In 1991, $34m was spent on SPECT dual-head multi-detector units, and sales are expected to reach $127.6m in 1996.

The future of nuclear medicine continues to be extremely interesting as scientists and clinicians research and develop new technologies, radiopharmaceuticals and therapies.

Nuclear medicine in the UK

Nuclear medicine represents an estimated 8.1 per cent of the total imaging market. It involves patients from all age groups and races, and is used extensively in the diagnosis and management of heart disease and cancer (the two diseases with the highest annual death rates in western Europe). There is, however, an enormously wide variation in the use of nuclear medicine in the world. With new structures in health care emerging within the European Community (EC), there is a particular challenge between continental Europe and the UK in the development, maintenance and expansion of nuclear medicine.[1]

In 1983, half the hospitals in the USA had nuclear medicine facilities, compared with one-third in the UK, and five times as many tests were performed.[2] In 1985, the rate of nuclear medicine investigations in the USA was 29,600 per million inhabitants per year. In 1988, 200 hospitals in the UK were estimated to have at least one gamma camera. The annual rate of nuclear medicine procedures in the UK was 8000 per million inhabitants per year.

Within the EC countries, the UK had the second largest number of gamma cameras in 1991, with 6.82 cameras per million inhabitants, the EC average being 9.46 cameras per million. The number of scintigraphies per 1000 inhabitants and the number of studies per camera were well below the European average.[3]

Possible reasons for the low use of nuclear medicine in the UK include:

- In 1990, it was estimated that only one-third of hospitals in the UK had nuclear medicine facilities.

- Median camera age is five years, with some centres having ten-year-old cameras. This equipment is relatively old given the rapid changes in camera and computer design and suggests a relatively low level of capital investment.
- There is little formal undergraduate training in nuclear medicine available in the UK. In 1988, there were eight senior registrars, 29 consultants and six senior lecturers or professors.
- There is tremendous diversity of clinical staff that supervise nuclear medicine studies: nuclear medicine physicians, radiologists, radiotherapists. For many, nuclear medicine is not the primary specialty.
- There are no comprehensive publications on efficacy and cost-effectiveness of nuclear medicine procedures or on the use of nuclear medicine procedures in the management of patients. The diagnosis and management of patients with coronary artery disease (CAD) have recently been reviewed in a joint paper from the Royal College of Physicians and the British Cardiac Society in which little mention was made of the use of myocardial perfusion imaging (MPI) in the management of patients with suspected or proven CAD. Utilisation of nuclear medicine does not appear to fit with the proven effectiveness in providing diagnostic and prognostic information.

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2

COSTS, EFFICACY AND COST-EFFECTIVENESS

Costs

Imaging techniques are complex activities, requiring space, equipment, isotopes and human and other resources. The fundamental principle of costing is that all expenditure incurred has to be included in the final costing. The second principle is that capital (in the form of building and equipment) has to be maintained or the service cannot continue and that this must also be included in the final costing. Costs are difficult to present because they can be determined in different ways. For a review of the costing of imaging procedures, definition and types of costs in the NHS, see Bretland.[1,2]

Detailed costings have been reported for nuclear medicine procedures in the UK[3] but no works were found that included comparative costings of all the procedures discussed in this review. A number of papers reported costs of imaging procedures used in nuclear cardiology but again no one paper gave a comparison of the costs of all techniques. However, from the literature reviewed, if the cost of a stress electrocardiogram (ECG) is taken as the lowest basic cost, then a rest echocardiogram cost fell within the same range. The cost of a stress echocardiogram and Thallium-201 myocardial perfusion imaging (MPI) was 1.3–7.4 times higher and angiography was 5.3–18.5 times higher. Informal surveys held at the Royal Brompton Hospital and Guy's & St Thomas's Hospital Trust showed that costs in these institutions were in the middle of these ranges (see Table 4). The costs of these techniques ranged from £60 for a stress ECG to £700 for coronary angiography (CA).

Table 4 Relative costs of nuclear cardiological imaging techniques

	A	B
Stress electrocardiogram	1.0	1.0
Rest echocardiogram	1.0	1.3
Stress echocardiogram	1.3– 7.4	1.8
Myocardial perfusion imaging	1.3–7.4	2.8–3.7
Magnetic resonance imaging	–	4.6–5.0
Coronary angiography	5.3– 18.5	9.6–11.6

A – from the literature (n = 8)
B – from The Royal Brompton Hospital and Guy's and St Thomas's Hospital Trust

A value of 1.0 has been accorded to stress ECG and the other values and ranges are orders of magnitude greater.

Efficacy and cost-effectiveness

When resources are limited, it becomes necessary to select those diagnostic tests which are most useful. To do this, the benefits of a test have to be weighed against the risks, and the value of a given outcome has to be measured. Most of nuclear medicine deals with diagnoses which may affect subsequent management. In theory, the most valid approach to show the usefulness of a particular scan would be to measure the well-being of a patient ten years later. In practice, such an approach would be complicated, labour-intensive and costly.

Efficacy is defined as 'the power to produce effects or intended results' and is measured under ideal conditions such as in a clinical trial, while effectiveness is usually measured under normal conditions of use. There are three types of *intended results* in medicine:

- correct diagnosis;
- correct patient management;
- favourable patient outcome.

Diagnostic efficacy

The utility of those diagnostic tests which facilitate patient care (diagnostic efficacy (efficacy-D)) is measured by test performance, which in turn depends on a specific task[4] and this must be proportional to the change in diagnostic certainty caused by the procedure. Measures of test performance include sensitivity, specificity, predictive value, accuracy, diagnostic utility, post-test versus pre-test probability, or area under a receiver operating characteristic (ROC) curve.

Management efficacy

The management efficacy (efficacy-M) of a diagnostic procedure is measured by whether the test changes how the patient is managed or treated, and asks questions such as whether the test aimed treatment in the right direction or averted unnecessary costs or risks. If efficacy-D equals zero because the diagnostic certainty of the clinician is the same before and after the procedure, then the test would in no way change the management of the patient and efficacy-M would also equal zero. Assessing efficacy-M for a given diagnostic test is difficult because there are many other factors influencing clinician decisions.

Outcome efficacy

Outcome efficacy (efficacy-O) is the most difficult to assess. It is much easier to determine efficacy-O for radionuclide therapy than it is for a diagnostic test. Outcome evaluation of patients is very arbitrary because much of it involves the measurement of the patient's state of health or illness and depends upon subjective evaluation by the patient. Efficacy-O would not exist unless there were some efficacy-M; therefore if a diagnostic test does not affect management, it cannot affect outcome.

Cost-effectiveness

A procedure is cost-effective if the benefits of correct diagnosis, effective management/treatment and outcome are worth the additional costs. Costs associated with nuclear medicine procedures include: direct costs of labour and consumables; indirect costs consisting of variable overheads, such as service contracts and stationery; fixed overheads, including heat, light and maintenance; and capital costs. Other non-financial costs to be considered are patient discomfort; possible drug reactions; radiation dose; and the very low risk of radiation-induced cancer.

Three questions must be answered in order to demonstrate cost-effectiveness:

- How much health benefit does a procedure provide?
- What are the monetary costs?
- Is achieving the benefit worth the cost?

The answers to the first two questions are analytical and provide vital information for the third judgemental evaluation to be made by the clinician. In deciding which test to prescribe, the clinician needs to know the answers to the following questions:

- What is the specific value in patient management and outcome of the information provided by each test?

- What is the sensitivity (number of true positives defined in a study), specificity (number of true negatives defined in a study) and predictive accuracy (of both a positive and negative result) of each test?
- How do the tests compare against each other?
- What degree of sensitivity, specificity and predictive accuracy is appropriate for a given clinical circumstance?
- What added value does a test provide to information already available?
- What are the costs of a given test?

In this report, the clinical utility and limitations of nuclear medicine procedures and other imaging modalities as well as sensitivity and specificity data (where available) are documented. Those papers which make an informed judgement of the overall efficacy and cost-effectiveness of a nuclear medicine procedure are reported in detail.

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3

◦ HEART ◦

One hundred and thirteen references were used and are quoted in the Bibliography under 'Heart'.

Background

Over the past two decades, there has been substantial growth in the practice of nuclear cardiology and an increasing understanding of the role that nuclear medicine has to make in the diagnosis and management of cardiac disease, especially in the USA. Advances have been made in both radiopharmaceuticals and instrumentation. An extensive up-to-date review of the medical progress of nuclear cardiology has been reported by Zaret & Wackers.[1,2]

Underwood *et al*,[3] showed that nuclear cardiology techniques are used much less frequently in the UK than in countries such as the USA and Germany. In a survey carried out on behalf of the British Nuclear Cardiology Group, it was found that 74 per cent of the hospitals that responded performed cardiac studies, and 11.7 per cent of all nuclear medicine studies were cardiac. Sixty-four per cent of centres performed no first-pass radionuclide ventriculography and 20 per cent performed no Thallium-201 scintigraphy. Fifty-seven per cent did report that their cardiac workload was increasing, although this was in the larger centres (over 2000 investigations per year).

Cardiac imaging techniques

When a patient presents with chest pain, there can be one of a number of underlying causes: coronary heart disease (CAD), valvular disease, congenital disease or cardiomyopathies. The clinical questions to be answered when a patient presents with chest pain are:

- Are the symptoms cardiac in origin?
- What is the underlying cause?
- What therapy can follow?
- Can complications be detected or anticipated?

This study concentrates on both diagnosis and prognosis of ischaemic heart disease (IHD), myocardial infarction (MI) and follow-up after intervention. For a full account of the use of nuclear medicine imaging in cardiac disease, the reader is referred to Chalmers *et al.*[4]

A variety of imaging procedures are available to the clinician for the assessment of cardiac disease. These can be divided into *invasive*, such as cardiac catheterisation, and *non-invasive*. Below is a list of procedures available for the diagnosis and prognosis of cardiac disease:

- History and clinical examination.
- Electrocardiography, at rest and during exercise.
- Echocardiography, at rest and during exercise.
- Radionuclide techniques: radionuclide ventriculography, myocardial perfusion imaging (MPI), both single photon and positron emission computed tomography.
- Magnetic resonance imaging (MRI).
- X-ray computed tomography.
- Coronary angiography. (Invasive technique, used as the gold standard for all data presented.)

Electrocardiography

Clinical utility of electrocardiography

- Provides an objective assessment of exercise tolerance.
- Easily accessible.
- Simple to use.
- Cheap.

Limitations of electrocardiography

- Low sensitivity and specificity (see Table 5).
- Changes in the surface electrocardiogram are late manifestations of myocardial ischaemia.
- Many conditions obscure the response of the ST segment within the ECG to exercise.

Table 5 Electrocardiography – exercise ST segment measurement compared with angiography

	Sensitivity %	*Specificity* %	*n*
All CAD	68	81	24,074
MV	77	68	

From Gianrossi *et al*,[4] meta-analysis of 147 reports

Stress echocardiography

Clinical utility of stress echocardiography

- Not used as a routine examination. Used in some centres when ECG is equivocal, where there is ST depression without symptoms or hypotension, or when a patient is unable to stress adequately.
- Wall motion detected at rest or exercise in multiple planes.
- Role in diagnosis of CAD (more accurate for MV than SV).
- Role in determining prognosis after MI.
- Role in demonstrating recovery of function after intervention.
- Dobutamine infusion can identify viable but non-contractile myocardium.
- Low cost.
- No time delay.
- No radiation exposure.

Limitations of stress echocardiography

- Interpretation of images needs more expertise than other techniques.
- High interobservational variability.
- Variable accuracy for identifying SV (see Table 6 for sensitivity and specificity data).
- Difficulties in relating wall motion abnormalities to anatomy.
- Difficult to assess patients with obstructive airways disease.
- Not available in all hospitals.

Table 6 Echocardiography – before and after exercise (treadmill) compared with angiography

	Sensitivity %			Specificity %	n
	ALL CAD	SV	MV		
Armstrong *et al*[6]	87.3	80.9	93.2	86.4	123
Limacher *et al*[7]	91.0	4.0	93.2	88.0	83
Crouse *et al*[8]	97.1	4.0	100.0	64.2	228

Radionuclide techniques (single photon)

Among the various techniques of nuclear cardiology, MPI is the most widely used to assess the adequacy of blood flow to the myocardium. The importance of MPI is that it is an assessment of the functional significance of CAD. Myocardial perfusion can be performed as either a planar or SPECT study, with or without stress. The conventional agent used is Thallium-201. New Technetium-99m-labelled agents are now licensed for use which are optimally suited for imaging with a gamma camera. These are Technetium-99m Sestamibi (Cardiolite) and Technetium-99m Tetrafosmin (Myoview). This study reports on planar and SPECT MPI with stress Thallium-201 and Technetium-99m Sestamibi imaging.

Clinical utility of myocardial perfusion imaging

- Able to diagnose and prognose acute and chronic CAD.
- Able to distinguish viable from non-viable myocardium.
- Able to predict the extent and severity of underlying CAD.
- Able to localise ischaemia to a specific area/s.
- Able to evaluate the effects of coronary bypass surgery.
- Able to assess prognosis following MI.
- Pharmacological stress imaging with dipyridamole and adenosine can be employed as an alternative to exercise stress.

Limitations of Thallium-201 and myocardial perfusion imaging

- Thallium-201 has a half life of 73 hours which results in a radiation dose of 23mSv.
- The recommended UK administered dose of Thallium-201 (80MBq) results in low-count density.
- The photon energy of Thallium-201 (68-80keV) is not best suited to gamma camera use which operates optimally at 140keV.
- Planar imaging has a number of limitations: intra-observer variability; limited diagnostic accuracy (see Table 7 for sensitivity and specificity comparisons); superimposition of normally and abnormally perfused myocardium can occur (more with Technetium-99m than Thallium-201 agents). SPECT imaging can overcome these difficulties.

Clinical utility of Technetium-99m Sestamibi

- There is very little redistribution, therefore imaging following injection can be delayed.
- High-count rates give the potential of assessing exercise ejection fraction and myocardial perfusion in one study.
- It is possible to assess the amount of myocardium at risk in acute MI without delay in thrombolytic therapy.
- The potential exists for a dual-isotope approach where the entire study could be accomplished in less than two hours, using rest Thallium-201 and stress Technetium-99m Sestamibi.

Limitations of Technetium-99m Sestamibi

- There is debate as to whether sensitivity of Technetium-99m Sestamibi imaging is better than Thallium-201 imaging when SPECT is used (see Tables 8 and 9).
- Long preparation time (30 minutes).
- Has to be administered within six hours of preparation.
- Lung, gall bladder and bowel uptake can present technical difficulties and affect image interpretation.

Table 7 Myocardial perfusion imaging

Planar ^{201}Thallium imaging and coronary angiography

	Sensitivity %	*n*	*Specificity* %	*n*
ALL CAD	84	2118	84*	1140
SV	78	247		
DV	89	275		
MV	92	328		

From Kotler & Diamond,[9] analysis of 122 reports

SPECT ^{201}Thallium imaging and coronary angiography

	Sensitivity %	*n*	*Specificity* %	*n*
ALL CAD	90	1042	70*	239
SV	83	387		
DV	93	351		
MV	95	222		

From Mahmarian & Verani,[10] analysis of 6 reports

* Only some analyses reported specificity

Table 8 Diagnosis of CAD – comparison of Technetium-99m-Sestamibi and Thallium-201 with coronary angiography

	n	Sensitivity %		Specificity %	
PLANAR		^{99}Tc-mibi	^{201}Tl	^{99}Tc-mibi	^{201}Tl
KIAT[11]	19	73	73	–	–
TAILLERFER[12]	65	70	74	–	–
WACKERS[13]	36	89	97	–	–
MULTICENTER U.S.	195	86	88	89	63
MULTICENTER INT A	80	89	91	–	–
MULTICENTER INT B	162	95	–	78	–
[AVERAGE		83.7	84.6]		
SPECT					
KIAT[14]	19	93	80	–	–
TAILLERFER[15]	39	82	82	100	82
WACKERS[16]	38	95	84	–	–
MULTICENTER U.S.	192	89	90	49	41
MULTICENTER INT A	81	93	99	–	–
MULTICENTER INT B	85	87	–	–	–
[AVERAGE		86.8	85.8]		

From Wackers[17]

Table 9 Identification of diseased vessels with Technetium-99m-Sestamibi and Thallium-201

Sensitivity %

	ALL CAD			SV		
	^{99}Tc-mibi	^{201}Tl	*n*	^{99}Tc-mibi	^{201}Tl	*n*
PLANAR	81	85	51	63	66	197
SPECT	90	83	81	82	66	10

Specificity %

	ALL CAD			SV		
	^{99}Tc-mibi	^{201}Tl	*n*	^{99}Tc-mibi	^{201}Tl	*n*
PLANAR	94	88	17	80	73	71
SPECT	100	77	17	77	75	61

From Berman *et al*,[18] analysis of 3 reports

Radionuclide techniques (positron emission tomography)

Positron emission tomography (PET) imaging of the heart, with generator-produced Rubidium-82, cyclotron-produced Nitrogen-13-ammonia or Fluoro-18-deoxyglucose, provides a physiological and functional basis for the diagnosis and prognosis of CAD. Although there are many more positron radionuclides for PET imaging of myocardial behaviour, all but the three mentioned above are research tools.

Clinical utility of positron emission tomography

- Can be used in diagnosis and prognosis in a similar way to Thallium-201 to define viable and non-viable myocardium, to assess the need for revascularisation and to predict the outcome of coronary artery surgery.
- Particularly useful in severe cases of CAD with significantly impaired ventricular function.
- Can assess myocardial metabolism and perfusion separately.
- Can measure the dynamic variables and therefore provide information about actual reaction rates and substrate flux.
- Sensitivity and specificity higher than other radionuclide techniques.

Limitations of positron emission tomography

- Equipment and running costs are very expensive.
- The isotopes used are short-lived therefore it is necessary to have a cyclotron close by to prepare radiopharmaceuticals.
- Availability is limited. There is only one clinical installation in the UK.

Magnetic resonance imaging

Clinical utility of magnetic resonance imaging

- Three-dimensional assessment of cardiac anatomy.
- Electrocardiographic-gated MRI studies can demonstrate the thickness of the myocardium and wall motion abnormalities.
- Can provide information on blood flow and function, possibly coronary artery anatomy.

Limitations of magnetic resonance imaging

- Expertise in cardiac MRI is not widely available.
- Costly.
- Availability is limited.

Magnetic resonance imaging and PET will not be discussed further in this section of the report.

Coronary angiography

Clinical utility of coronary angiography

- Used as the gold standard.
- Gives a uniquely detailed anatomical record of coronary arteries and their stenoses.
- Provides valuable information in risk stratification and is an essential prelude to intervention.
- Digital subtraction angiography with intravenous contrast injection can be used to produce images of cardiac chambers, great vessels and proximal portion of the coronary arterial tree.

Limitations of coronary angiography

- High mortality (< 0.5 per cent) and morbidity (< 2.0 per cent).
- Costly.
- Limitations in determining the extent of disease and degree of collateral supply because, strictly speaking: (a) does not diagnose coronary atheroma since vessel wall disease may be present when the lumen is normal, and (b) does not diagnose myocardial ischaemia because it does not give full information about coronary flow.
- Can result in haemorrhage from a punctured vessel.
- Thrombus at the site of arterial puncture may cause vascular insufficiency.
- Atrial and ventricular arrhythmias are common.
- Distal or peripheral embolism may occur.
- Prior treatment with atropine is often necessary to prevent vasovagal attacks.
- Hypersensitivity to contrast agent can occur.

Overview of cardiac imaging techniques

In the last decade, substantial progress has been made in the field of nuclear cardiology and especially MPI. The diagnostic sensitivity and specificity of exercise Thallium-201 scintigraphy are superior to those obtained from exercise ECG alone. Both planar and SPECT MPI have enhanced the capability of detecting MV CAD, and high- and low-risk subsets of patients can now be defined by information from stress imaging. Pharmacologic stress can be used successfully for risk stratification prior to interventional surgery and after MI. SPECT imaging allows assessment of myocardial viability utilising the injection of a second dose of Thallium-201 at rest following redistribution. Stunned or hibernating myocardium can be assessed in the resting state.

Some of the problems that had previously limited the widespread use of echocardiography have been solved by the development of digital recording and side-by-side cine loop display of two-dimensional echocardiograms. Respiratory defects can therefore be eliminated, the examination is faster, and the comparison between stress images has become practical and reliable with improved sensitivity.

Currently, there are no available studies of large series of patients who have undergone radionuclide and echocardiological stress studies and who have angiographic correlations. Limited studies have shown 85–95 per cent concordance. For a review of stress ultrasonography compared with MPI, see Salustri *et al.*[19]

In all the studies mentioned in this report, angiography has been used as the gold standard. As angiography has cost implications in terms of morbidity, mortality and money, it is important to consider which individuals with an initial negative test underwent angiography in each study. It is possible that the patients used will be a biased sample of those with a negative test. For example, it is probable that clinicians that suspect CAD based on other clinical evidence will suggest angiography for such patients but not for patients with less clinical evidence of CAD. This may have an effect on the results of an analysis because false negatives results would be increased and true positives results decreased. Under such circumstances, sensitivity and specificity of the initial test would be decreased.

Cost-effectiveness of nuclear cardiological techniques

The literature search of the cost-effectiveness of different procedures in the management of patients with cardiac disease produced a surprisingly small number of papers. Some papers mentioned cost-effectiveness but did not in fact produce any costings. Others gave costs but made no attempt to analyse cost-effectiveness. The five papers that made an attempt to do so are described below.

- Machecourt *et al*[20] analysed 88 patients from an initial sample of 105 with clinical or ECG evidence of possible CAD who were referred for confirmation of the diagnosis. The main objective of the study was to identify the most appropriate and efficient sequence of diagnostic tests using exercise ECG, Thallium-201 MPI and angioscintigraphy. The authors used Bayesian analysis in their calculations and considered the risk of CAD in relation to age, sex and symptoms. Their gold standard was angiography. In the analysis, the most effective sequence was: clinical information, exercise ECG and MPI before angiography. Angioscintigraphy did not add new information. The analysis of costs was superficial as it included only direct costs, but the conclusions that the cost is less when Thallium-201 MPI is used before angiography seem appropriate.
- The main aim of a paper by Fagan *et al*[21] was to assess the prognostic value of exercise ECG and Thallium-201 scintigraphy in patients with suspected or proven CAD, and Stage 3 Bruce performance in a multiple regression analysis. This was a non-concurrent cohort study. Patients with MI or revascularisation were excluded from the analysis. Both exercise ECG and Thallium-201 scintigraphy contributed independently to CAD prognosis. The incidence of cardiac events was defined in terms of admission for severe chest pain, coronary revascularisation (not attributable to tests) or non-fatal MI and cardiac death. The authors conclude that when exercise ECG is normal, Thallium-201 scintigraphy is not

necessary but it is a very helpful test when exercise ECG is positive. The cost consideration in this study was to restrict the use of Thallium-201 scintigraphy if exercise ECG was negative and clinical symptoms were atypical.

- Wassertheil *et al*[22] analysed 439 patients referred with suspected IHD, of whom 161 had been scheduled for cardiac catheterisation. Using resting and exercise gated blood pool studies and exercise Thallium-201 scintigraphy, cardiac catheterisation was cancelled in 98 of them. Of the 278 patients in whom no catheretisation was planned, 38 subsequently underwent catheterisation. The overall reduction in catheter studies was 37 per cent and the net effect of the nuclear medicine studies was to reduce overall costs and risks.

- Patterson *et al*[23] compared four clinical policies in the diagnosis of CAD using a Bayesian analysis. The four clinical policies were:

  (i) exercise ECG and then angiography if exercise ECG was positive or uninformative;
  (ii) Thallium-201 scintigraphy and then angiography if Thallium-201 scintigraphy was positive or uninformative;
  (iii) angiography immediately;
  (iv) exercise ECG first, then Thallium-201 scintigraphy if exercise ECG was positive or uninformative, and finally angiography if Thallium-201 scintigraphy positive or uninformative.

  The authors used information from several published studies and costs were calculated based on fees for tests allowed by New York City Medicaid-Medicare. Costs were calculated as direct costs and costs related to complications resulting from tests and misclassification. A sensitivity analysis was included in the economic appraisal. The main conclusion of the paper is that the cost-effectiveness sequence of tests will be dependent on the prevalence of CAD in the examined group. In terms of costs for patient tested, the sequence using all the tests is more efficient up to a prevalence of 70 per cent. In groups where the prevalence of CAD is above 75 per cent, angiography on its own is more efficient (for example, in patients with typical angina pectoris). The analysis also explored cost-effectiveness in terms of outcome using quality-adjusted life years (QUALY). The authors conclude that the most important element of the estimate is *outcome* and not cost of the tests. This paper is a serious attempt to evaluate cost-effectiveness of the diagnostic tests. Unfortunately, it is based on data collected in the 1970s before the techniques were developed.

- Reed *et al*[24] in an abstract presented to the American College of Cardiology reported a prospective study of cost-benefit in patients with uncomplicated MI using four diagnostic procedures. Although relevant, this paper is difficult to assess with the limited information given. Management with Thallium-201 scintigraphy as the first procedure was reported as being less expensive with substantial savings. Although reported as leading to more coronary by-pass grafts or percutaneous coronary angiography initially, costs were less than other management strategies when calculated over a three-year period.

The search of the literature did not produce a vast amount of data on cost-effectiveness in nuclear cardiology. Only Patterson *et al*[25] attempted a thorough economic appraisal and the report makes explicit all the components of the analysis in terms of costs and outcomes. In spite of being the earliest study in the field, its main conclusion, that Thallium-201 scintigraphy has an important role to play in the diagnosis of groups in which the prevalence of CAD is intermediate, has not been challenged. Several studies concur to conclude that Thallium-201 scintigraphy does not have a role in patients with atypical chest pain and negative exercise ECG. Two of the reports[26,27] provide evidence that Thallium-201 studies can substantially change the management of patients by appropriately identifying those who require catheterisation and surgery. Unfortunately, these two studies do not provide information on the outcome associated with the change of clinical management.

From these studies, a clear picture emerges indicating that Thallium-201 scintigraphy has a role in the diagnosis and management of CAD. However, there is little published evidence to indicate whether MPI can positively alter patient outcome.

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4

KIDNEY

Nineteen references were used and are quoted in the Bibliography under 'Kidney'.

Background

Of the patients who present with hypertension, approximately 95 per cent have essential hypertension, while the remaining 5 per cent have secondary hypertension; only 3–5 per cent of the latter have renovascular hypertension usually associated with renal artery stenosis.

Diagnosing renal vascular hypertension is difficult because of the lack of a single, inexpensive, screening test. Surgery or percutaneous correction are the treatments of choice.

Renal allograft transplantation is generally considered the preferred treatment for end-stage renal disease. Rejection remains a frequent problem and effective treatment requires early recognition and prompt therapeutic intervention.

One-third of children with a history of urinary tract infection (UTI) have damaged kidneys caused by vesico-ureteric reflux which allows infection from the bladder to reach the kidney. Intravenous urography and radionuclide scintigraphy are the techniques used to detect scarring caused by UTI.

Renal techniques

Many tests, both physiological and anatomical, are available for the evaluation of renovascular hypertension, renal transplants and damage caused by UTI. These tests cover invasive and non-invasive techniques and are listed below:

- Clinical examination, including biochemical tests.
- Ultrasound with and without Doppler.
- Renal scintigraphy, with and without captopril.
- Intravenous urography.
- Magnetic resonance angiography.
- Fine-needle aspiration biopsy.*
- Contrast angiography.*

(*Invasive techniques).

Ultrasound

Clinical utility of ultrasound

- Non-invasive, simple procedure.
- Best in transplant patients as a screening test.
- Can detect enlarged and hypoechogenic renal pyramids in acute rejection of transplants.
- Can detect renal artery stenosis with low-frequency sonographic scanheads which can evaluate differential velocity between renal arteries and the aorta.
- Sensitivities of 62.5–100 per cent and specificities of 73–93 per cent in the evaluation of renovascular disease.
- Can detect scarring in grossly affected kidneys after UTI with a sensitivity of approximately 100 per cent.

Limitations of ultrasound

- Very operator-dependent.
- Patients have to lie still for long periods of time.
- Diminished vascular flow in elderly people inhibits imaging.
- Overlying bowel gas, mesenteric vessels, abdominal aortic aneurysm or recent surgery cause technical problems.
- Limited data on sensitivity and specificity.
- Cannot detect scarring in mildly or moderately affected kidneys after UTI. Sensitivity of 10–37 per cent.

Renal scintigraphy

Three radiopharmaceuticals are used in renal scintigraphy:

- DTPA – Technetium-99m-diethylene-triamine-penta-acetic acid. DTPA is secreted rapidly by glomerular filtration. It has excellent physical properties for imaging and gives a low patient radiation dose. It may, however, result in a non-diagnostic study in the setting of a low glomerular filtration rate.
- DMSA – Technetium-99m-dimercapto-succinic acid. DMSA is used in the diagnosis of UTI.
- MAG_3 – Technetium-99m-mercapto-acetyl-triglycine. MAG_3 is the newest imaging agent for renal scintigraphy. It is filtered by the glomeruli and secreted by the tubules. It can be used in UTI scintigraphy.

One of the most widely accepted screening tests for the evaluation of renal artery stenosis is renal scintigraphy with the administration of captopril. Captopril prevents the conversion of angiotensin I to angiotensin II, thus reducing the constriction of the efferent arteriole and thereby reducing glomerular pressure.

Clinical utility of dynamic renal scintigraphy

- Easy to perform.
- Non-invasive apart from intravenous injection.
- Relatively inexpensive.
- Provides functional information.
- Important in renal transplant patients in order to avoid use of contrast media in already compromised states of renal function.
- Sensitivities of 70–95 per cent and specificities of 50–94 per cent for captopril scintigraphy in detecting renovascular hypertension in SV renal artery stenosis.
- Limited evidence that captopril scintigraphy can assess stenosis in patients with multiple renal arteries.
- Renography is unique in providing a unilateral functional assessment of the kidney, and captopril studies may provide prognostic as well as reliable follow-up information following therapy.

Clinical utility of static renal scintigraphy

- Static DMSA scintigraphy is able to detect scarring (sensitivity of approximately 90 per cent).

Limitations of dynamic renal scintigraphy

- Sensitivities and specificities are very variable.
- Medication may interfere with the captopril test.
- Captopril scintigraphy has limited use in patients with renal failure and bilateral disease.
- After one dose of captopril, patients may (rarely) become hypotensive.
- Renal failure after captopril has been reported in bilateral disease or in patients with one kidney.
- Unable to distinguish rejection from cyclosporin toxicity in a reliable way.

Limitations of static renal scintigraphy

- Only moderate specificity for scar detection.

Intravenous urography

Clinical utility of intravenous urography

- Anatomical and functional test.
- Main value is to demonstrate the anatomy of the renal tract, identify renal tract masses and confirm or exclude the presence of obstruction.

Limitations of intravenous urography

- High-contrast media dose.
- Lack of sensitivity in detecting branch stenosis and bilateral stenosis.
- Minor transient symptoms such as nausea or flushing experienced in 60 per cent of patients.
- Allergic reactions in 1–2 per cent of patients.

Intravenous urography is no longer an acceptable test for renovascular hypertension or transplant patients and will not be discussed further in this report.

Magnetic resonance renal angiography

Clinical utility of magnetic resonance renal angiography

- Can identify single or multiple renal arteries independent of functional change.
- In stenotic lesions of >50 per cent, sensitivities of 87–100 per cent and specificities of 92–100 per cent.
- Possible use in patients with renovascular hypertension who are not stable enough to undergo contrast angiography.
- Potential use in patients with suspected renovascular failure when renal scintigraphy is limited in sensitivity and contrast angiography is contraindicated.
- Potential use of Gadolinium-enhanced MRI for characterising renal lesions in patients with renal insufficiency.
- Comparable accuracy with contrast angiography.

Limitations of magnetic resonance renal angiography

- Anatomical information only.
- Technique relies on indirect factors because there is no signal due to motion of blood.
- Only the proximal third of the renal artery can be adequately examined, which is a disadvantage in patients with suspected fibromuscular dysplasia.
- Motion artifacts are a problem.
- High cost and limited availability (see Chapter 2).

MRI may be useful in patients in whom Doppler evaluation or captopril renal scintigraphy show equivocal results and when proceeding to angiography is not prudent. Because of cost, MRI will not be considered further in this report.

Fine-needle biopsy

Clinical utility of fine-needle biopsy

- Of use in transplantation because it allows direct examination of infiltrating cells, renal parenchymal cells and glomeruli.
- Low morbidity and cost.
- Sensitivity of 90 per cent reported in the diagnosis of acute interstitial rejection.
- Does not require expensive imaging equipment.

Limitations of fine-needle biopsy

- Invasive.
- Technically difficult.
- Low sensitivity in predominantly vascular rejection or when acute rejection is superimposed on chronic rejection.

Contrast angiography

Clinical utility of contrast angiography

- The accepted gold standard for direct visualisation of the renal arteries.
- Recent development of both intra-venous and intra-arterial contrast digital subtraction angiography (DSA) has greatly widened the scope of angiography.
- DSA is less susceptible than conventional contrast angiography to motion artifact.
- DSA is comparable to conventional contrast angiography but is less invasive and requires reduced amount of contrast media.
- Average sensitivity of 88 per cent and specificity of 90 per cent for intravenous DSA.
- Angiography plays a role in final diagnosis, *not* in general screening for renovascular disease.

Limitations of contrast angiography

- Purely anatomical test.
- Intra-venous contrast load puts patients at risk of nephropathy or contrast reaction.
- Complication rates of 1.5–6 per cent due to arteriotomy, catheter manipulation and contrast media injection.
- Intravenous DSA is highly operator-dependent and is being replaced by intra-arterial DSA which is more expensive, invasive and requires more time.
- Not all anatomic stenoses are physiologically significant.

Overview of renal techniques

Renovascular hypertension

Many options are available for the diagnosis of patients with suspected renovascular hypertension and the literature supports the idea that clinical judgement is the most appropriate means of assessing patients with very mild hypertension and a low likelihood of renal artery stenosis.

Although the role of nuclear medicine in the differential diagnosis of renovascular hypertension is a controversial one, the captopril renogram appears best suited for use in those patients with a clinical index of suspicion for renal artery stenosis, whose antihypertensive medications cannot be discontinued and possibly in patients with moderately impaired renal function. It is one of the best screening tests because it is safe, non-invasive, easy to perform, non-operator-dependent and accurate.

Renal transplant

Renal scintigraphy is well tolerated by transplant patients and can be repeated daily because of the low radiation dose. It is simple to perform and rapid to analyse so that results are available on the same day.

Doppler sonography also shows promising results in transplant patients, being non-invasive, relatively inexpensive and capable of assessing renal architecture and perinephric areas. Sensitivity is however low, unless rejection is predominantly vascular.

Urinary tract infection

Renal scintigraphy is useful in investigating and following UTI. It is a reliable method of detecting structural abnormalities and identifying children at risk of progressive renal damage.

Cost-effectiveness of renal techniques

The literature search only provided three papers that reported costs and made an attempt to analyse cost-effectiveness. These all originate in the USA and are described below.

- Delaney *et al*[1] examined 150 episodes of allograft dysfunction in 128 renal transplant patients using core biopsy, FAB, Doppler ultrasound and renal scintigraphy performed within a 24-hour period and before any specific therapeutic intervention. Renal scintigraphy was the most sensitive test for the diagnosis of acute rejection. None of the tests was of value in the diagnosis of a reversible component of chronic rejection. The authors conclude that Doppler ultrasound or a Technetium-99m-MAG_3 scintogram to assess the integrity of the vascular system is the most cost-effective. The unit cost to the patient of each test was used in the discussion but no real analysis of cost-effectiveness was made.

- Lal *et al*[2] report the results of using renal scans and biopsies in a retrospective study of 20 patients following renal allograft transplantation. Serial scans and kidney biopsies were performed at various time intervals in the post-operative recovery period (up to one month) and when clinical signs suggested acute graft rejection. One hundred and forty-four DTPA and Iodine-131 ortho-iodohippurate (OIH) renograms were performed on the 20 patients and one percutaneous biopsy per patient. Of the 20 patients, 18 showed histological evidence of allograft rejection, whereas only seven of the 18 renal scans were reported as consistent with rejection. Unit costs of the tests are given and the authors suggest that in order to be cost-effective, the renal scan should be restricted to the immediate post-operative period when documentation of renal blood flow is important. No real cost-effectiveness analysis was made.

- Blaufox[3] looks at the cost-effectiveness of the role of nuclear medicine procedures following a report from the National Institutes of Health[4] that the clinical value of intravenous DSA exceeded that of nuclear medicine in the diagnosis of renal hypertension. A careful review of the relative cost of renal scintigraphy and DSA in high- and low-prevalence populations using algorithms demonstrates that there is a cost-effective role for renal scintigraphy in the diagnosis of renal hypertension at all stages of investigation. Results show that routine renography, when interposed between DSA studies, significantly reduced the cost per case of renal hypertension diagnosed.

Much more work needs to be done on the cost-effectiveness of nuclear medicine procedures in renal disease. However, the very limited information reported above does suggest a cost-effective role for renography in the diagnosis and follow-up of renovascular hypertension.

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5

LUNG

Eleven references were used and are quoted in the Bibliography under 'Lung'.

Background

The incidence of pulmonary embolism (PE) is estimated to be 630,000 per year in the USA population. Untreated PE is associated with a morbidity of 26 per cent in the first eight weeks after diagnosis, which can be reduced to 2 per cent with appropriate anticoagulant therapy (ACT).

PE represents a dilemma for diagnosticians. This complication can result in sudden death which can be prevented if the presence of the condition is known. Anticoagulants which can reduce the incidence of sudden death are associated with potentially dangerous side-effects and are usually prescribed with caution. Traditionally, the diagnosis of PE was made on the basis of clinical history and physical examination, with the aid of blood gas analysis, chest radiography and ECG. Unfortunately, PE is associated with many non-specific clinical signs and symptoms, and laboratory tests do not enable a dependable diagnosis to be made. Imaging techniques ranging from pulmonary scintigraphy to pulmonary angiography (PA) now make major contributions to the diagnosis. Notwithstanding the acceptance of PA as the reference standard, it was considered unsuitable as a screening method due to its limited availability and morbidity. In 1964, the perfusion (P) lung scan was introduced as a screening test for PE and subsequently the ventilation (V) lung scan was added to improve the diagnostic utility of the perfusion scan.

Lung imaging techniques

Apart from clinical history and examination, a chest X-ray is usually required to exclude other disease abnormalities. The other imaging techniques that are used in the diagnosis of PE are listed below:

- Radionuclide perfusion imaging.
- Radionuclide ventilation imaging.
- Radionuclide ventilation/perfusion imaging.
- Pulmonary angiography.*

(*Invasive test. Used as the gold standard for the diagnosis of PE).

Radionuclide perfusion imaging

Clinical utility of perfusion imaging

- Perfusion scanning is assessed with either microspheres or macroaggregates labelled with Technetium-99m. The labelled particles are injected intravenously and impact in the pulmonary capillary bed.
- Used in the assessment of surgical operability of lung cancer.
- Used to measure right-to-left shunts.

Limitations of perfusion imaging

- Cannot distinguish between embolus and infarct, therefore perfusion scintigraphy alone cannot establish the diagnosis of PE.
- In patients with right or left cardiac shunt, the administered dose has to be reduced because the macroaggregates will enter the systemic circulation and could cause microemboli in the brain and kidneys.

Radionuclide ventilation imaging

Clinical utility of ventilation imaging

- Ventilation imaging is performed with gases such as Xenon-133, Xenon-127, Krypton-81m, or by using aerosols of Technetium-99m-labelled DTPA to study the distribution of the ventilation agent in the airways.
- Used in the assessment of regional ventilation.
- Used in the assessment of small-airways function.

Limitations of ventilation imaging

- Technetium-99m-labelled DTPA aerosols do not penetrate into the peripheries of the lung in patients with chronic airflow limitations. New smaller-particle aerosols include Technegas (Technetium-99m-labelled carbon particles) and aerosol production system nebuliser (APE) which delivers small diameter Technetium-99m-labelled DTPA.

Radionuclide ventilation/perfusion imaging

Clinical utility of ventilation/perfusion imaging

- More sensitive and specific than P or V alone in the diagnosis of PE.
- An abnormal perfusion image together with evidence of normal ventilation of the affected lung regions allows a positive diagnosis of PE.
- The probability of a correct diagnosis using V/Q scanning is high for high-probability, normal and low-probability groups.

Limitations of ventilation/perfusion imaging

- There is a low degree of interobserver agreement in intermediate indeterminant and low probability groups (30–40 per cent of patients).

Pulmonary angiography

Clinical utility of pulmonary angiography

- Involves the placement of a catheter into the right side of the heart with an injection of contrast media into the pulmonary arteries.
- Regarded as the reference method for the diagnosis of PE and the definitive diagnostic tool for the confirmation of PE.
- Sensitivity of 98 per cent and specificity of 96 per cent.
- Used when V/Q study is indeterminate or when special consideration for a patient makes it advisable.

Limitations of pulmonary angiography

- Mortality 0.2 per cent.
- Morbidity 1.9 per cent.
- Patients can suffer from severe allergic reaction to contrast media, cardiac perforation and rhythm disturbances requiring treatment.

Overview of lung imaging techniques

The diagnosis of PE is unreliable. Pulmonary angiography is the accepted reference standard but is considered unsuitable for initial screening due to its invasive nature. The normal perfusion scan virtually excludes PE, and ACT can be withheld from such patients; however, an abnormal perfusion scan is not proof of PE. Ventilation scanning improves the diagnostic utility of the perfusion scan and a number of studies have shown that a high-probability V/Q scan corresponds with angiographically proven PE in approximately 90 per cent of patients.[1]

Cost-effectiveness of lung imaging techniques

The literature search provided only two papers that present a cost-effective analysis. These are described in detail below.

- Specker *et al*[2] analysed data taken from a study by The Society of Nuclear Medicine that was designed to determine the efficacy or usefulness to referring physicians of V/Q lung scan in the diagnosis of PE. Twenty-three hospitals took part and information was used from 2023 patients. Entropy minimax detection analyses and logistic regression showed that V/Q lung scans had a significant influence on the referring physician's diagnostic thinking and affected the therapeutic management in a beneficial direction. In addition to studying efficacy, a cost-effectiveness analysis on the lung scan relative to the management of PE was performed. Costs of lung scans were reported for each institution. The data were divided into four subgroups dependent on prior probability determined by the clinician before imaging. Cost-effectiveness of the lung scan, in terms of incremental cost and cost per life saved, was determined for these groups. Management of PE was considered appropriate/inappropriate if ACT was administered or not. In 20 per cent of the patients the prescription of ACT was appropriately changed after V/Q scanning and confirmed in 67 per cent of patients. The greatest benefit in lives saved occurred when the prior probability was 25–74.99 per cent.

- Oudkerk *et al*[3] in a study from the Netherlands considered the consequences of nine different diagnostic management strategies for clinically suspected pulmonary emboli. After a review of the literature, assumptions were derived and used in a model to calculate the effects of lung scanning on mortality, morbidity, diagnostic efficacy and diagnostic and therapeutic costs using a decision-based analytic model. Additionally, a cost-effectiveness analysis was performed using incremental costs per additional life saved. The management strategies looked at different combinations of ultrasonography of the legs, V/Q scanning and angiography. The costs per life gained were calculated for each strategy compared with a strategy in

> which none of the patients were symptomatic. Use of V/Q scanning and ultrasonography of the legs resulted in a 40–50 per cent reduction in the number of patients requiring PA and was cost-effective.

V/Q scanning plays a major role in the diagnosis of PE. It is not as accurate as angiography, but this is an invasive method and as clinicians have no other reliable screening test at hand, lung scanning is usually requested for patients with suspected PE. At present, the most efficient approach appears to be a combination of V/Q scanning, B-mode ultrasonography of the legs and PA for difficult cases. Recently suggested alternatives to this approach such as serial, non-invasive techniques for deep vein thrombosis detection, using D-dimer and thrombin-antithrombin III complex determinations, have been reported, but they need further clinical evaluation before they can be addressed in a cost-effectiveness analysis.

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6

BRAIN

Twenty-eight references were used and are quoted in the Bibliography under 'Brain'.

Background

Cerebrovascular disease (CVD) is the third most common cause of death in the USA and Europe. The annual incidence of cerebrovascular accidents (CVAs) which rises with age is approximately 1 per cent. Cerebrovascular disorders can range from CVAs caused by haemorrhage or infarction, to headaches and dementia.

Headache is the most frequent pain affecting humans. One population survey in the UK showed 12 per cent of men and 19 per cent of women had consulted a physician in the previous year for a headache.

Between 3 and 5 per cent of people over 65 years of age suffer from impairment of memory, personality changes and dementia (including Alzheimer's disease). There is a clear association of dementia with age, rising from 1 per cent in people under 65 to more than 15 per cent in those over 85 years of age.

Radionuclide brain scanning (RBS) for cerebral abnormalities was introduced in 1963 and depended on whether there was a breakdown in the blood–brain barrier. For years RBS using Technetium-99m-pertechnetate and Technetium-99m-gluconate proved effective in the diagnosis of focal lesions of CVA patients, with sensitivity rates of approximately 85 per cent.

In 1973, computed tomography (CT) which permitted direct observation of cerebral anatomy was introduced. With the development of CT scanning and MRI throughout the 1970s, the radionuclide brain scan declined in popularity. Recent developments in radiopharmaceuticals and instrumentation, as well as new approaches to diagnosis which have been developed for SPECT exclusively, have given radionuclide brain scanning new promise in the routine clinical evaluation of CVD through the assessment of regional cerebral blood flow (rCBF). Although PET facilities provide accurate diagnosis for some cerebrovascular disorders, their limited availability restricts their clinical application.

At this time, the appropriateness of diagnostic procedures in CD is being questioned. A reappraisal of the potential benefits, risks and costs is ongoing. No cost-effectiveness studies of cerebrovascular imaging using radionuclide techniques were found. Only clinical utility and limitations of techniques will be listed.

Brain imaging techniques

- X-ray computed tomography.
- Radionuclide scintigraphy-SPECT.
- Magnetic resonance imaging.
- Positron emission tomography.

Computed tomography

Clinical utility of computed tomography

- Used for the demonstration of structural changes.
- Cross-sectional images demonstrate the ventricular system, the white and grey matter, the skull vault and any intracranial calcification.
- Contrast media allow clear demonstration of vascular lesions (e.g. arteriovenous malformations, aneurysms, tumour and infective processes).

- Used to exclude significant pathology as a cause of headache.
- Able to evaluate meningiomas and differentiate tumours from oedema.
- Rapid imaging.
- Preferable in patients with acute trauma, as well as very young or elderly patients.
- Used in the neuroradiologic evaluation of AIDS patients.
- Quantitative values of tissue X-ray attenuation can be obtained, but no direct relationship of these values to pathological processes has been defined.

Limitations of computed tomography

- Few recently published data either supporting or refuting its usefulness in patients with headache.
- Not as sensitive as MRI in detecting lesions in patients with multiple sclerosis (MS).
- Lack of specificity; different intracranial processes may have identical appearance on CT scans.

SPECT imaging using Ceretec or Neurolite

SPECT imaging measures CBF and requires radiotracers that cross the blood–brain barrier or an inert gas which is cleared rapidly from the brain. The first brain perfusion tracer was Iodine-123-isopropyl-iodoamphetamine (IMP, Spectamine). This has been superseded by Technetium-99m brain perfusion agents, which have optimal physical characteristics. Technetium-99m-hexamethyl-propylene-amine-oxide (HMPAO, Ceretec) is currently the most widely used. It does have limitations and new Technetium-labelled tracers such as ethyl cysteinate dimer (ECD, Neurolite), which is stable *in vitro*, are being developed.

Clinical utility of SPECT

- Intravenous injection of radiotracers results in regional brain uptake that correlates well with independent measures of rCBF.

- Useful in diagnosis and prognosis of acute stroke since SPECT is superior to anatomical imaging techniques in detecting focal cerebral ischaemia.
- Able to detect focal hypoperfusion during the first hours following ictus in patients with epilepsy.
- Useful in the diagnostic evaluation of patients with memory and cognitive abnormalities. In severe Alzheimer's disease, sensitivities of 95 per cent are reported. Sensitivities of between 80 and 87 per cent are reported for mildly impaired patients.

Limitations of SPECT

- No typical patterns of perfusion have been recognised in patients with psychiatric disease.
- The implementation of SPECT imaging in clinical practice has been slow. There needs to be closer collaboration between nuclear medicine clinicians, neurologists, psychiatrists and neurosurgeons.
- Problem of transporting patients to other hospitals if nuclear medicine facilities are not available locally.

Magnetic resonance imaging

Clinical utility of magnetic resonance imaging

- The efficacy of MRI is similar to CT in some diseases such as radioculopathy and infection but is superior for detection and characterisation of posterior fossa lesions, spinal cord myopathies, MS, refractory partial seizure, brain tumours and in AIDS patients.
- Quantitative measurements of proton density and relaxation times can be obtained, but no relationship of these parameters with pathological processes has been defined.

Limitations of magnetic resonance imaging

- Expensive compared to CT scanning.
- Issues of diagnostic and prognostic impact are not well documented.

Positron emission tomography

Clinical utility of positron emission tomography

- Interictal PET scans of glucose metabolism consistently demonstrate discrete foci of hypometabolism in patients with complex partial seizures. The localising power is not substantially different between SPECT and PET.
- The limited studies available suggest a prognostic as well as a diagnostic role for PET in paediatric patients.
- Glucose metabolism has been shown to be abnormal in the brains of patients with obsessive compulsive disorder.
- Evidence for frontal-lobe dysfunction in certain subtypes of schizophrenia.
- Useful applications are emerging for the mapping of cholinergic neuron integrity in studies of ageing and Alzheimer's disease.

Limitations of positron emission tomography

- Cost and availability of equipment.
- Efficacy data are very limited.

Overview of brain imaging

Although over the last decade newer and more sensitive imaging techniques have been shown to detect subtle abnormalities in CVD, there is no good evidence in the literature yet that such imaging studies will substantially affect cost-effectiveness in the diagnosis, prognosis or management of patients. Studies have been reported that show that the use of MRI in the neurosciences is not cost-effective.[1] It is possible that scintigraphic imaging alone will provide enough information to be diagnostically useful. Applications are now beginning to emerge, as clinical trials of efficacy and patient outcome establish the usefulness of imaging techniques in CVD.

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7

BONE

Twenty-three references were used and are quoted in the Bibliography under 'Bone'.

Background

Radionuclide bone scanning was first reported in 1961 using Strontium-85. Strontium-87 and Fluorine-18 were introduced in the 1970s and bone scanning became a clinically accepted procedure in patients with malignant disease. The development of Technetium-99m-labelled phosphonate compounds and improvements in the specificity of diagnostic interpretation changed nuclear medicine bone imaging, and this is now one of the most frequently requested nuclear medicine studies.

Radionuclide bone scintigraphy is not a reliable technique for the differential diagnosis of primary bone tumours: this usually depends on a combination of radiology and biopsy. Considerable information, however, is available on the use of bone scanning for routine staging in breast and prostate cancer, and consensus is emerging on prognosis and changes in management. This chapter will concentrate on the reports in the literature concerning the efficacy and cost-effectiveness of imaging of bone metastases following breast and prostate cancer. Other bone disorders will be mentioned briefly. For a review of bone scanning in benign and malignant bone disease see McKillop & Fogelman.[1]

Bone imaging techniques

To demonstrate the presence of metastatic disease in bone, several imaging techniques are available, including X-ray, bone scintigraphy, bone marrow scintigraphy, CT and MRI.

X-ray and bone scintigraphy are the two techniques most often used and are discussed below.

X-ray

Clinical utility of X-ray

- Can detect pathologies which do not excite an osteoblastic response (e.g. myeloma).
- Easy access.
- High specificity for detection of localised problems associated with marked changes in bone structure.
- Used as a complementary technique to bone scintigraphy to identify single lesions.

Limitations of X-ray

- Positive in purely osteolytic processes.
- Relatively insensitive in detecting skeletal metastases because structural changes are required and a lesion has to be bigger than 1–1.5cm in diameter with a loss of approximately 50 per cent of bone mineral before radiolucencies are seen.
- Ribs, sternum and scapulae are difficult to image.
- Whole body imaging increases the radiation dose to the patient.

Bone scintigraphy

Technetium-99m-diphosphonates are the radiopharmaceuticals of choice. They are characterised by a high bone uptake and better bone-to-soft-tissue ratio than earlier agents. A lesion to normal bone ratio is also important and a number of new compounds which show higher ratios are being investigated.

Clinical utility of bone scintigraphy

- Accepted as the appropriate initial investigation in detection and confirmation of bone metastases.

- Can examine the whole skeleton.
- Lesions of only a few millimetres can be detected as actively metabolising lesions by uptake into the osteoblasts.
- High sensitivity. Incidence of false negative bone scans of metastases is less than 3 per cent.
- Lesions in radiologically difficult areas, such as the ribs, sternum and scapulae, can be identified.
- High sensitivity of 90 per cent in detecting acute osteomyelitis.
- More sensitive than routine X-ray for the detection of Paget's disease.
- Traumatic fractures can be identified within 24 hours of injury in 95 per cent of patients under 65 years of age. A negative scan at 72 hours excludes significant bone injury.
- In athletes, early diagnosis of acute stress injuries allows immediate correct clinical management.

Limitations of bone scintigraphy

- Cannot reliably differentiate between malignant and benign primary lesions.
- Osteoblastic response is common to many pathologies therefore bone scan changes are non-specific.
- X-rays are necessary to complement bone scintigraphy.
- Cannot diagnose osteolytic lesions such as occur in melanoma (50 per cent sensitivity).
- Diphosphonate hypersensitivity occurs in less than 10 per cent of patients.

Overview of bone imaging techniques

Although bone scintigraphy for metastases is one of the most common procedures in nuclear medicine, the literature did not reveal any full analyses of cost-effectiveness.

Up to 85 per cent of patients dying from breast cancer show evidence of bone metastases and through the 1970s high positivity rates of 15–40 per cent led to routine scanning of all patients presenting with breast cancer. More recently, low positive rates of

1 per cent in Stage I and less than 3 per cent in Stage II have made the case for routine scanning less clear.[2,3] There does not appear to be any overall agreement on whether all patients presenting with breast cancer at all stages should have bone scans.[4]

Fogelman & Coleman[5] reviewed the literature on serial scans during follow-up of patients presenting with breast cancer and concluded that most studies did not recommend follow-up scans and that cost-efficient routine follow-up scans should be influenced by the lead time over symptoms, the frequency of scanning and the therapy available. Systemic therapy suggests that early treatment of asymptomatic metastatic disease can prolong life, and as bone scintigraphy is the most sensitive diagnostic technique for identifying bone pathology, attempts to identify early metastatic disease are important to the patient.[6] The authors concluded that the general consensus was that the contribution of serial bone scanning to clinical management, in patients with a good prognosis, is considered to be negligible.

In prostatic cancer, up to 70 per cent of patients have evidence of metastases at autopsy. When classified by stage, the rate of positivity is reported to be approximately 5 per cent for Stage I, 10 per cent for Stage II and 20 per cent for Stage III. Current trends in management tend towards withholding hormone treatment until symptoms develop and, with false positive rates of 6–15 per cent, routine follow-up scans are not considered necessary, being neither cost-effective nor efficacious. Bone scanning has three indications in prostate cancer:

- it is a critical part of the initial staging process;
- it is useful in evaluating newly symptomatic patients;
- it is necessary to observe the metastatic response to therapy.[7,8]

Although a number of patients will convert during follow-up, it is uncertain whether bone scanning can provide any additional information beyond that available from biochemical tests.[9]

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8

BOWEL

Eight references were used and are quoted in the Bibliography under 'Bowel'.

Background

The number of cases of inflammatory bowel disease (IBD) has increased in the last 25 years. IBD is most common in the UK, Scandinavia and the USA. In the USA, in the 1980s, there were 25,000 new cases treated per year. There appears to be a bimodal distribution in young adults and patients over 60 years of age.

IBD comprises mainly Crohn's disease, which is defined as subacute or chronic inflammation of the large/small bowel with transmural involvement, and ulcerative colitis which is the recurrent, acute inflammation of the mucosa of the rectum or colon. Barium X-ray studies and endoscopy have routinely provided the diagnosis of IBD. There are, however, situations where both of these procedures are relatively contraindicated: in cases of acute fulminant colitis or in patients with intestinal strictures or obstruction.

Gallium-67-citrate was introduced in 1971 as the first radionuclide to be used in the evaluation of patients with IBD, but it had several limitations. Imaging characteristics were poor and several days were required for completion of the test. Gallium-67-citrate was excreted normally into the gastrointestinal tract which could obscure areas of inflammation or falsely suggest regions of involvement.

Over the last ten years, labelled leucocytes which migrate to areas of infection have become a useful tool for localising inflammation. The most commonly used radiopharmaceuticals are Indium-111 and Technetium-99m-HMPAO-labelled leucocytes.

The literature search did not reveal any work on costs or cost-effectiveness of these procedures. This chapter will concentrate on the use of radionuclide-labelled leucocytes in the diagnosis of IBD. There is no ideal gold standard technique for imaging patients with IBD. Usually, scans are compared with conventional diagnostic techniques and operative findings when available.

Radionuclide imaging techniques

Indium-111 leucocyte scintigraphy

Clinical utility of Indium-111 scintigraphy

- Validity studies have reported scans to be both sensitive (approximately 96 per cent) and specific (approximately 97 per cent) for detecting inflammation.
- Faecal excretion of Indium-111-labelled leucocytes closely correlates with the degree of inflammation, although problems may arise due to incomplete collection of faeces and poor labelling.
- Can accurately differentiate fibrotic or inflammatory stricture.
- Can be used to monitor and assess disease extent and activity in response to therapy.

Limitations of Indium-111 scintigraphy

- Separation of leucocytes is a lengthy procedure. Indium-111 compounds label all blood cells.
- High radiation dose to lymphoid tissue which limits serial scanning after therapy (half-life of 67.5 hours).
- Overestimation of the area of inflammation can occur if there is migration of white cells within the bowel lumen.

- False-positive ILS can occur when haematomas, intramuscular injections, accessory spleens and gastrointestinal haemorrhage are present.
- Produced by a cyclotron, therefore has limited availability (has to be ordered).

Technetium-99m-HMPAO WBC scintigraphy

Clinical utility of Technetium-99m scintigraphy

- Preparation time shorter than Indium-111 labelling.
- Better imaging characteristics.
- Higher affinity for neutrophils and monocytes.
- No day-to-day problem of availability of HMPAO kits.
- Shorter half-life (six hours). Therefore less irradiation of organs.
- Sensitivity of 95 per cent and specificity of 97 per cent in patients with active Crohn's disease and ulcerative colitis.

Limitations of Technetium-99m scintigraphy

- Non-specific excretion into the bowel within three hours.
- More bone marrow uptake than with Indium-111-labelled leucocytes.
- Renal excretion can confuse interpretation of activity in the abdomen.
- Overestimation of the area of inflammation can occur if there is migration of white cells within the bowel lumen.
- False-positive scans can occur when haematomas, intramuscular injections, accessory spleens and gastrointestinal haemorrhage are present.

Overview of imaging of inflammatory bowel disease

Radionuclide scintigraphy is becoming a vital adjunct to X-ray and endoscopy in the diagnosis and management of patients with IBD. The introduction of Technetium-99m-labelled-HMPAO leucocyte scintigraphy has provided a safer, easier-to-perform and reliable means of identifying the active sites and extent of the disease. No cost-effectiveness analyses were found for IBD in the literature search.

9

THYROID

Thirteen references were used and are quoted in the Bibliography under 'Thyroid'. This chapter will focus on the management of patients with suspected thyroid cancer.

Background

Thyroid cancer accounts for 90 per cent of all endocrine malignancies and is responsible for 1.5 per cent of all cancer deaths. Thyroid neoplasia can present as either a discrete nodule or nodules, or a diffusely enlarged gland, although the former is more likely to be malignant.

Thyroid nodules are relatively common and occur in 3–8 per cent of European and US adults and represent the most common structural abnormalities found in the thyroid gland. They are more likely to be malignant in patients under age 25 and in men older than age 60. However, the nature of these nodules is not readily discerned by history or physical examination, and surgical incision of the majority of nodules to ascertain malignancy is not justifiable. Detection of malignant nodules is hampered by the presence of an estimated 300,000 benign nodules in the same population.

Clinically diagnosed thyroid cancer is a rarity. Approximately 10,300 new cases are discovered annually in the USA and the annual death rate is about 1000. Accurate diagnostic techniques are necessary in order to avoid unnecessary surgery and costs.

The internationally accepted classification of thyroid carcinoma is well documented, the principal histologic types being papillary, follicular, Hürthle cell, medullary and anaplastic. To a large extent, the prognosis for an individual patient is dependent on the stage of the tumour at primary diagnosis. The prevalence and mortality of thyroid cancers differ significantly with histologic types.[1]

Well-differentiated papillary, follicular and mixed papillary-follicular thyroid carcinoma represent approximately 90 per cent of all primary thyroid cancers. Current modes of treatment involve thyroidectomy followed by Iodine-131 ablation and occasionally external beam radiation therapy. Thyroid cancer requires long-term surveillance because it has a 30 per cent recurrence rate at 20 years and a propensity to metastasise. Biochemical serum markers and radionuclide scintigraphy are the most useful tests for detecting recurrence.

Radionuclide evaluation of the thyroid was initially achieved 40 years ago by point-by-point counting of radioiodine distribution in the thyroid using a Geiger-Müller detector. This test was not specific for benign versus malignant tissue and there has been a gradual evolution of thyroid imaging techniques over the past three decades. There are a number of techniques now available to predict malignancy but there have been few comparative studies for evaluation of diagnostic tests.[2,3] The gold standard for diagnostic thyroid techniques is surgical excision with histological interpretation.

Thyroid techniques

The diagnosis of thyroid carcinoma is performed first by clinical history and examination. Biochemical tests including serum measurements of thyroxine, triiodothyronine and thyroid-stimulating hormone (TSH) have a negligible role in diagnosis, although they and measurements of serum thyroglobulin and carcinoembryonic antigen are useful for monitoring the adequacy of treatment and detection of recurrent cancer. The role of tumour markers depends on tumour type and therapy used. Other techniques are listed below:

- Fine-needle aspiration biopsy.
- Ultrasound imaging.
- Radionuclide imaging.

- Computed tomography and magnetic resonance imaging. As these tests are not used routinely, they are not discussed in this section of the report.

Fine-needle aspiration biopsy

Clinical utility of fine-needle aspiration biopsy

- Most effective method currently available for identifying patients with malignant nodules.
- False negatives range from 0.3–14 per cent, false positives from 0–2.5 per cent. A malignant finding is a strong indication for surgery, but a negative finding cannot rule out malignancy.
- Cheap and less time-consuming than other tests.
- If the nodule is a cyst, the procedure can be combined with aspiration of the cyst and curative sclerosant injection.

Limitations of fine-needle aspiration biopsy

- Inadequate specimens occur at a rate of 20 per cent, requiring repeat studies.
- Highly experienced operator and cytologist required.
- Impossible to distinguish a benign follicular lesion from a follicular carcinoma.
- Mild morbidity.

Ultrasound

Clinical utility of ultrasound

- High-resolution real-time scanning can detect nodules as small as 1–6mm.
- Primary purpose is to predict size and whether solid, cystic or multi-nodular.
- Used to guide FNAB.
- Cheap and accessible.
- Can be used after thyroxine suppressive therapy to evaluate change in size of the nodule.

Limitations of ultrasound

- No reliable ultrasonagraphic criteria on which to base diagnosis of malignancy.
- Unreliable after surgery due to anatomical distortion.

Radionuclide imaging

The functional state of a nodule can only be assessed by radionuclide imaging. Three major types of imaging agents are currently available:

- Technetium-99m-pertechnetate is the preferred agent for screening because it has a high sensitivity, low radiation exposure and short test time of one hour. It is readily available and relatively cheap. The mechanism of trapping appears to be the same as for iodine, but this agent does not enter the thyroid hormone synthetic pathway (not organified).
- Radioactive Iodine-123 has a distinct advantage over other radiopharmaceuticals as it gives the best images and is the only agent that is both trapped and organified by the thyroid gland. Iodine-123 is the preferred agent as it has a short half-life. However, it is cyclotron-produced and therefore expensive and not routinely available.
- Iodine-131 is the agent routinely used in the diagnosis and treatment of recurrent thyroid cancer.
- Sensitivity and specificity can be improved if Thallium-201 chloride scans are combined with Technetium-99m scans.

Clinical utility of radionuclide imaging

- Able to determine if a nodule is functioning before doing biopsy.
- First test used in diagnosis if FNAB is unavailable.
- Used if FNAB reveals a solid but benign mass.
- Used when a gland is enlarged with no palpable nodule.

- An essential investigation in the follow-up of patients with differentiated thyroid carcinoma to assess the presence or absence of functioning metastases.
- Used to study patients with ectopic thyroid tissue.

Limitations of radionuclide imaging

- Artifactual problems with cold nodules underlying normal thyroid tissue resulting in reduced sensitivity.
- Lesions in the area of the isthmus and at the periphery of the gland are difficult to image.
- Cannot differentiate benign from malignant cold nodules.

Overview of techniques used in thyroid cancer

In the last decade, FNAB, if available, has become the diagnostic test of choice in the USA. Radionuclide scanning remains a first-line tool if FNAB is unavailable and is also performed to evaluate the functional status of nodules that are benign on fine-needle aspiration. Radionuclide scintigraphy is the method of choice after surgery or thyroxine suppression in patients with thyroid cancer.

Cost-effectiveness of thyroid techniques

The literature search only revealed two recent papers that dealt with cost-effectiveness of techniques used in the management of thyroid cancer. These are described below and confirm the results in other papers written in the early 1980s.

- Ng *et al*[4] assessed the cost-effectiveness of FNAB in 170 patients with solitary thyroid nodules. After clinical history and examination the authors considered three different management schemes using ultrasound, radionuclide imaging and FNAB. Following the results of initial diagnostic testing with one or other of these techniques, 90 per cent of those having ultrasound or radionuclide imaging and only 51 per cent of those having FNAB had surgery. The authors conclude that FNAB used with other clinical criteria was found to be the safest and most cost-effective management path.

- Campbell & Pillsbury[5], in a review article, also looked at the approach to the patient with a palpable solitary thyroid nodule. They consider ultrasound, radionuclide imaging and FNAB, and the costs of the individual techniques are given. Although the authors conclude from the literature that FNAB is a highly accurate, relatively safe and cost-effective procedure, and with the exception of surgery, provides the most direct information, no real cost-effective analysis is done.

These two papers were the only ones found on the cost-effectiveness of thyroid disease and looked at the diagnosis of malignancy of thyroid nodules. FNAB was found to be the most cost-effective procedure. With the refinement of this technique and radionuclide imaging the specific application of these procedures needs to be re-evaluated for efficacy and cost-effectiveness. A uniform policy on the management of patients with solitary nodules is needed.

Radionuclide imaging is accepted as the follow-up procedure for assessment for thyroid cancer after surgery.

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10

CONCLUSIONS AND NEXT STEPS

Conclusions

Four hundred and fifty-four papers were accessed from a literature search of Index Medicus and Medline, Biosis and Healthplan databases. After review, 328 of these papers were found to be relevant and were used for this study. These are listed in the Bibliography.

The number of papers that performed cost-effectiveness analyses were limited.

Many more papers gave costs of actual procedures and discussed cost-effectiveness without carrying out any analysis.

Heart

Substantial progress has been made in the field of MPI which has the best sensitivity and specificity of the techniques reviewed in this report. New radiopharmaceuticals provide excellent predictive value for the detection of coronary heart disease in patients with chest pain and in the assessment of viable myocardium. The net result of the five papers reviewed was that MPI reduces overall costs and risks in cardiovascular disease. Although limited, there are enough positive data in the literature to suggest the need for a thorough prospective analysis of the cost-effectiveness of MPI.

Kidney

The role of nuclear medicine in renal hypertension and transplant patients is controversial. The limited cost-effectiveness data suggests that renal scintigraphy has a role to play in the diagnosis of renal hypertension at all stages of investigation; that scanning is only cost-effective in transplant patients in the immediate post-operative period; and that although no cost-effectiveness data were found on the use of scanning in children after urinary tract infections, the literature does suggest that radionuclide imaging is the safest, most accurate test to detect renal scarring.

Lung

Although there are limited data on cost-effectiveness of ventilation/perfusion scanning for pulmonary embolism, it appears to be cost-effective when used as the first test in diagnosis. The literature suggests that ventilation/perfusion scanning can reduce the numbers of patients needing invasive pulmonary angiography and is efficacious in management decisions, being cost-effective in both situations.

Brain

The use of radionuclide techniques in cerebrovascular disease has increased dramatically in recent years with the development of new brain perfusion agents. Brain perfusion imaging is still in the research phase, and there is no real evidence from the literature that it is cost-effective in the diagnosis, prognosis or management of patients. Initially, clinical trials of efficacy and patient management are required to establish the utility of imaging techniques in cerebrovascular disease.

Bone

Bone scintigraphy for metastatic disease is one of the most common procedures in nuclear medicine. It is recommended as a cost-effective test in the initial diagnosis of bone metastases, but the literature shows that the contribution of serial bone scanning to clinical management, in patients with a good prognosis, is considered to be negligible.

Bowel

Radionuclide scintigraphy using labelled white blood cells is a relatively new procedure for the diagnosis of inflammatory bowel disease. There is no cost-effectiveness data available in the literature, but this technique appears to be a reliable means of identifying active sites and the extent of the disease and would benefit from a clinical trial on efficacy and cost-benefit.

Thyroid

The two papers reviewed on cost-effectiveness of imaging techniques in thyroid disease showed fine-needle aspiration biopsy to be the most cost-effective method of assessing the malignancy of thyroid nodules. The literature suggests more work is needed on efficacy and cost-effectiveness. After surgery, radionuclide imaging is the accepted follow-up procedure for the assessment of patients with thyroid cancer.

Overall, the conclusion from this research is that although nuclear medicine procedures are used internationally on a large scale, the amount of work published on the cost-effectiveness of radionuclide imaging is very limited. Although nuclear medicine techniques are highly sensitive and specific procedures for the diagnosis and prognosis of many diseases and can have a beneficial effect on patient management, there are no agreed standards either in the UK or internationally for assessing their use. It is important that such methods are established if nuclear medicine is to be used to its full potential in the future.

Although an increase in cost-effectiveness data would be appropriate for all diseases reviewed, myocardial perfusion imaging, inflammatory bowel disease and renal disease show the most potential for future research.

Next steps – Phases II & III

From the preceding analysis, radionuclide myocardial perfusion imaging has been shown to be both sensitive and specific in the diagnosis of CAD and is also seen to have a role in management planning for patients with established CAD. Five studies of cost-effectiveness have been undertaken, but all the studies so far reported are flawed in various respects. A large prospective cost-effectiveness analysis is therefore required, and following the Phase I analysis it is proposed to carry out such a study. This will be undertaken as a randomised controlled multi-centre study in the UK (Phase III) and will utilise both cardiologists who routinely use myocardial perfusion imaging in the investigation of patients with CAD, and cardiologists who do not routinely use this technology. Patients in each arm of the study will be monitored for significant life events, exercise performance and quality of life. The cost of management of each sub-group will also be determined.

Through this study it will be possible to determine:

- whether the integration of radionuclide myocardial perfusion imaging into a management protocol achieves better outcomes for the patient both as a diagnostic tool and in determining subsequent management;

- whether the appropriate use of radionuclide myocardial perfusion imaging reduces the number of patients subsequently referred for further investigation and intervention, including coronary angioplasty and coronary artery bypass surgery;
- the costs associated with the various management protocols utilised in the study.

This study will be piloted (Phase II) in two centres in the UK to evaluate the proposed protocol, including questionnaires to be used during the study. Following the pilot study and modifications of protocols and questionnaires, the large multi-centre study will be initiated which will run for a five-year period. As in the Phase I study, the Phase II study will be undertaken under the management of the Steering Group containing representatives from the British Nuclear Medicine Society, the King's Fund, Department of Health Economics, Brunel University, Academic Department of Public Health, United Medical and Dental Schools, Guy's and St Thomas's Hospital, Department of Cardiology, Nottingham University, Sales & Marketing Associates.

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Nuclear medicine is a medical specialty that uses tiny quantities of radioactivity to produce diagnostic images. It also has a role in therapy for some thyroid diseases and certain tumours.

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