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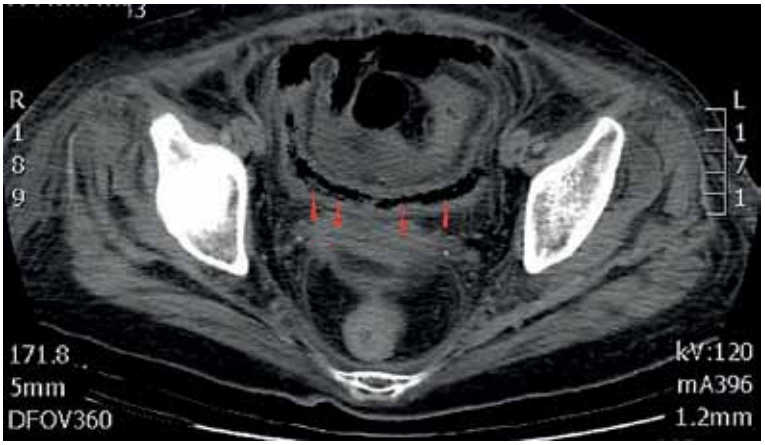

"Bubbles in the bladder: what is your diagnosis?"

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EDITORIAL

Lyme borreliosis: the challenge of accuracy

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KEYWORDS

Lyme disease; Lyme borreliosis; *Borrelia burgdorferi*

'The challenge of Lyme disease: tired of the Lyme wars', a recent editorial by Kullberg *et al.* in the Netherlands Journal of Medicine,[1] is presented as a plea for balance and reason in the ongoing 'wars' concerning this infectious disease. The editorial, in part, contrasts a review article on Lyme borreliosis published in the same issue[2] with anticipated revisions of the 2004 Dutch CBO Treatment Guidelines for Lyme Disease, developed in conjunction with a Lyme advocacy group from the Netherlands, and expected to be published in late 2011.

All can agree with Kullberg *et al.*[1] that the field would be well-served by a dispassionate and reasoned consideration of the evidence and that physicians must listen carefully to their patients, reach rational conclusions based on evidence and then recommend appropriate treatment. Unfortunately, the editorial contained a number of statements that fall short of these standards.

Kullberg *et al.*[1] use misleading dualities to advance their arguments. The second sentence sets the tone– 'whether or not persisting fatigue, cognitive dysfunction, and musculoskeletal pain are "real disease" and related to persistent infection....' Such a statement juxtaposes two distinct concepts. Patients with such symptoms have a clinically important disorder, and they need appropriate management. However, one or more of such symptoms occurs on a chronic basis in a sizable proportion of the adult population (>20%), which for the vast majority cannot be explained on the basis of a chronic infection; this is well-illustrated by the many studies on the aetiology of chronic fatigue.[3] Evidence also indicates that persistent infection is not the explanation for similar kinds of subjective symptoms in patients who have been previously diagnosed and treated for Lyme borreliosis [see below].

Kullberg *et al.*[1] also make statements that are incorrect. They assert that little is known about treatment success rates among patients with a delay in either the diagnosis or initiation of treatment for *Borrelia burgdorferi* sensu lato infection. However, most patients with Lyme arthritis have a delay in diagnosis, since the average time from onset of infection with *B. burgdorferi* sensu stricto to development of this late clinical manifestation is six months.[4] Nevertheless, the outcome of antibiotic treatment is generally very good and well understood, as documented extensively in many clinical reports, most of which are summarised in the 2006 clinical practice treatment guidelines for Lyme disease developed by the Infectious Diseases Society of America (IDSA).[5] Of course, no drug, including antibiotics, would be able to reverse permanent tissue damage of joints, nerves or skin. Earlier rather than delayed treatment is presumably desirable,[5,6] as shown by the success in prevention of Lyme arthritis when patients with erythema migrans, the most common manifestation of early Lyme borreliosis, are treated with antibiotics.[5]

Kullberg *et al.*[1] state that it is unknown whether long-term antibiotic treatment of patients with unexplained symptoms after standard therapy for Lyme borreliosis is beneficial. This is not true in North America, since the published results of four NIH-sponsored placebo-controlled treatment trials either showed no benefit at all, or a benefit so modest or ambiguous that the investigators themselves felt that any potential benefit was outweighed by the risks associated with the treatment.[7-10] Although

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the species of Lyme *Borrelia* are more diverse in Europe compared with North America, it is not expected that these conclusions would be any different in Europe, as suggested by the findings of a Finnish study of prolonged antibiotic treatment.[11]

Kullberg *et al.*[1] dismiss the findings of the Klempner trials,[7,8] in which retreatment with 30 days of parenteral ceftriaxone (2 grams/day) followed by an additional 60 days of oral doxycycline (200 mg/day) provided no benefit compared with placebo. To explain away these important findings, Kullberg *et al.*[1] assert that the trials were discontinued prematurely due to slow recruitment and thereby had inadequate enrolment, and that they failed to report the primary endpoint of success in the intent-to-treat population. Both assertions are incorrect. The trials were ended based on the recommendations of an independent Data and Safety Monitoring Board, after a ***planned* interim analysis** of the first 107 patients enrolled indicated that it was highly unlikely (<5%) that a significant difference in treatment efficacy between the groups would be observed with the planned full enrolment of 260 patients. In the publication of their findings, Klempner *et al.*[7] explicitly stated that: 'The primary clinical endpoint was the proportion of patients whose condition was categorised as improved, unchanged, and worse on the basis of the summary scores for the mental and physical components of the SF-36 at 180 days. Patients who withdrew from the study were categorised as having worsened health status on both of these scales'. Thus, it was the ***intent-to-treat*** analysis specifically that showed no significant differences in the primary outcome measure in the prolonged retreatment groups compared with the groups who received placebo. Furthermore, consistent with these findings and perhaps equally important, Klempner *et al.* did not find any evidence, based on over 700 samples from 129 patients that were examined by culture and polymerase chain reaction (PCR) assays, for persistent *B. burgdorferi* sensu stricto infection in patients with persistent symptoms after treatment for Lyme borreliosis.[7,12] They also found no evidence of an *Ixodes scapularis*-transmitted co-infection with *Anaplasma phagocytophilum* or *Babesia microti* to explain the symptoms.[7] Kullberg *et al.*[1] omitted any mention of these findings in their editorial, although they stressed the importance of making 'reasonable attempts to rule out relapse or persistent infection.'

Kullberg *et al.*[1] suggest that serological assays for detection of antibodies to *B. burgdorferi* sensu lato are suboptimal by citing a recent paper from the Netherlands that showed inconsistent results among the various assays tested.[13] Unfortunately, that study had a number of potentially significant methodological concerns, not the least of which is that the patient population was poorly defined, as has already been pointed out by other investigators from the Netherlands.[14] However, if the comments and conclusions of Kullberg *et al.*[1] on serological testing are to be interpreted as providing support for the need for proper validation of diagnostic tests before they are used in routine patient care, we are in complete agreement. Use of appropriately validated tests, in conjunction with considerations of pre- and post-test probabilities, is extremely important in the serological diagnosis of most of the clinical manifestations of Lyme borreliosis other than erythema migrans in both the United States and Europe.[15]

Lastly, Kullberg *et al.*[1] consider use of the term 'post-Lyme disease syndrome' as 'deceitful,' an unusual, if not inappropriate, choice of words for an editorial in a medical journal. The term, 'post-Lyme disease syndrome,' for which there is a published definition,[5] is widely used in the medical literature and in international guidelines[16] and is generally meant to describe this particular medical condition, without making any assumptions as to the mechanism(s) involved. In contrast, the term, 'chronic Lyme disease – which clearly needs to be distinguished from well-defined late manifestations of Lyme borreliosis such as acrodermatitis or late neuroborreliosis – is undefined, means quite different things to different people, and is based on the assumption of a persistent infection for which there is no valid scientific evidence in this patient group.[7,10,12] The definition of post-Lyme disease syndrome was developed to provide a framework for future research and to reduce diagnostic ambiguity in study populations. Evidence of having had *B. burgdorferi* infection at some point is an **absolute** requirement of the case definition.[5] Such an inherently sensible standard is quite different from that used for 'chronic Lyme disease' by many of the healthcare providers who argue for this term. Indeed, in the United States the majority of patients being treated with indefinite courses of antibiotic therapy for 'chronic Lyme disease' have no valid evidence of ever having had *B. burgdorferi* sensu stricto infection.[17,18]

Lyme disease activists in the United States[19] often take issue with the term 'post-Lyme disease syndrome,' since they believe it conveys the message that there is no active infection to explain persistent symptoms. Actually, it is the microbiological and clinical evidence gathered by Klempner *et al.*[7,8,12] and corroborated by other investigators,[10,20] rather than the term per se, that warrants such a conclusion.

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REVIEW

Diagnostic management of chronic obstructive pulmonary disease

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ABSTRACT

Detection of early chronic obstructive pulmonary disease (COPD) in patients presenting with respiratory symptoms is recommended; however, diagnosing COPD is difficult because a single gold standard is not available. The aim of this article is to review and interpret the existing evidence, theories and consensus on the individual parts of the diagnostic work-up for COPD.

Relevant articles are discussed under the subheadings: history taking, physical examination, spirometry and additional lung function assessment.

Wheezing, cough, phlegm and breathlessness on exertion are suggestive signs for COPD. The diagnostic value of the physical examination is limited, except for auscultated pulmonary wheezing or reduced breath sounds, increasing the probability of COPD. Spirometric airflow obstruction after bronchodilation, defined as a lowered ratio of the forced volume in one second to the forced vital capacity (FEV1/FVC ratio), is a prerequisite, but can only confirm COPD in combination with suggestive symptoms. Different thresholds are being recommended to define low FEV1/FVC, including a fixed threshold, and one varying with gender and age; however, the way physicians interpret these thresholds in their assessment is not well known. Body plethysmography allows a more complete assessment of pulmonary function, providing results on the total lung capacity and the residual volume and is indicated when conventional spirometry results are inconclusive. Chest radiography has no diagnostic value for COPD but is useful to exclude alternative diagnoses such as heart failure or lung cancer.

Extensive history taking is of key importance in diagnosing COPD.

KEYWORDS

COPD, diagnosis, history taking, physical examination, spirometry

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a cluster of heterogenic disorders, characterised by expiratory flow limitation that is not completely reversible and in most cases progressive.[1] Patients with COPD show an abnormal inflammatory reaction to tobacco smoke or other air pollution exposures, resulting in airway obstruction, destruction of lung tissue and hyperinflation. COPD is among the leading chronic disorders worldwide regarding frequency, impact on quality of life and mortality.[1]

Often COPD stays undiagnosed until it has developed to a more severe stage. This underdiagnosis of early COPD[2,3] is illustrated by the relatively low number of mild COPD cases in the Netherlands: of all patients with established COPD in the year 2000, 27% had mild, 55% moderate, 15% severe and 3% very severe disease.[4]

Early detection of COPD is relevant because adequate treatment, especially stop smoking interventions, but also inhaled medication, lifestyle counselling and influenza vaccination reduce exacerbations and improve quality of life.[1] Nonetheless, diagnosing COPD is difficult, because a single gold standard is not available. A diagnosis requires the assessment of symptoms, signs and spirometry results combined, while spirometry abnormalities can be subtle in the early phase.[1,5] Possibly, these diagnostic difficulties contribute to the present underreporting of COPD.

This manuscript discusses the diagnostic management of COPD, with an emphasis on early COPD. The viewpoint will be from a primary care perspective, where the majority of the patients are diagnosed and treated.

WHICH PATIENTS ARE AT RISK?

International guidelines discourage screening non-symptomatic subjects for COPD because there is no evidence of the long-term effects,[1,5-7] but strongly recommend to evaluate COPD in (former) smokers older

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than 40 - COPD is rare below this age – who seek healthcare for respiratory symptoms,[1,5] such as cough, wheeze or dyspnoea. These symptoms are probably not always perceived as signs of possible COPD, but frequently labelled as respiratory infections. A first step in the diagnostic process is therefore increased awareness that such respiratory symptoms, which are among the most frequently seen in primary care, can suggest COPD. Hereafter, the results of history taking, physical examination, spirometry and additional lung function assessment can be helpful in the diagnostic work-up for COPD. This manuscript will discuss these diagnostic tests, in the order they are used in daily practice.

HISTORY TAKING

History taking for COPD includes the assessment of possible aetiological risk factors on the one hand and suggestive symptoms on the other hand. The biggest risk factor, tobacco smoking, is often quantified in 'pack-years', with one unit representing one year of smoking 20 cigarettes a day. There is a dose-response relation between smoking duration and lung function decline,[8] but the genetic susceptibility for COPD varies largely between individuals,[9] and COPD sometimes even develops in never smokers.[10] Accordingly, no threshold for smoking duration can be recommended; however, several studies found that more than 20 pack-years substantially increased the risk of COPD.[11,12] Other airway exposures such as dust, chemicals or fumes, which are often occupation related, (for example farmers, bakers or drivers), should also be evaluated. In general, the risk of COPD increases with the air pollution level, including indoor air pollution from biomass fuel which is only relevant in developing countries.[10]

Other risk factors for COPD that can easily be evaluated by history taking or reviewing the medical file are: low birth weight, asthma, respiratory tract infections including tuberculosis and a family history of COPD.[1,13] The exact causal mechanisms for COPD are less straightforward here than for the respiratory exposures, but the aetiology of COPD is beyond the scope of this article.

Regarding symptoms, cough, wheeze, and phlegm have diagnostic value for COPD, especially if chronic (longer than three months) or recurrent.[1,14-17] Screening the medical file for diagnostic codes of 'acute bronchitis' or 'cough' may help to identify earlier episodes of respiratory symptoms, which might have been exacerbations of hidden COPD. Another symptom is shortness of breath on exertion. This is common in early COPD, despite limited spirometric obstruction, merely caused by an increasing functional residual volume (air trapping) during higher breathing frequency, also called 'dynamic hyperinflation'.[18] Shortness of breath at rest is often present in severe COPD, but unusual as presenting symptom[1] and requires evaluation of alternative more acute disorders, including for example pulmonary embolism, pneumonia and acute heart failure.

PHYSICAL EXAMINATION

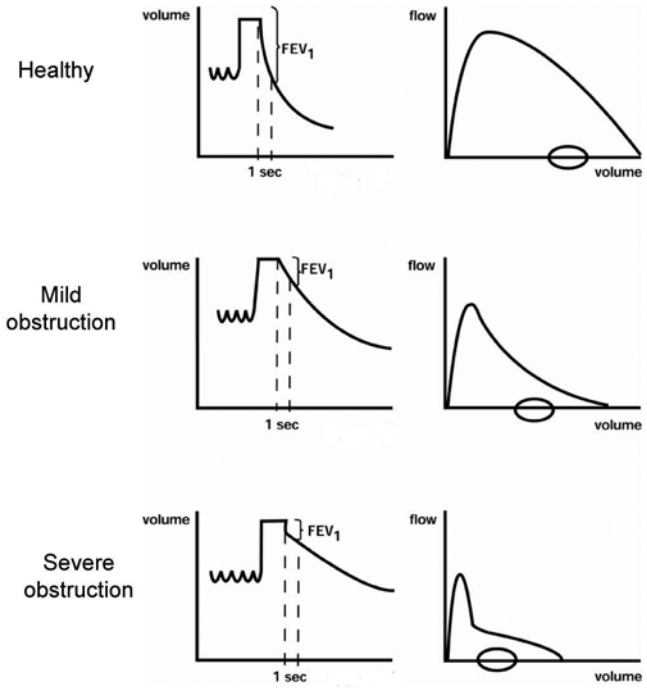
In most cases the diagnostic value of physical examination for COPD is limited. The most useful diagnostic items are 'diminished breath sounds' and 'wheezing' on lung auscultation, which have higher positive than negative predictive values and can therefore not exclude COPD.[11,12,19-23] There are various other well-known and evidence-based physical manifestations of COPD, including barrel chest, accessory muscle use,[14] weight loss[24] and peripheral oedema,[25] but these are merely confined to severe and usually established COPD. Nonetheless, these typical pulmonary signs can aid to assess and monitor exacerbations of established COPD. Other evidence-based signs, for example forced expiratory time,[22,23,26] laryngeal height,[11] and subxyphoid apical impulse,[14] are not part of the routine physical examination and therefore less helpful for practice. Resuming, wheezing and reduced breath sounds suggest COPD, but normal physical examination results do not exclude COPD.

SPIROMETRY

Spirometry is a non-invasive test quantifying flow and volume of the vital capacity, which is the amount of air that can be inhaled and exhaled. Results should be measured before and after an inhaled bronchodilator. The measurement validity depends on the technician's instruction skills regarding the patient's required forced breathing manoeuvres. Spirometry has been implemented in many primary care settings during the last decade, where rigorous training of practice staff has shown to allow for adequate measurement quality.[27] Results are visualised in a time-volume and flow-volume curve (a simplified representation is given in *figure 1*) and the most relevant results for COPD are the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC).

For a COPD diagnosis, spirometric airflow obstruction is a prerequisite, defined as a lowered ratio of the FEV1 to the FVC (FEV1/FVC ratio), persisting after bronchodilation. Several thresholds are recommended to define low FEV1/FVC. An often recommended threshold is a fixed value of <0.7. However, this fixed value causes potential overdiagnosis of COPD in the elderly, and underdiagnosis in the young because FEV1 decreases with ageing resulting in a FEV/FVC ratio <0.7 in more than 20% of healthy elderly people (>60 years).[28,29] Therefore, others define low FEV1/FVC by the 'lower limit of normal' according

Figure 1. *Simplified volume-time and flow-volume spirometry curves*



	result	pred	%pred
FEV1 (l)	2.98	2.91	102
FVC (l)	3.95	3.39	117
FEV1/FVC	0.75	0.86	87

	result	pred	%pred
FEV1 (l)	2.55	2.92	87
FVC (l)	3.86	3.39	114
FEV1/FVC	66	86	77

	result	pred	%pred
FEV1 (l)	1.2	2.79	43
FVC (l)	2.26	3.59	63
FEV1/FVC	53	75	71

Results of forced breathing spirometry manoeuvres are shown. FEV1 = forced expiratory volume in one second; FVC = forced expiratory volume; pred = predicted value according to age, gender and height; % pred = percentage of the predicted value. Post-bronchodilator results are shown of three individuals.

to age and gender, instead of a fixed value, identifying the lowest 5% of a population.[30,31] To define the normal range, several regression equations were derived from different populations, with the National Health and Nutrition Examination Survey (NHANES III) as most used standard.[32] Most modern spirometry software allows calculation of thresholds by several methods. How physicians interpret spirometry results and thresholds in their assessment of COPD is unknown; however, the controversy on spirometric definitions illustrates that COPD is a clinical diagnosis which can not be based on spirometry results only.[1,5]

Besides the size of the volumes, one should judge the shape of the spirometric flow volume curve, to verify the quality and reproducibility of the measurements. Moreover, in many patients with severe COPD the descending limb of the expiratory loop is typically concave (*figure 1*);[1,33] however, standardised measures for this assessment are lacking.

ADDITIONAL LUNG FUNCTION ASSESSMENT

When there is diagnostic uncertainty, for example when symptoms are suggestive but spirometry is normal, or when a patient cannot sufficiently perform the forced breathing manoeuvres of conventional spirometry, additional lung function tests in a laboratory are helpful. Only those tests that are most efficient and commonly used in the diagnostic workup for COPD will be briefly discussed: body plethysmography and diffusion capacity of the lungs.

Besides the vital volumes, body plethysmography results include the total lung capacity (TLC) and the residual volume (RV) which is the TLC minus the vital capacity. Moreover, it allows quantification of the pulmonary gas diffusion capacity, most commonly using carbon monoxide (CO) as tracer gas.[34] Body plethysmography measurements are non-invasive tests performed on a patient sitting in a small enclosed space (body box). Results are expressed as absolute numbers and percentage predicted according to age, height and gender reference values[31] and the normal variability range is commonly defined as 80% to 120% predicted.[31,35] Body plethysmography allows a more complete assessment of gas exchange and chest mechanics than conventional spirometry. Although not specific, abnormal results can strongly suggest COPD. An enlarged RV and TLC are indicative of COPD, representing hyperinflation and enlarged air spaces (emphysema). A low DLCO suggests COPD[36] as well but can also be found in other disorders, for example interstitial lung diseases, pulmonary embolism, and pulmonary hypertension.[37] Finally, a low FVC limits interpretation of spirometry

results and requires referral for body plethysmography, to discriminate restrictive (low TLC) from obstructive lung disorders (normal/high TLC and high RV).[5,35]

REVERSIBILITY TESTING

For a long time airflow obstruction in COPD was considered to be completely irreversible and accordingly, a large improvement of the spirometric FEV1 - often called reversibility – was assumed to suggest reversible airway disorders such as asthma, and a lack of improvement typical for COPD. However, nowadays it is increasingly acknowledged that although obstruction in COPD by definition cannot normalise, it varies largely within individuals.[38] Contrary to earlier assumptions, a 12% FEV1 increase after inhaled bronchodilators or oral steroids is common in COPD, and more frequent than in healthy subjects.[39-41] Therefore, reversibility after treatment or time does not exclude COPD, except when lung function results normalise completely.

When spirometry results show both reversibility and persistent obstruction, differentiation between asthma, COPD, or a combination of both can be challenging but is nonetheless relevant because therapeutic management differs, with an emphasis on inhaled corticosteroids and other anti-inflammatory drugs in asthma, and inhaled bronchodilators in COPD.[1,42] In the elderly, asthma and COPD characteristics overlap; especially patients with asthma exposed to cigarette smoke or other inhaled exposures can develop incompletely COPD-like reversible obstruction.[43] Careful history taking is the most efficient tool to differentiate between COPD and asthma,[44] with allergy, eczema, symptoms in childhood, fluctuating symptoms with symptom-free periods, bronchial hyper-reactivity, and eczema being more suggestive of asthma.

INFLAMMATION MARKERS

Several acute-phase proteins including C-reactive protein and ferritin are increased in subjects with COPD, attributed to assumed systemic ongoing inflammation.[45,46] Whether these markers have added diagnostic value over symptoms, signs and spirometry is unknown and therefore measurement is not recommended in the diagnostic work-up for COPD.

SEVERITY STAGING

The GOLD criteria define COPD severity according to the post-bronchodilator FEV1 as percentage predicted (% pred): mild (FEV1 >80% pred), moderate (FEV1 50-80% pred), severe (FEV1 30-50% pred) and very severe (FEV1 < 30% pred). Most newly diagnosed subjects show mild or moderate disease.[16,47,48]

The association between spirometric obstruction and symptoms is, however, limited and additional assessment of severity should address symptoms, frequency and severity of exacerbations, and complications as respiratory failure, right heart failure and weight loss.[1] Validated questionnaires to judge and monitor health state are the British Medical Research Council (MRC) dyspnoea scale[49] and the Clinical COPD Questionnaire (CCQ)[50] on COPD-related symptoms, daily functioning and mental health.

DIFFERENTIAL DIAGNOSIS

In patients presenting with persistent or recurrent cough, wheeze and/or breathlessness, the differential diagnosis besides COPD is extensive, and includes asthma as previously addressed, heart disorders, pulmonary hypertension, lung infections, malignancy, interstitial lung disease and gastro-oesophageal reflux.[1] Of these, congestive heart failure, lung cancer and chronic bronchiectasis will be briefly discussed.

In the elderly, especially those older than 70, unrecognised heart failure is frequent, but also the combination of COPD and heart failure, because of overlapping aetiology (smoking history) and susceptibility.[51] Brain natriuretic peptide (BNP) measurement in blood, chest radiography and electrocardiography help to make heart failure more or less likely. If results suggest possible heart failure, echocardiography is indicated to diagnose heart failure with certainty. Lung cancer should be considered in all smokers presenting with a persistent cough, with chest radiography as a useful first diagnostic step. Because chest radiography is not 100% sensitive to exclude pneumonia, clinical suspicion of lung cancer warrants more advanced imaging (computerised tomography (CT) scanning). Bronchiectasis is characterised by complaints of large volumes of purulent phlegm, sometimes low-grade fever and is usually associated with bacterial infections. Bronchial wall thickening and bronchial dilatation are suggestive signs on chest radiography or CT scanning.[1]

Overall, a chest radiography is helpful to evaluate alternative diagnoses, but has limited diagnostic value for COPD, except in case of apparent bullae which are rare in early COPD.[1]

IMPLICATIONS FOR PRACTICE AND RESEARCH

In most patients presenting with persistent respiratory symptoms, COPD can be diagnosed or excluded by

history taking, physical examination and spirometry. History taking is most relevant, not only to evaluate COPD presence but also to alternative diagnoses. Physical examination can be completely normal in early COPD. In case of doubt, repeated spirometry and/or more extensive lung measurements are helpful. Chest radiography and electrocardiography are useful to exclude or suggest alternative diagnoses.

Finally, there is debate on the benefit of detection of early COPD. Arguments for detection include evidence that smokers diagnosed with COPD are more successful in quitting,[52,53] and improved quality of life and reduced exacerbations after treatment.[1] Moreover, a diagnosis could help to reduce unnecessary treatments (antibiotics and antitussives) and diagnostic procedures, but whether this is true is unknown. Arguments against detection are the associated costs for detection and treatment, the unpredictable individual course of mild COPD, lacking evidence on treatment of mild COPD and possible fear and distress of the patients by being labelled with COPD. Studies on the effects of standard treatment of mild COPD including quality of life and patient perception are needed to estimate the cost effectiveness of early COPD detection.

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REVIEW

Drug-induced vasculitis: a clinical and pathological review

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ABSTRACT

Drug-induced vasculitis is an inflammation of blood vessels caused by the use of various pharmaceutical agents. Vasculitis causes changes in the walls of blood vessels, including thickening, weakening, narrowing and scarring. Inflammation can be short-term (acute) or long-term (chronic) and can be so severe that the tissues and organs supplied by the affected vessels do not get enough blood. The shortage of blood can result in organ and tissue damage, even death. Drug-induced vasculitis is the most common form of vasculitis. The differential diagnosis between drug-induced and idiopathic vasculitic conditions may be difficult in the individual patient. Withdrawal may be helpful to distinguish between these syndromes. Withdrawal of the offending agent alone is often sufficient to induce prompt resolution of clinical manifestations, obviating the need for immunosuppressive and anti-inflammatory drugs. Increasing understanding of the pathophysiological characteristics of all inflammatory vasculitides should lead to better diagnostic and therapeutic approaches to drug-induced vasculitis.

KEYWORDS

Vasculitis, drug induced vasculitis, antineutrophil cytoplasmic antibodies (ANCA)

INTRODUCTION

This review aims to draw attention to the features that distinguish drug-induced vasculitis from those of idiopathic autoimmune syndromes, first and foremost primary vasculitides. A systemic drug-induced syndrome only develops in a minority of patients treated with a drug over a prolonged period of time, whereas cutaneous vasculitis occurs quite commonly.[1,2] The most frequent symptoms at onset are arthralgia, myalgia and skin rash. Early withdrawal of the offending drug usually leads to complete recovery while more advanced disease and late withdrawal of the drug may necessitate use of immunosuppressive therapy. The recent discovery of anti-neutrophil cytoplasm antibodies (ANCA) directed to myeloperoxidase (MPO) in a large serological subset of drug-induced vasculitis caused by long-term anti-thyroid drug treatment has opened new avenues for differential diagnostics.[2,3] Certain medications such as propylthiouracil can induce ANCA-associated vasculitis. This review focuses on the data on causal drugs, possible pathogenesis, clinical description, diagnosis, treatment and prognosis of patients with drug-induced vasculitis. ANCA with specificity to more than one lysosomal antigen combined with the presence of antibodies to histones and beta-2 glycoprotein 1 constitutes a unique serological profile for drug-induced vasculitis.[4]

The pathogenesis of drug-induced ANCA-associated vasculitis might be multifactorial. The clinical manifestations are similar to those of primary ANCA-associated vasculitis, but ANCA with multi-antigenicity may help to differentiate it from primary ANCA-associated vasculitis.[5] Rational use of laboratory marker profiles is likely to aid in distinguishing drug-induced from idiopathic syndromes. However, the use of ANCA and other autoantibodies as biomarkers of different phenotypes of drug-induced vasculitis is one of the focuses of this review.

Evidence is mounting that these specific antibodies are pathogenic in small-vessel vasculitis.[6,7] However, the aetiology of ANCA-associated vasculitis is largely unknown.

The diagnosis of drug-induced ANCA-associated vasculitis is based on the temporal relationship between clinically evident vasculitis and administration of the offending drugs, and excluding medical conditions that mimic

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vasculitis and other definable types of vasculitis.[8] After the diagnosis of drug-induced ANCA-associated vasculitis is made, the offending drugs should be withdrawn immediately, and appropriate immunosuppressive therapy should only be administered to patients with vital organ involvement. The duration of immunosuppressive therapy should be much shorter than that in primary ANCA-associated vasculitis and long-term maintenance therapy might not be necessary. The prognosis of patients with drug-induced ANCA-associated vasculitis is good as long as the offending drug is discontinued in time.

Table 1. *Medications associated with drug-induced vasculitis*

Antibiotics
Cephotaxime
Minocycline
Anti-thyroid drugs
Benzylthiouracil
Carbimazole
Methimazole
Prophythiouracil
Anti-tumour necrosis factor-α agents
Adalimumab
Etanercept
Infliximab
Psychoactive agents
Clozapine
Thioridazine
Miscellaneous drugs
Allopurinol
D-Penicillamine
Hydralazine
Levamisole
Phenytoin
Sulfasalazine

GENERAL FEATURES

Drug-induced vasculitis usually attacks the skin and sometimes the subcutaneous part of the skin, but sometimes also the kidneys and the lungs.[9,10] Clinical symptoms include arthralgias and myalgias but usually do not develop into overt arthritis or myositis, manifested as muscle weakness. End-stage kidney disease due to glomerular vasculitis may occur, but early removal of the offending drug usually leads to resolution of the glomerular inflammation. A few cases of drug-induced vasculitis presenting with a haemorrhagic syndrome due to lung capillaritis have been reported. Patients with drug-induced vasculitis typically harbour ANCA directed to one or more neutrophil cytoplasm antigens, the most common antigens being the granule proteins MPO, HLE, cathepsin G, and lactoferrin.[11-14] In one study the levels of MPO-ANCA were found to be much higher in 30 patients with drug-induced MPO-ANCA vasculitis than those usually found in idiopathic vasculitides, and there was a strong association between presence of HLE-ANCA and lactoferrin-ANCA and exposure to the candidate drugs.[15] Other research showed a strong association between heredity and development of drug-induced vasculitis during treatment with propylthiouracil in monozygotic triplets with Graves' disease.[16] Two of these children, who were treated with propylthiouracil, had multispecific ANCA including HLE-ANCA, while the third triplet had no signs of drug-induced vasculitis and no ANCA during treatment with carbimazole.

To date, many studies have indicated that drug-induced vasculitis may be a complication of therapy with prior use of certain medications in some patients, and unreported and/or undiagnosed cases may be beyond our imagination. As shown in *table 1*, the most often implicated drug in the published work is propylthiouracil, which may result from more frequent prescriptions in clinical practice.[13,17,18] Propylthiouracil is a common anti-thyroid drug widely used all over the world. In the published work, over 100 cases of propylthiouracil-induced vasculitis have been reported. Further studies in pathogenesis, treatment and long-term outcomes of patients with propylthiouracil-induced vasculitis provide useful information on understanding drug-induced vasculitis.[19] It has been shown that propylthiouracil is implicated in 80 to 90% cases of vasculitis induced by anti-thyroid drugs, while cases related to other drugs, such as methimazole, carbimazole and benzylthiouracil, are less frequent.[20] Clear evidence for an association with the development of drug-induced vasculitis has also been shown for the following drugs: hydralazine, anti-tumour necrosis factor-α (TNF-α) agents, sulfasalazine, D-penicillamine and minocycline; however, most of this evidence was limited to case reports.[21-25] The increasing use of so-called 'biological' agents in medical practice has been accompanied by growing evidence on the toxicity profile of these agents, including drug-induced vasculitis. Anti-TNF-α drugs, such as adalimumab, infliximab and etanercept, are now established therapy in the management of rheumatoid arthritis and several other chronic inflammatory diseases. Repeated treatment with these agents can lead to the development of autoantibodies, including antinuclear antibodies (ANA), anti-dsDNA and anti-cardiolipin antibodies, in up to 10% of patients.[26] The autoantibody synthesis is associated with a greater cumulative dose of therapy. Although uncommon, some patients receiving anti-TNF-α agents were found to develop vasculitis.[22] Medications, such as biological agents, are geared toward targeting specific immune mechanisms, and they may skew the immune response dramatically.

Leukotriene antagonists (LTA, such as montelukast and zafirlukast) have been implicated in the pathogenesis of

Churg-Strauss syndrome (CSS). Further studies showed that no significant association was observed between CSS and LTA after controlling for the use of other anti-asthma drugs.[27] In a case-crossover study, it was suggested that the onset of CSS might not be associated with montelukast but a phenomenon possibly associated with a group of medications prescribed for long-term control of severe asthma.[28] Based on this evidence, the National Institutes of Health/USA Food and Drug Administration panel concluded that no one class of LTA was associated with CSS and that LTA are safe.[29] Our study group described two patients treated for a few years before they developed symptoms of CSS.[30]

PATHOGENESIS

The pathogenesis of drug-induced vasculitis is unclear. A variety of agents may produce a typical clinical picture together with a similar autoimmune profile, suggesting a common mechanism for drug-induced vasculitis. To date, the mechanism is far from fully understood and it might be multifactorial. Most drugs are low-molecular-weight substances, and require the formation of a complex to stimulate antibody formation and then to drive an immune response.[31] One hypothesis proposed that activated neutrophils in the presence of hydrogen peroxidase released MPO from their granules, which converted the offending drugs such as prophythiouracil and hydralazine into cytotoxic products; then the drugs and their metabolites were immunogenic for T cells, which in turn activated B cells to produce ANCA.[32] The offending drugs and their metabolites may accumulate within neutrophils, bind to MPO and modify its configuration, with subsequent intermolecular determinant spreading the autoimmune response to other autoantigens and turning neutrophil proteins (including elastase, lactoferrin and nuclear antigens) immunogenic.[3] Some drugs such as sulfasalazine could induce neutrophil apoptosis.[23] Moreover, neutrophil apoptosis, in the absence of priming, is associated with translocation of ANCA antigens to the cell surface, which then induce the production of ANCA, and ANCA in turn are able to bind the membrane-bound antigens, causing a self-perpetuating constitutive activation by cross-linking PR3 or MPO and Fcγ receptors.[33]

CLINICAL MANIFESTATIONS

The clinical manifestations of drug-induced vasculitis are similar to those of primary vasculitides, which range from less specific syndromes (fever, malaise, arthralgia, myalgia, weight loss) to single tissue or organ involvement and life-threatening vasculitis.[34] Some researchers suggested that more severe specific organ involvement might develop in patients with non-specific systemic syndrome when the causal drug was not withdrawn in time.[35] The kidney is the most commonly involved organ and the renal features vary widely, including haematuria, proteinuria and elevated serum creatinine.[36] Intra-alveolar haemorrhage is the most commonly reported pulmonary manifestation with consequent cough, dyspnoea and haemoptysis.[37] Some patients may only have lung involvement such as acute respiratory distress syndrome and interstitial pneumonia and without renal injury.[38] Contrary to idiopathic vasculitides, drug-induced vasculitis usually has a milder course, and fewer patients have rapidly progressive glomerulonephritis in drug-induced vasculitis.[39] Rare clinical manifestations were also described in case reports such as sensorineural hearing loss, pericarditis, pyoderma gangrenosum, central nervous system vasculitis presenting as cognitive symptoms and cerebral pachyleptomeningitis.[40-46]

There is no unique clinical pathological or laboratory marker for discrimination between drug-induced vasculitis and other vasculitides.[8] A low percentage of patients treated long term with a drug risk develop hypersensitivity reactions, some of which appear as vasculitis. There are laboratory markers that can help distinguish drug-induced vasculitis from idiopathic autoimmune diseases, and thorough knowledge about such serological changes may help to differentiate drug-induced from idiopathic syndromes (summarised in *table 2*).

The laboratory abnormalities could indicate organ involvement. Anaemia is common in patients with drug-induced vasculitis.[34] Urine abnormalities have consisted of haematuria and proteinuria in patients with kidney vasculitis.[34] Accurate assessment of disease activity within the lungs may be difficult because disease activity correlates poorly with pulmonary symptoms. A plain chest radiograph is a tool to monitor disease activity and high-resolution computed tomography (CT) scanning of the chest offers a more sensitive imaging technique.[38]

Table 2. *Laboratory marker differences between drug-induced vasculitis and idiopathic systemic lupus erythematosus and ANCA-associated vasculitis*

	Drug-induced vasculitis	SLE	AAV
Antihistone abs.	Can be seen	Rare	Absent
AntidsDNA abs.	Absent	Common	Absent
ANCA	Common[a]	Rare	Common[b]
Antiphospholipid abs.	Common	Common	Rare
Immune complexes	Rare	Common	Absent

SLE = systemic lupus erythematosus; AAV = anti-neutrophil cytoplasmic antibody-associated vasculitis, abs. = antibodies; [a] Multispecific; [b] Single ANCA specificity.

Although acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are usually elevated in patients with drug-induced vasculitis on diagnosis, they are neither sufficiently sensitive nor specific in making the diagnosis.[4]

Because detection of ANCA might serve as a warning of the possibility of drug-induced vasculitis, ANCA assays using combined IIF and antigen-specific enzyme-linked immunosorbent assays (ELISA) rather than relying on either test alone are recommended in all patients suspected of drug-induced vasculitis.[47] Tissue biopsy is usually necessary to provide a definitive diagnosis of vasculitis and to exclude other diseases. Specimens may come from skin lesions, renal and lung biopsies.[34]

However, the diagnosis of drug-induced vasculitis is complicated and difficult for several reasons, including: (a) physicians often do not recognise the syndrome as drug-induced (inappropriate diagnosis); (b) variable and often prolonged duration between the commencement of therapy and initial vasculitic symptoms; and (c) failure to evaluate appropriate laboratory and invasive tests. The awareness of drug-induced vasculitis by physicians is important in order to make a prompt diagnosis and start treatment and thus achieve a favourable outcome. It is essential that a comprehensive drug history is obtained in patients with vasculitis. Clinicians should seek information on drug use for at least six months before presentation. The evaluation of pertinent laboratory data and prompt histological confirmation of the disease may aid in the diagnosis. Biopsies are strongly encouraged to confirm the presence of vasculitis and to determine the disease severity.[47] We suggest that drug-induced vasculitis should be defined further by the following: (a) the signs and symptoms of vasculitis are temporally related to using the offending drug, and regressed with its discontinuation; (b) serum ANCA is positive, especially those with multi-antigenicity; and (c) medical conditions that mimic vasculitis are excluded, especially infections and malignancies, and other definable types of vasculitis.[47]

Table 3. *Treatment strategy for patients with drug-induced vasculitis*

Management of causal agents	
Withdrawal	
Avoid re-challenges	
Consider avoiding similar drug classes	
Individualised therapy	
Non-specific symptoms	Withdrawal of causal agents alone
Organ involvement	Corticosteroid and/or immunosuppressive drugs
Severe organ involvement (e.g. necrotising GN, focal segmental necrotising GN, diffuse alveolar haemorrhage)	Methylprednisolone pulse therapy, followed by combined corticosteroid and immunosuppressive drugs
Massive pulmonary haemorrhage	Plasmapheresis
Special notes for patients with drug-induced vasculitis	
A shorter course of immunosuppressive therapy	
Long-term maintenance may not be necessary	
Monitoring of serum ANCA Surveillance for emergence of a chronic underlying vasculitis	

ANCA = anti-neutrophil cytoplasmic antibodies; GN = glomerulonephritis.

TREATMENT

There is no standard approach to the treatment of drug-induced vasculitis (summarised in *table 3*). Because the pathogenesis is different between primary and drug-induced vasculitis, the cornerstone of treatment for primary ANCA-associated vasculitis, including induction therapy and maintenance therapy with combined corticosteroid and cyclophosphamide, might not be suitable for patients with drug-induced vasculitis. Treatment should be based on individualised assessment in patients with drug-induced vasculitis. Therefore, treatment for patients with organ involvement should depend on the severity of clinical manifestations and histopathological lesions. In drug-induced vasculitis, the first step is the discontinuation of the medication. For patients with severe and active organ involvement, intensive immunosuppressive therapy could improve organ function and prevent progression to severe, irreversible disease. As shown in *table 2*, prednisone should be administered at 1 mg/kg per day for the first four to eight weeks, followed by a gradual tapering within six to 12 months.[48] In the setting of respiratory failure, alveolar haemorrhage and progressive renal failure, therapy should include cyclophosphamide and high-dose corticosteroids. Intravenous methylprednisolone in doses of 1000 mg/day for three days may be considered.[48] Different approaches have been described. In the first one, cyclophosphamide is administered in monthly boluses for six months, then every three months for two years. The alternative is to give the monthly boluses for six months, and then use azathioprine daily for two years.[48] In addition, patients with life-threatening massive pulmonary haemorrhage may respond to plasmapheresis.[49] Mycophenolate mofetil is an alternative in the treatment of severe drug-induced vasculitis.[48] It is an immunosuppressive agent: inosine monophosphate dehydrogenase 23 inhibitor.[50] It is well accepted that treatment for patients with primary ANCA-associated vasculitis comprises both induction and maintenance therapy. However, for patients with drug-induced vasculitis, the duration of immunosuppressive therapy is still inconclusive. The duration of

immunosuppressive therapy in patients with drug-induced vasculitis could be much shorter than that in primary ANCA-associated vasculitis, and that as long as the offending drug was withdrawn, maintenance therapy might not be necessary.[48] Although ANCA detection may provide a clue to the diagnosis of drug-induced vasculitis, positive seroconversion alone may not be a sufficient reason to discontinue the offending drug, because only a small proportion of the patients with positive ANCA will actually develop clinically evident vasculitis.[47] Physicians should carefully monitor those with drug-induced ANCA but without clinical vasculitis. Resolution of most symptoms has generally occurred within one to four weeks except for severe organ involvement.[8] Nonspecific symptoms may resolve dramatically only after cessation of the causal drug. Although complete resolution of vasculitis occurred in most of the reported cases, some patients do have persistent laboratory abnormalities (elevated serum creatinine, proteinuria) throughout a long-term follow-up. As we mentioned before, if necrotising crescentic glomerulonephritis was present, the patients were at high risk of developing chronic renal failure.[39]

CONCLUSION

There are no clear data on the prevalence of drug-induced vasculitis due to lack of prospective studies. Several cross-sectional studies reported that the prevalence of propylthiouracil-induced vasculitis ranged from 20% to 64%.[51] Prospective, longitudinal studies with a larger cohort of patients are needed to establish the true prevalence of drug-induced vasculitis. The clinician needs to be aware of this risk and quickly stop the offending drug therapy if signs of drug-induced vasculitis develop. In conclusion, patients undergoing treatments with the drugs able to induce vasculitis should be monitored closely during long-term therapy. ANCA is a useful tool to diagnose vasculitis. Appropriate immunosuppressive therapy should only be administered to patients with vital organ involvement in order to prevent progression to severe, irreversible disease. The duration of immunosuppressive therapy should be much shorter than that of primary ANCA-associated vasculitis and long-term maintenance therapy might not be necessary.[48] Identification of predisposing factors to drug-induced vaculitis may provide insight into the pathogenesis of primary vasculitis. Finally the recommendations for clinicians are:

- Avoid use of the drugs able to induce vasculitis in the long term, and patients on long-term treatment with these drugs should be monitored carefully.
- Discontinue the offending drug immediately upon diagnosis of drug-induced vasculitis.
- Individualised immunosuppressive therapy should be initiated according to the severity of organ involvement.
- Adequate documentation of the potentially serious drug-induced reaction in patients' medical records is necessary to avoid re-challenge.

As new classes of medications for the treatment of many disorders are developed, we expect that the number of agents causing drug-induced vasculitis will increase, especially in the era of targeted immune modulation. Drug-induced vasculitis and the unexpected effects of these newer medications continue to be described, demonstrating our present limited understanding of the immune system, and our inability to predict the consequences of manipulating its complex homeostatic mechanisms.

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REVIEW

Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a common major dose-limiting side effect of many chemotherapeutic agents, including platinum compounds, taxanes, vinca alkaloids, thalidomide and newer agents such as bortezomib. The incidence and degree of neuropathy depends on the type of cytotoxic drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy. Because of increasing survival rates of patients treated with neurotoxic agents, CIPN is accompanied by a significant decrease in the patient's quality of life among cancer survivors. Therefore, several neuroprotective strategies, including calcium/magnesium infusion, amifostine, gluthatione, glutamine, acetyl-L-carnitine and erythropoietin as most promising, have been investigated to decrease the neurotoxicity without compromising anti-tumour efficacy. However, clinical evidence for the efficacy of these drugs is sparse. In this review we will give an outline of the neurotoxic effects of chemotherapeutic agents, their clinical manifestations and potential neuroprotective strategies.

KEYWORDS

Bortezomib, chemotherapy, cisplatin, neurotoxicity, oxaliplatin, paclitaxel

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is due to the inability of chemotherapeutic agents to differentiate between malignant and healthy cells.[1] CIPN is a common major dose-limiting side effect of anti-tumour treatment.[2-5] As a result of this dose reduction, delay and withdrawal may lead to decreased chemotherapy efficacy and survival.[1-7] The incidence of CIPN varies from 30 to 40% of patients receiving chemotherapy and depends on the type of cytotoxic drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy.[2-7] Symptoms are predominantly sensory, but the neurotoxicity also appears as a sensory-motor neuropathy and occasionally it will be accompanied by dysfunction of the autonomic nervous system.[5,6] Although the peripheral nervous system has a high regenerating capacity, the cell body needs to be spared and a period of recovery is needed to achieve sufficient repair. In severe damage, CIPN is only partly reversible and sometimes even completely irreversible.[4,5] Since survival of cancer increases, CIPN may significantly interfere with a patient's quality of life among cancer survivors.[1-8] Despite multiple studies there is still no consensus on how to prevent CIPN. In this review we will give an outline of the neurotoxic effects of chemotherapeutic agents, their clinical manifestations and new developments in neuroprotective strategies.

NEUROTOXIC CHEMOTHERAPEUTIC AGENTS

Frequently used chemotherapeutic agents associated with neurotoxicity include platinum compounds, taxanes and vinca alkaloids *(table 1)*.[2-7] In addition, proteasome inhibitors, such as bortezomib, and treatment with thalidomide, are associated with CIPN.[2,4,6]

Platinum compounds

The platinum compounds oxaliplatin and cisplatin are commonly associated with CIPN.[2,3,9] The mechanism by which neuropathy is induced is unclear. Several trials have suggested that platinum compounds accumulate in the dorsal root ganglia and oxaliplatin also produces

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Table 1. *Chemotherapeutic agents causing peripheral neuropathy*

Chemotherapeutic agents
Platinum compounds
Cisplatin
Oxaliplatin
Carboplatin
Taxanes
Paclitaxel
Docetaxel
Vinca alkaloids
Vincristine
Vinblastine
Vinorelbine
Other agents
Bortezomib
Thalidomide
Lenalidomide

axonal hyperexcitability and repetitive discharges due to changes in voltage-dependent Na^+ channels.[4,9-12] The neuropathy, due to cisplatin, is usually reversible and typically appears three to six months after treatment has started, and continues after discontinuation, which is called coasting.[2,5,13] It is predominantly sensory and presents with paresthesias, loss of vibration sense and decreased tendon reflexes. In severe cases, patients develop sensory ataxia and Lhermitte's syndrome.[14] Lhermitte's syndrome is a shock-like sensation of paresthesia radiating from the back to the feet during neck flexion. These clinical manifestations are accompanied by interference in activities of daily living in 6% of patients.[2,5,13,14] Unlike cisplatin, oxaliplatin causes no nephrotoxicity and only mild haematological toxicity, but CIPN occurs in approximately 90% of patients.[9,12,15] The neurotoxicity presents as two different types of neurotoxicity: firstly an acute, mainly cold-triggered neuropathy, and secondly, a chronic sensory neuropathy. Shortly after oxaliplatin infusion, the majority of patients develop distal paresthesias, dysesthesias and mild muscle contractions of the hands, feet and perioral region, which are characteristically reversible within a week.[3-5,9-11] In addition, the symptoms associated with chronic neurotoxicity are mainly sensory and partly reversible in 80% of patients in four to six months. In 40% of patients, symptoms disappear completely in six to eight months.[4,5,9]

Taxanes

The most important dose-limiting side effect of the taxanes, paclitaxel and docetaxel, is neurotoxicity.[2-5] The underlying mechanism is not entirely understood. Preferentially large myelinated fibres, responsible for tactile sensation, vibration perception and proprioception, are affected by paclitaxel.[2,13] In 59 to 78% of patients a cumulative dose-dependent, painful sensory neuropathy sometimes occurs 24 to 72 hours after administration.[13] The clinical manifestations are paresthesias, numbness, tingling and burning, hyperalgesia, and loss of tendon reflexes, vibration sensation and proprioception. Motor neuropathy is less common and includes a mild distal muscles weakness.[2,4,5,13] The incidence of docetaxel-induced peripheral neuropathy is much lower than that of paclitaxel-induced peripheral neuropathy (1-9% versus 30%). The symptoms are similar, but they are usually mild and disappear spontaneously after discontinuation.[5,13]

Vinca alkaloids

Neurotoxicity due to vinca alkaloids, with vincristine as the most neurotoxic, is usually reversible on discontinuation. Nevertheless, the recovery is slow and can last for months.[3,13] Vincristine induces alterations in the cellular micro-tubuli structure, which leads to disruption of the axonal flow. This damage may cause a painful sensory neuropathy and autonomic dysfunction occurs in one third of the patients.[2,3,5,13] In advanced stages, muscle weakness up to paralysis may appear.[2,4,5,13] In patients with pre-existing hereditary neuropathy, administration of vincristine could lead to rapidly evolving paralysis similar to Guillain-Barré syndrome.[2,4,5]

Other chemotherapeutic agents

Thalidomide-associated neurotoxicity appears in approximately 40% of patients, is also cumulative dose-dependent and is due to damage to the dorsal root ganglia.[2,3,13,16] Clinically, it is characterised by paresthesias and a considerable loss of tactile and pain response.[2,3,13] Bortezomib, a novel agent for the treatment of multiple myeloma, usually causes a painful sensory neuropathy with a sharp or burning pain of the feet and fingertips and in approximately 10% of patients also autonomic dysfunction.[2,3,6,13,16] Motor neuropathy is not common with bortezomib and thalidomide.[6,16,17] Symptoms are completely reversible in 60 to 75% of patients receiving bortezomib within a median follow-up of six months, versus 25% of patients receiving thalidomide.[6,16,17]

NEUROPROTECTIVE STRATEGIES AND EVIDENCE

Neuroprotective agents aim to decrease the neurotoxicity associated with cytotoxic agents by providing protection for healthy tissue without compromising anti-tumour efficacy.[1,7,14] Multiple strategies to prevent CIPN have been investigated (*table 2*). However, clinical evidence for the efficacy of these strategies is sparse. Because of the higher risk of CIPN developing in patients with pre-existing

Table 2. *Trials for prevention of CIPN*

Agent	Number of patients	Results	Design	Reference
Dosis	623	No difference in response rate with dose modification	RT; oxaliplatin	18
Modification	333	No difference in response rate with dose modification	RT; bortezomib	20
Amifostine	242	CIPN between two arms differ significantly after 6 cycles (p=0.029), with grade 0 CIN in 55% of amifostine arm vs (vs) 39% in the control arm. Grade 3-4 in 9 vs 15%	RCT open-label phase III trial; cisplatin	25
	187	CIPN grade 3-4 in 3.7% amifostine patients vs 7.2% (p=0.02) in control group	Multicentre randomised open label phase III trial; paclitaxel	26
	31	Not effective	Non randomised trial; case-control: paclitaxel/doxorubicin/cyclophosphamide	22
	90	No CIPN in 40% vs 49% of patients with amifostine (n.s.). Grade II 12 vs 2% and grade III 2% vs 1% in amifostine arm	RCT open phase II trial; paclitaxel/carboplatin	21
	71	Not effective	RCT placebo-controlled; double blind paclitaxel/carboplatin	23
Glutathione	52	Significantly less neuropathy after 8 cycles: 79% in placebo group vs 43% in the GSH group (p=0.04). Less grade 3-4 neuropathy in the GSH group (p=0.003)	RCT placebo-controlled; double blind, oxaliplatin	27
	27	No grade 3-4 CIN in the GSH group. Grade 2 in 50% in GSH arm vs 69% and grade 3 in 31% (p=0.0037) in the control arm	RCT placebo-controlled; oxaliplatin	28
	151	CIPN in 49% patients treated with cisplatin alone compared to 39% in the GSH arm (p=0.22)	RCT placebo-controlled; double blind, cisplatin	29
Ca/Mg infusion	161	69 of 161 patients received Ca/Mg. CIPN in 20% patients Ca/Mg vs 45% without Ca/Mg (p=0.003). Less grade 3 in Ca/Mg group (8 vs 20% p=0.003)	Retrospective study	31
	174	Initially worse response rate in Ca/Mg arm	RCT placebo-controlled; double blind; oxaliplatin	32
	102	Terminated after results CONcePT. Analysis with remaining data: CIN grade 2 or more in the Ca/Mg group compared to placebo (22% vs 41%; p=0.038)	RCT placebo-controlled; double blind; oxaliplatin	33
	144	Preanalysis in 52 patients: no difference in response rate (50% vs 53%; p=0.45). Neurotoxicity grade 3 was 5% vs 24% (p<0.001) between groups (blinding yet unbroken)	RCT placebo-controlled; double blind; oxaliplatin	34
	732	The incidence of all grade sensory neurotoxicity was 85% vs 92% in favour of the Ca/Mg arm (p=0.02). No significant difference in response rate	Retrospective study	35
Glutamine	86	Less grade 1 and 2 neuropathy and grade 3-4 neuropathy in the glutamine group after four cycles (5% vs 18%; p=0.05) and six cycles (12% vs 32%; p=0.04)	Open-label; oxaliplatin	36
	45	Less weakness (56 vs 25%; p=0.04) and interference with ADL (85 vs 27%; p=0.001) in the glutamine arm	Prospective cohort study; paclitaxel	37
	86	Less weakness (p=0.02), less loss of vibratory sensation (p=0.04) and less toe numbness (p=0.004) than controls	Case-control; paclitaxel	38
	43	Not effective	RCT placebo-controlled; double blind pilot study; paclitaxel	39
Vitamin E	37	CIPN in 3/16 (19%) of patients with vitamin E vs 10/16 (63%) of controls (p=0.03)	Randomised open-label; paclitaxel	40
	30	CIPN occurred in 3/14 (21%) of patients in vitamin E group vs 11/16 (69%) of the control group (p=0.026)	Randomised open-label; cisplatin	41
	41 (108)	Significant lower incidence of neuropathy in the vitamin E group (6%) than in the placebo group (42%)	Phase III; RCT placebo-controlled; cisplatin	42
	207	Not effective	Phase III; RCT placebo-controlled; double blind; multiple agents, mainly taxanes (108)	43
Erythropoietin	In vivo	EPO significantly reduced impaired sensory nerve conduction (p<0.05), increased thermal threshold	In vivo 62 rats; cisplatin	44
	In vivo	EPO significantly improved the thermal threshold (30%) (p=0.05), nerve conduction velocity by 10-12% (p<0.05) and intra epidermal nerve fibre density	In vivo 344 rats; docetaxel	45
Acetyl-L-carnityl	25	Patients received 1g ALC. The sensory neuropathy grade improved in 15 of 25 (60%), and motor neuropathy in 11 of 14 patients (79%). Total neuropathy score (TNS) improved in 23 (92%). Symptomatic improvement persisted in 12 of 13 evaluable patients at median 13 months after ALC	Experimental; phase I trial; cisplatin, paclitaxel	53

Table 2. *Trials for prevention of CIPN*

Agent	Number of patients	Results	Design	Reference
ACTH/ ORG	55	Vibration perception was maintained in the intervention arm compared to the control arm	RCT placebo-controlled; double blind cisplatin	54
	220(196)	Not effective	RCT placebo-controlled; double blind cisplatin	55
RHuLIF	117	Not effective	RCT placebo-controlled; double blind paclitaxel/carboplatin	59
Anti-epileptica	36	Not effective	RCT; oxaliplatin	56
	13	Not effective	Phase I study; oxaliplatin	57
Nerve growth factors	62	Significant correlation between the decrease in circulating levels of NGF and the severity of CIPN (r=-0.58; p<0.001)	Observational study	58
Nimo-dipine	50	Not effective	RCT placebo-controlled; double blind	60
Etho-suximide	In vivo	Decrease of pain in rats	In vivo rats; paclitaxel	61

iRT = randomised trial; RCT = randomised controlled trial

neuropathy, alcohol abuse and poor nutritional state, prevention should begin by identifying those patients before starting chemotherapy.[1,2,4,7]

Treatment modification

Since to date clinical evidence for the efficacy of neuroprotective agents is sparse (see below), alternative dosing regimens and early detection and the use of treatment modification schemes based on common toxicity criteria may be necessary to limit the amount of damage associated with neurotoxic chemotherapy. A neurologist can be helpful in establishing the exact grade of CIPN and sometimes in differentiating CIPN from other causes of neuropathy, since this may have important therapeutic consequences. Discontinuation and reintroduction of oxaliplatin administration in a stop-and-go strategy showed the same response rate with a lower incidence of CIPN in the OPTIMOX study.[2,18] Nevertheless in general dose reduction may be associated with impaired overall and disease-free survival, especially in the adjuvant setting, so that it is necessary to carefully outweigh the benefits and level of toxicity of treatment. Dose-modification strategies based on common toxicity criteria have also been described and reported to be effective in thalidomide- and bortezomib-induced peripheral neuropathy.[19,20] Therefore it seems an effective intervention in decreasing CIPN.

Amifostine

Amifostine serves as an antioxidant and binds to the metabolites of platinum compounds and alkylating agents, which protect normal tissue against the cytotoxic effects.[1,14,21-24] In addition to a radioprotective role, it has been proposed as a potential neuroprotective agent.[21,22] The best evidence in cisplatin- and paclitaxel-induced neurotoxicity is shown in two randomised controlled trials.[25,26] In both studies, patients were randomised to receive amifostine before administration or not. Although the primary study endpoint was the ability of amifostine to prevent haematological toxicity, neurotoxicity was studied as well. In cisplatin-receiving patients, the difference in neurotoxicity between the two treatment arms was statistically significant after six cycles.[25] In paclitaxel-receiving patients, amifostine appeared to be neuroprotective in grade 3 and 4 neuropathy.[26] Other studies demonstrated no significant difference in neurotoxicity.[21-23] All trials demonstrated hypotension as the major side effect and no difference in survival between groups.[21-23,25,26] In conclusion, amifostine potentially reduces neurotoxicity. However, as neurotoxicity was not the primary endpoint of the studies, more trials are needed to investigate this drug. Besides, amifostine is accompanied by serious side effects, stressing the importance of more clinical evidence before standard use can be recommended.

Glutathione

Glutathione (GSH) is involved in detoxification and protection of tissue from oxidant injury and might prevent accumulation of platinum compounds in the dorsal root ganglia.[1,4,7,27,28] Two small randomised placebo-controlled trials showed promising results on oxaliplatin-induced neurotoxicity, with significantly less grade 2 to 4 neuropathy in the GSH arm.[27,28] Another larger trial with cisplatin showed a trend with less neuropathy in favour of GSH, although, the results were not statistically significant (p=0.22).[29] Furthermore, dropout rates were very high with only 39% versus 58% patients receiving six cycles in the

control and intervention arm, respectively. Nevertheless, the difference in discontinuation was significantly lower in the GSH arm.[29] No significant difference in tumour-response rate was found.[27-29] These results provide evidence indicating that GSH might decrease CIPN. However, more studies are needed as dropout rates were high and long-term follow-up was lacking. Furthermore, the largest phase III trial demonstrated no significant results.

Calcium and magnesium infusion

Calcium and magnesium (Ca/Mg) have been proposed as neuroprotective agents by increasing extracellular calcium concentration.[4,7,30] First a retrospective study demonstrated significantly less neurotoxicity with prophylactic calcium 1 g and magnesium 1 g infusion before and after oxaliplatin, compared with a historic control group (p=0.003) without compromising anti-tumour effect.[31] However, three years later the CONcePT trial was terminated because of a presumed lower tumour-response rate in the Ca/Mg arm, although a critical appraisal after discontinuation of this study could not confirm these findings.[7,32] A concomitant study of the North Central Cancer Treatment Group (NCCTG) was terminated because of the suspected effect on anti-tumour response.[32,33] Remaining data of the prematurely aborted NCCTG study demonstrated a significantly lower incidence of grade 2 or more neurotoxicity in the Ca/Mg group.[33] Nevertheless, long-term follow-up data are lacking and the planned number of patients was not achieved. In response to these trials, early analyses of the Neuroxa study have been revealed and a large retrospective study has been performed.[34,35] They both confirmed the neuroprotective results from Ca/Mg infusion without compromising response rate.[34,35] All studies used the same dosage of Ca/Mg as the first retrospective study. Correlation of clinical effects with alterations in plasma levels could not be determined, as the plasma Ca and Mg levels were either not observed or not reported in these studies. Thus, although concerns about the safety of Ca/Mg infusions are valid, clinical trials did not demonstrate convincing differences in tumour-response rates in the Ca/Mg infusion arms compared with placebo, while there are data supporting a neuroprotective effect of Ca/Mg infusion in oxaliplatin-induced neuropathy.[32-35] Ideally, regarding the contradictory results from the presented studies, the effect of Ca/Mg on CIPN and tumour growth should be confirmed in larger randomised controlled trials.

Glutamine

Glutamine, a non-essential amino acid stored in skeletal muscle (75%) and liver (25%), is another investigated agent to prevent neurotoxicity.[4,36,37] During long periods of stress, such as malignancy, glutamine depletion develops with negative impact on tissue functions.[4,7,36,37] Two pilot studies suggested glutamine (10 g three times a day for four days) as a neuroprotective agent without interfering with chemotherapy response.[37,38] Accordingly, a randomised trial with colorectal patients reported significantly less CIPN and interference with ADL in the glutamine arm (15 g twice a day for seven consecutive days) compared with control.[36] However, there were no differences in electrophysiological examination between groups.[36] Furthermore, a randomised pilot study revealed no difference in the use of glutamate 500 mg.[39] Since plasma glutamine levels were not assessed in any of these studies, no correlation with altered glutamine plasma levels could be determined. These results suggest that glutamine may reduce CIPN; however, results are inconsistent and need to be confirmed in large randomised, placebo-controlled trials.

Vitamin E

Many studies have examined the role of antioxidants such as vitamin E, vitamin C and alpha-lipoic acid. The best evidence is reported concerning vitamin E.[2,4,7,40,41] Two small studies investigated the role of vitamin E in preventing CIPN due to cisplatin or paclitaxel.[40,41] In both studies, the incidence of neurotoxicity was approximately 20% versus 68% (p=0.03) in the vitamin E arm compared with the control arm, respectively.[40,41] In 2010, a phase III study showed a significantly lower incidence of neuropathy in the vitamin E group. However, only 41 out of 108 patients, with 17 in the vitamin E group, were eligible for analysis and no intention-to-treat analysis was preformed.[42] Another large trial reported no difference in neuropathy.[43] In conclusion, there is no convincing evidence that vitamin E is beneficial in the prevention of CIPN and we do not recommend its use. Studies were of poor quality and populations were small. Besides, the largest phase III trial reported no difference in neurotoxicity in the vitamin E group compared with placebo.[43]

Erythropoietin

Erythropoietin (EPO), used in the treatment of haematological toxicity for its effect on erythropoiesis, has also been demonstrated to have neurotrophic activity and receptors in nerve axons, Schwann cells and dorsal root ganglia which protect cells from injury and apoptosis.[44-48] After injury, these receptors are over-expressed and the basis for therapeutic use. EPO has been shown to prevent cisplatin and docetaxel-induced neurotoxicity without compromising chemotherapeutic activity and increasing tumour growth in animal studies.[44,46,49] These results are very promising, especially because of its concomitant use against haematological toxicity. Therefore, the neuroprotective effect of EPO should be confirmed in clinical trials.

Acetyl-L-carnitine

Also acetyl-L-carnitine (ALC) was shown to reduce neuropathy in animal studies, with beneficial effect of ALC administration in rats receiving oxaliplatin.[50-52] A clinical study included 25 patients who developed neuropathy due to paclitaxel or cisplatin. After discontinuation of chemotherapy, they received ALC 1 g for eight weeks. Sensory neuropathy and motor neuropathy decreased in 60 and 79% respectively. Furthermore, a significant improvement in sensory action potential occurred.[53] These results should also confirmed in randomised trials.

Other agents

Numerous other agents have been studied for their potential effectiveness in reducing chemotherapy-induced neurotoxicity, including ORG 2766,[54,55] antiepileptic agents such as carbamazepine and oxacarbazepine[56,57], nerve growth factor,[58] recombinant human leukaemia inhibitory factor (rhuLIF),[59] nimodipine[60] and ethosuximide.[61] Ethosuximide has been demonstrated to decrease pain induced by paclitaxel in rats.[61]However, other agents showed no evidence of neuroprotection and/or were only investigated in very small studies of poor quality.[54-57,59,60]

SYMPTOMATIC TREATMENT OF ESTABLISHED CIPN

Neuropathic pain is a frequent problem in many chemotherapy-induced neuropathies. Recommendations on treatment of neuropathic pain in cancer patients are usually based on studies concerning 'benign' neuropathic pain, such as painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia.[62] Although chemotherapy-induced pain may be very different from benign neuropathic pain, almost no randomised controlled studies exist for this specific condition.[63,64]

Dutch guidelines on neuropathic pain in cancer patients recommend treatment with the antiepileptic agents gabapentin or pregabalin, or tricyclic antidepressants (TCAs).[65] However, TCAs are accompanied by many adverse effects and a phase III trial did not report any difference between gabapentin compared with placebo in chemotherapy-induced neuropathic pain specifically.[64,66,67] Recently, the antidepressant venlafaxine, a serotonin and a norepinephrine reuptake inhibitor (SNRI), has been investigated in preventing acute oxaliplatin-induced neurotoxicity and demonstrated a significant relief of acute neurotoxicity (31% versus 5%; p=0.03) and, as secondary endpoint, less grade 3 toxicity after three months (0% versus 33%, p=0.03).[67,68]

CONCLUSIONS AND RECOMMENDATIONS

The overall and progression-free survival in cancer patients was shown to be increased after the introduction of treatment with oxaliplatin, taxanes and bortezomib. Therefore, quality of life plays an increasingly important role among cancer survivors. CIPN is one of the major dose-limiting toxicities associated with these agents. Treatment of CIPN remains difficult, especially because recommendations on treatment of neuropathic pain in cancer patients are usually based on studies concerning 'benign' neuropathic pain. Therefore, we should focus on prevention. Several neuroprotective strategies, including Ca/Mg infusion, amifostine, GSH, glutamine, acetyl-L-carnitine and erythropoietin as most promising, have been investigated.[21-23,25-29,44-53,69] Particularly erythropoietin is a hopeful approach to reduce CIPN because of the concomitant effect on haematological toxicity and effect on the quality of life. In addition, it has a toxicity profile itself. However, clinical evidence for standard use is insufficient. Therefore, alternative dosing regimens, early detection, and the use of treatment modification schemes based on common toxicity criteria may be necessary to limit the amount of damage associated with neurotoxic chemotherapy.

In summary, clinical evidence for the efficacy of these drugs is sparse. Consequently, no explicit recommendations on neuroprotective strategies can be given yet except for the importance of identifying high-risk patients before starting chemotherapy. In the future, trials concerning neuroprotective agents should continue. Meanwhile, alternative dosing regimes, early detection and treatment modification schemes are necessary tot limit CIPN.

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ORIGINAL ARTICLE

Imaging modalities for the staging of patients with colorectal cancer

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ABSTRACT

Dutch guidelines made the following recommendations for staging colorectal cancer (CRC). For liver metastases, computed tomography (CT) or magnetic resonance imaging (MRI) could be used. For lung metastases, imaging could be limited to chest X-ray. The primary aim of this survey was to summarise the use of imaging modalities and the variation in techniques.

Three surveys were created and sent to three groups of medical specialists, namely surgeons, radiologists and nuclear medicine physicians. The management survey included questions on the role of different modalities for evaluation of synchronous liver, lung and extrahepatic metastases. The radiological survey included questions concerning the technical aspects of ultrasound (US), CT and MRI. The nuclear medicine survey included questions concerning the technical aspects of FDG-PET and FDG-PET/CT. The management and radiological surveys were sent to abdominal surgeons and abdominal radiologists within 88 hospitals and the nuclear medicine survey to specialists within 34 hospitals.

Response rates were 75.0% (n=66/88), 77.3% (n=68/88) and 64.7% (n=22/34) for the management, radiological and nuclear medicine surveys, respectively. For liver metastases, the first modality of choice was CT in 52 (78.8%) and US in 12 hospitals (18.2%). Lung metastases were evaluated by either chest X-ray or chest CT and extrahepatic metastases mainly by CT (n=55). In the radiological and nuclear medicine surveys, some variations in techniques of US, CT, MRI, FDG-PET and FDG-PET/CT were seen.

CT is primarily used for liver and extrahepatic metastases and both chest CT and chest X-ray for lung metastases. There are discrepancies between the survey of daily practice and the present guidelines. Comparative studies on different staging strategies for colon and rectal cancer, including comparing a strategy of CT liver/abdomen versus MRI liver/abdomen for the evaluation of liver and extrahepatic disease and chest X-ray or chest CT for lung metastases would be important for well-founded adjustments of the present guidelines.

KEYWORDS

Colorectal neoplasms, diagnostic imaging, metastasis, staging

INTRODUCTION

Colorectal cancer (CRC) is diagnosed in the Netherlands in over 10,000 new patients per year, making colorectal cancer the third most diagnosed cancer in men, next to prostate and lung cancer. In women it is the second most diagnosed cancer, next to breast cancer. It is expected that in 2015 the incidence of colorectal cancer will have increased to approximately 14,000 new patients per year.[1]

A Dutch national evidence-based guideline on the diagnosis and treatment of patients with colorectal liver metastases was published in 2006.[2,3] The guidelines were developed by a working group mandated by the disciplines involved in this field, including surgeons, medical oncologists, gastroenterologists, radiologists and nuclear medicine physicians. The recommendations for detection of synchronous metastases by diagnostic imaging were as follows. For synchronous liver metastases, spiral computed tomography (CT) with an intravenous contrast agent (more

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than 45 gram iodine), or magnetic resonance imaging (MRI) with a contrast agent were indicated as imaging modality. For the evaluation of lung metastases, imaging could be limited to conventional chest X-ray, based on the low prevalence of lung metastases and the occurrence of false-positives at CT. No recommendations were made for the use of ^{18}F fluorodeoxyglucose positron emission tomography (FDG-PET) and FDG-PET/CT for this patient group, since data and the use of these modalities were limited at that time.

Since the introduction of this evidence-based guideline, several improvements have been made in imaging such as the extensive use of multispiral CT, new available MRI-contrast liver agents and the more widespread use of FDG-PET and the introduction of FDG-PET/CT. [4-9] In addition, many new studies have evaluated the role of the different modalities or techniques for this patient population.[10-15]

At this time point it is unclear if and to what extent these improvements have led to variations in the management. To gain information on the use of imaging modalities and the variation in techniques, we performed a digital survey in all hospitals in the Netherlands. The aim of this survey was to summarise the use of imaging modalities in staging of patients with CRC and the extent of variation in techniques used by radiologists and nuclear medicine specialists.

METHODS

Survey

Three different surveys were sent to three groups of medical specialists who are mainly involved in the staging of patients with colorectal cancer, by using imaging modalities.

1) The management survey. This survey included general questions, such as information on the hospital, specialist and years of experience, and specific questions on the role of the different imaging modalities in the staging of CRC, for the evaluation of liver, lung and extrahepatic disease. The specific questions are described in *table 1*.

2) The radiological survey. This survey also included general questions, such as information on the hospital, specialist and years of experience, and the specific questions concerning the technical aspects of ultrasonography (US), CT and MRI. The specific questions are described in *table 2*.

3) The nuclear medicine survey. This survey also included general questions, such as information on the hospital, specialist and years of experience, and the specific questions concerning FDG-PET and FDG-PET/CT. The specific questions are described in the *table 3*.

Table 1. *The management survey to define the role of imaging modalities*

Questions	Answers
Is an imaging modality used for the detection of synchronous liver metastases?	Always (100%), Often (50-90%) Sometimes (<50%) Never
Which imaging modality is used for the detection of synchronous liver metastases? Indicate which modality is the first, second, third choice, etc.	US CT MRI FDG-PET FDG-PET/CT
Is imaging performed for the detection of synchronous lung metastases?	Always (100%) Often (50-90%) Sometimes (<50%) Never
Which imaging modality is used for the detection of synchronous lung metastases? Indicate which modality is the first, second, third choice, etc.	Chest X-ray Chest CT Other
Is imaging used for the detection of synchronous extrahepatic abdominal metastases?	Always (100%) Often (50-90%) Sometimes (<50%) Never
Which imaging modality is used for the detection of synchronous extra-hepatic abdominal metastases? Indicate which modality is the first, second, third choice, etc.	US CT MRI FDG-PET FDG-PET/CT
What is the frequency of multi-disciplinary meetings for colorectal cancer patients held in your institution? Are these meetings held with consultants from the Comprehensive Cancer Centres (CCC) or with specialists from other hospitals?	Times per week CCC Other hospitals
To what extent are surgeons, oncologists, gastroenterologists, radiologists, nuclear medicine physicians or internists involved in the care of these patients?	4-point scale varying from no role to major role
To what extent do findings in the literature, availability of techniques, available expertise, associated costs, available personnel and waiting lists affect the choice for a diagnostic modality?	4-point scale varying from no role to major role

Participants

Since surgeons are mainly involved in the management of these patients, the management survey was sent to abdominal surgeons in all 88 Dutch hospitals with the help of the 'Dutch Surgical Society' (NVvH) in November 2010. The radiological survey was sent to abdominal radiologists in all 88 Dutch hospitals with the help of the 'Radiological Society of the Netherlands' (NVvR) in November 2010. The nuclear medicine survey was sent to nuclear medicine physicians within 34 hospitals in January 2011: only hospitals with the availability and use of FDG-PET or FDG-PET/CT (based on the results of the management survey) were contacted.

Table 2. *The radiological survey to summarise the technical aspect of US, CT and MRI*

Modality	Questions	Answer
US	What part of the abdomen is imaged using US for the detection of synchronous metastases?	Solely the liver Upper abdomen Lower abdomen
	What type of transducer is used?	Convex Convex+Linear
	What is the frequency of the transducer?	Mhz
	Which US technique is used?	Grayscale imaging Tissue-harmonic imaging
	Is a contrast agent used for US?	Yes (type, dose) No
CT	What part of the body is imaged using CT for the detection of synchronous metastases?	Solely the liver Upper abdomen Lower abdomen Thorax
	What type of CT scanner is used?	Single-slice or multi-slice Number of detectors
	Is intravenous contrast agent used?	Yes (type, dose) No
	Which phases are used and what is the timing of the phases?	Arterial, portal or late (timing)
MRI	What part of the body is imaged using MRI for the detection of synchronous metastases?	Liver/Upper abdomen Lower abdomen
	Which MRI scanner is used?	Strength and type of coil
	Is an intravenous contrast agent used for MRI in the detection of synchronous metastases?	Yes (type, dose, timing) No
	What sequences are used in MRI for the detection of synchronous metastases?	T1W-SE, T1W-GRE, T1W-FSE, T1W-FATSAT, T2W-SE, T2W-FSE T2W-FATSAT, Dynamic T1W with contrast agent, HASTE, Diffusion weighted sequence with ADC-mapping

Table 3. *The nuclear medicine survey to summarise the technical aspects of PET and PET/CT*

Modality	Questions	Answers
FDG-PET or FDG-PETCT	Is NEDPAS used*	Yes No
FDG-PET	What is the PET acquisition time?	Minutes per bed position
	What amount of FDG is used for the detection of synchronous metastases?	MBq/kg bodyweight
	What are the specifications for the patient preparation?	Fasting time Time interval between FDG injection and scanning
	How are the images evaluated	Quantitatively Qualitatively
	What modality is used for visually comparison?	CT MRI Other
FDG-PET/CT	What is the PET acquisition time?	Minutes per bed position
	What amount of FDG is used for the detection of synchronous metastases?	MBq/kg bodyweight
	What are the specifications for the patient preparation?	Fasting time and time interval between FDG-injection and scanning
	How is the evaluation of the images read?	Quantitatively Qualitatively
	Is a low dose or a high dose used for CT imaging?	Low dose (mAs, kV) High dose (mAs, kV)
	Is an intravenous contrast agent used for CT with FDG-PET/CT?	Yes (type, dose, phases, timing) No
	Is an oral contrast agent used for CT with FDG-PET/CT?	Yes (type, dose)
	Who evaluates the images from the FDG-PET/CT?	Nuclear medicine physician Radiologist

*** Boellaard R, Oyen W, Hoekstra C et al. The Netherlands protocol for standardisation of FDG whole body PET studies in multi-center trials (NEDPAS). Nucl Med. 2008;49 (Supplement 1):106P**

Response

After two months, all non-responders were contacted, initially via email, subsequently via telephone call. We aimed to reach a response rate of at least 70%.

Data presentation

We used a descriptive statistical analysis to summarise the results. Continuous, normally distributed data were expressed as means, with corresponding standard deviations. Continuous, not normally distributed data, were expressed as median with ranges or as modus with ranges, depending on the type of data. Categorical data were expressed as number and percentage.

RESULTS

Response rate

The response rates were 75.0% (n=66/88), 77.3% (n=68/88) and 64.7% (n=22/34) for the management, radiological and nuclear medicine surveys, respectively. All eight academic hospitals participated in the management and radiological surveys. Based on the results of the management surveys, concerning the use of FDG-PET or FDG-PET/CT for staging of CRC, specialists within 34 hospitals were invited to complete the nuclear medicine survey. For the nuclear medicine survey five out of six (83.3%) academic medical hospitals using either FDG-PET or FDG-PET/CT participated in this survey.

Management survey

This survey was completed by surgeons (n=62), oncologists (n=1), internists (n=1) or this was not described (n=2). The experience of the responders ranged from one year to 29 years, with a mean of 11.3±6.7 years. The availability of US, CT, MRI, FDG-PET or FDG-PET/CT was 100% (66), 100% (66), 100% (66), 56.1% (37) and 62.1% (41) hospitals, respectively.

Liver metastases: In 64 of the 66 hospitals (97.0%) imaging was always performed for the assessment of synchronous liver metastases, while in two hospitals (3.0%) imaging was often used, but not in all patients. The first modality of choice was CT in 52 hospitals (78.8%) and US in 12 hospitals (18.2%). The second choice was US in 34 hospitals (51.5%) and CT in 11 hospitals (16.7%). MRI, FDG-PET and FDG-PET/CT were not frequently used as first or second choice modality (*figure 1*).

Lung metastases: 53 of 68 hospitals (80.3%) always used an imaging modality for the assessment of lung metastases, in ten hospitals (15.2%) an imaging modality was often used and sometimes in three hospitals (4.5%). No imaging for lung metastases was performed in one hospital (1.5%). In all hospitals, assessment of synchronous lung metastases was done by either conventional chest X-ray or chest CT; FDG-PET or FDG-PET/CT was only used as third choice modality *(figure 2)*.

Extrahepatic abdominal metastases: For the detection of extrahepatic abdominal metastases, imaging was used in all patients in 40 of the 66 hospitals (60.6%). Twelve hospitals (18.2%) often used an imaging modality and in 13 hospitals this was sometimes used (19.7%). One hospital (1.5%) never used an imaging modality for the assessment of extrahepatic abdominal metastases. In most hospitals evaluating extrahepatic abdominal metastases was mainly done by CT (n=55) and to a lesser extent by US, MRI, PET and/or PET/CT *(figure 3)*.

In summary, CT is primarily used for the evaluation for liver and extrahepatic colorectal metastases. For evaluation of lung metastases, chest CT and conventional chest X-ray are used to a comparable extent.

Decision making

Specialists involved: Specialists primarily involved in decision making were predominantly surgeons in 51 and

Figure 2. *Choices of modalities used for the detection of synchronous lung metastases*

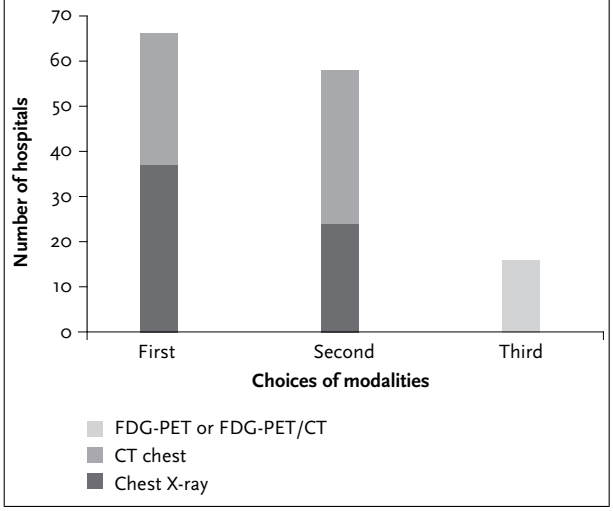


Figure 1. *Choices of modalities used for the detection of synchronous liver metastases*

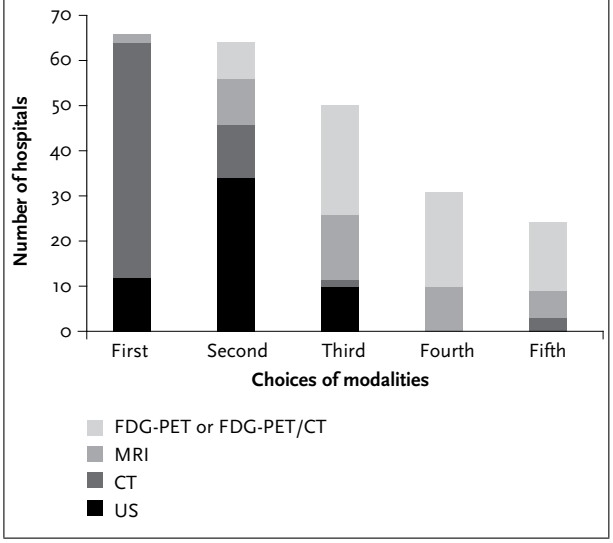
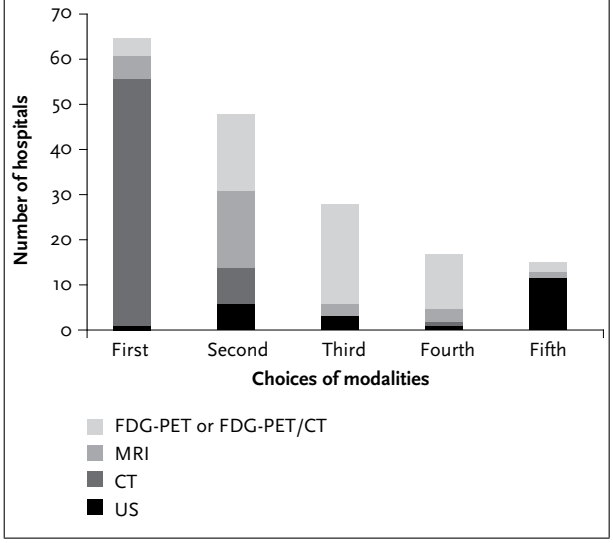


Figure 3. *Choices of modalities used for the detection of synchronous extrahepatic abdominal metastases*



medical oncologists in 22 hospitals. Gastroenterologist, radiologists, nuclear medicine physicians and internists were less involved in decision making.

Multidisciplinary meeting: Multidisciplinary meetings to discuss treatment options for colorectal cancer patients were routinely held in 65 hospitals (twice a week in six hospitals, weekly in 55 hospitals and every other week in four hospitals). Meetings with other hospitals were held in 19 hospitals and consultations from the Comprehensive Cancer Centres were requested in 47 hospitals. In seven hospitals, both other hospitals as well as specialists from Comprehensive Cancer Centres were involved. Seven hospitals did not have meetings with either the Comprehensive Cancer Centres or other hospitals.

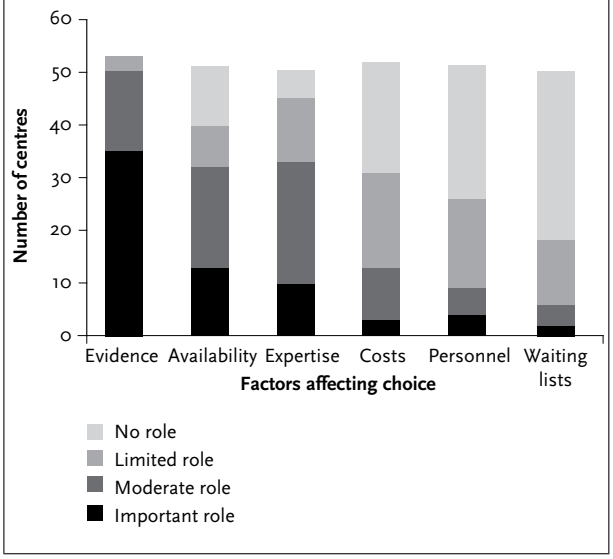
Factors affecting choices: The choice of imaging modality was mostly determined by evidence in the literature, followed by availability and expertise and occasionally by costs, personnel and waiting lists *(figure 4)*.

Radiological survey

The radiological survey was only completed by radiologists (n=68), with experience ranging from two to 32 years, with a mean experience of 12.2±7.2 years. The radiological surveys were not completed in exactly the same 66 hospitals as the management surveys; in 50 hospitals both surveys were completed.

Ultrasonography was performed in 31 (45.6%), CT in 67 (98.5%) and MRI in 20 (22.7%) hospitals for the detection of synchronous colorectal metastases.

Figure 4. *Factors such as literature, availability, expertise, costs, personnel and waiting lists affecting the choice for a diagnostic modality*



Ultrasonography: US was used for visualisation of the liver in all 31 hospitals (100%) where it was performed and for the evaluation of extrahepatic abdominal disease in 13 of these hospitals (41.9%). In all 31 hospitals (100%) a convex transducer was used and an additional linear transducer for detailed visualisation of the liver surface was used in three hospitals (9.7%). The frequency of the transducer ranges from 3 MHz to 8.5 MHz. US with harmonic imaging in combination with conventional US was performed in 22 hospitals (71.0%). One hospital (3.2%) occasionally used a contrast agent during ultrasound.

Computed tomography: CT was used for evaluation of liver metastases in all 67 hospitals (100%) were it was applied, for extrahepatic abdominal metastases in 63 hospitals (94.0%) and for lung metastases in 32 hospitals (47.8%). In 66 hospitals (98.5%), a multislice CT scanner was available, with the number of detectors ranging from 2 to 320 (modus 64 detectors), while one hospital (1.5%) had a single-slice CT scanner. CT was always performed with an intravenous contrast agent (100%) and the number of phases varied between hospitals. The portal phase was always used (100%), either as a single phase (52.2%) or in combination with arterial and late phases (*table 4*).

Forty-two hospitals (62.7%) used fixed timing for contrast; the arterial phase ranged from 20 to 40 seconds (modus 25 seconds), the portal phase ranged from 55 to 90 seconds (modus 70 seconds) and the late phase ranged from 120 to 360 seconds (modus 300 seconds). Twenty-three hospitals (34.3%) used bolus tracking and two hospitals (3.0%) did not report the type of timing.

The amount of iodine administrated ranged from 21 to 53 gram (mean 35.6±7.2 g). Ten hospitals (14.9%) used at least 45 gram iodine.

Magnetic resonance imaging: MRI was used for the evaluation of the liver disease in 12 of the 20 hospitals (60%) were it was used and for the evaluation of extrahepatic disease evaluation in nine hospitals (45.0%). The magnetic field strength of the available MRI scanners were predominantly 1.5 T (n=17), and further 3.0 T (n=2) and 1.0 T (n=2). In 15 hospitals (75.0%), an additional coil was used (14 phased array and 1 wrap around coil). Contrast agents were used in 15 hospitals (75.0%);

Table 4. *Phases used for the evaluation of synchronous liver lesions*

Phases used	Number of hospitals	Percentage
Portal phase	35	52.2%
Arterial + portal phases	11	16.4%
Arterial + portal +late phases	18	26.9%
Portal + late phases	3	4.5%

Gadolinium or a comparable contrast agent was used in ten hospitals and a liver specific contrast agent (Gadoxetic acid, Primovist, Bayer Schering, Berlin, Germany) was used in five hospitals. The sequences used for MRI were predominantly T2W-FSE (n=12), dynamic contrast-enhanced T1W (n=12) and diffusion weighted images (n=11).

Nuclear medicine survey

The nuclear medicine survey was completed by nuclear medicine physicians (n=21) and by one radiologist, with years of experience ranging from three to 28 years (mean 11.2±7.3 years). In 18 hospitals (81.8%), the Dutch protocol for standardisation of FDG (NEDPAS) was used. For evaluation of synchronous liver, lung and extrahepatic abdominal disease, FDG-PET was solely performed in two hospitals and FDG-PET/CT with either low-dose or high-dose CT in 14 hospitals.

FDG-PET (n=2): Patients fasted for six hours in both hospitals and were scanned 60 minutes after the injection of FDG (3 and 4.6 MBq/kg, respectively). The acquisition times were three and five minutes per bed position, respectively. Assessment was done qualitatively in both hospitals and visually compared with either CT or MRI.

FDG-PET/CT (n=14): In all hospitals, a multi-slice PET/CT scanner was available, with the number of detectors ranging from two to 64 (modus 16 detectors). Patients fasted for either four or six hours prior to the investigation. Administration of on average 2.99 Mbq/kg FDG (min: 1.7, max: 4.6) was predominantly 60 minutes prior to the investigation. Acquisition time ranges from 1.45 to 5 minutes per bed position. A low-dose CT image was performed in 13 hospitals (92.9%) and in eight of these hospitals (61.5%) an additional high-dose CT (diagnostic CT) was performed. Only one hospital (7.1%) performed a diagnostic CT solely. For the diagnostic CT, intravenous contrast agent administration with fixed timing and portal phase CT was always performed.

Data on radiation intensity, tube voltage, amount of contrast agent and phases are presented in *table 5*. The use of oral contrast agent was limited. Evaluation of the images was done by both the radiologist and nuclear medicine physician in 12 hospitals (85.7%). In two hospitals (14.2%) only the nuclear medicine physician evaluated the PET/CT images as only low-dose CT was used.

DISCUSSION

This study shows that a majority of hospitals use a comparable staging strategy, with CT as the first choice for staging of liver and extrahepatic disease and either chest CT or chest X-ray for evaluation of lung metastases. The role of US, MRI, FDG-PET and FDG-PET/CT as first choice techniques was limited.

In the radiological and nuclear medicine surveys, some variations in US, CT, MRI, PET and PET/CT techniques were seen. The majority of variation was within the accepted variation reported in the literature. In the Dutch guideline on colorectal liver metastases, recommendations were made concerning the use of a contrast agent for MRI and at least 45 grams of iodine for CT. Only a minority used at least 45 gram iodine for CT. However, this 45 gram iodine cut-off was chosen arbitrarily based on the results of a meta-analysis.[16] Not all hospitals used an MRI contrast agent, which could be explained by the use of recently introduced advanced MRI techniques (e.g. diffusion weighted imaging), which makes the use of contrast agent less critical.[17,18]

The strengths of this survey are the relatively high response rate and the participation of all types of hospitals (e.g. academic, tertiary). Therefore we believe that this survey does reflect the status of the use of imaging for the detection of synchronous colorectal metastases in the Netherlands.

This study has several limitations. First, the survey was relatively detailed and not all information requested was readily available, especially for the nuclear medicine physician dealing with the FDG-PET/CT technical features. This might explain the lower response rate for this part of the survey. Another limitation is that we did not separate the survey for colon and rectal tumours. As MRI is used for local staging of rectal cancer, there might be a difference in the utilisation of MRI for evaluation of the liver, lung and extrahepatic disease between patients with colon cancer or rectal cancer.[19] We chose not to perform a different survey for colon tumour and rectum tumour to enhance participation. Finally, not all management and radiology surveys were obtained from the same hospitals. However, the majority of these surveys were obtained from the same hospitals (n=50).

The Dutch guideline indicates either computed tomography (CT) or magnetic resonance imaging (MRI) as the first choice for liver staging.[1,20,21] This survey demonstrated that the role of MRI for staging is less prominent in daily practice as could have been expected based on the literature, where MRI has shown to have higher sensitivity rates for the detection of liver metastases than CT.[17,18,22,23] As the liver is the primary organ for metastatic spread (15%) of colorectal cancer, the use of the technique with the highest sensitivity seems obvious. Further, in patients with rectal cancer MRI is already part in the work-up for local staging. Presumably, lack of expertise, more limited availability and higher costs are important reasons for this rather limited use of MRI.

Table 5. *PET and PET/CT features in the hospitals using these modalities for evaluation of synchronous liver, lung and extrahepatic metastases*

PET features					CT features						PET/CT image analyses
Fasting (hours)	Amount FDG	Scan time	Time after FDG injection (min)	PET analyses	Slice CT	Low dose (mAs/kV)	High dose (mAs/kV)	IV contrast and amount Iodine	Phases (sec)	Oral contrast	Image analysis by
6	3 MBq/kg	3 min/bp	60	Qualitative* †							
6	4.6 MBq/kg	5 min/bp	60	Qualitative*							
6	NA	NA	60	Qualitative Quantitative	16	YES (50/120)	NO	NO		NO	Nuclear medicine physicians‡
6	3.45 MBq/kg	4 min/bp	55-65	Qualitative	16	YES (NA/NA)	NO	NO		NO	Nuclear medicine physicians
6	2.0 - 2.2 MBq/kg	3 min/bp Total 7 positions	60	Qualitative	40	YES (40/120)	NO	NO		NO	Radiologists and nuclear medicine physicians
6	3.0 MBq/kg	3 min/pb Total 7 positions	60	Qualitative	40	YES (20/130)	NO	NO		100 ml Telebrix 350	Radiologists and nuclear medicine physicians
4	3.2 MBq/kg	Total 24-32 min	50	Quantitative	16	NO	YES (150-250/120)	YES (36 gr)	Portal (70s)	NO	Radiologists and nuclear medicine physicians
4	Based on BMI	3 min/bp Total 7 positions	60	Qualitative Quantitative	16	YES (60/120)	YES 150/120	YES (30 gr)	Portal (60s)	25 ml Telebrix	Radiologists and nuclear medicine physicians
6	3.125 MBq/kg	1.45 min/bp	60	Qualitative Quantitative	10	YES (62/120)	YES (100/120)	YES (30-36 gr)		NA	Radiologists and nuclear medicine physicians
6	Based on BMI	3-5 min/pb Total 24-40 min	60	Quantitative	6	YES (40/130)	YES (90/130)	YES (36 gr)	Portal (70s)	NO	Radiologists and nuclear medicine physicians
6	3.0 MBq/kg	Total 25 min	60	Qualitative	16	YES (25/120)	YES (350/120)	YES (31.5 gr)	Arterial (NA) Portal (70s) Late (300s)	10 ml Omni-paque 350	Radiologists and nuclear medicine physicians
6	1.7 MBq/kg	3 min/bp	60-90	Qualitative Quantitative	6	YES (NA/NA)	YES (95/110)	YES (36 gr)	Portal (45-50s)	NA	Radiologists and nuclear medicine physicians
6	Based on BMI	Total 20-22 min	60	Qualitative	16	YES (30/140)	YES (250/120)	YES (NA)	Arterial (30s) Portal (90s)	100 ml Omni-paque	Radiologists and nuclear medicine physicians
4	2.7 MBq/kg	2.30 min/bp	45	Qualitative Quantitative	64	YES 20/120	YES§ (175/120)	YES‖ (39.6 gr)	Arterial (25s) Portal (70s) Late (360s)	50 ml Telebrix 350	Low dose: nuclear medicine physicians High dose: Radiologists and nuclear medicine physicians
4	3.0 MBq/kg	4 min/bp	60	Qualitative	64	YES (NA/NA)	YES§ (NA/NA)	YES‖ (NA)	Portal (NA)	NO	Radiologists and nuclear medicine physicians
4	Based on BMI	4 min/bp Total 5 -6 positions	60	Qualitative Quantitative	40	YES (30/120)	NO	NO		NO	Radiologists and nuclear medicine physicians

bp = bed position; * FDG-PET data were visually compared with either CT or MRI; mAs = radiation intensity; NA = not available; † FDG-PET data were used for fusion with CT using software; ‡ 80% is always performed with low-dose CT and therefore read by nuclear medicine physicians; § high-dose CT is not always performed; ‖ contrast agent is only administrated for high-dose CT scans.

For evaluating lung metastases, the Dutch guidelines recommend the use of conventional chest X-ray[1,20,21] as different studies, including a recent Dutch study, have shown the limited role of chest CT (chest CT has many false-positives).[12] However the UK guideline prefers chest CT[24] and USA guidelines recommend conventional chest X-ray for colon cancer,[25] and in case of resectable rectal cancer an additional chest CT.[26] From a practical point of view, a chest CT is a simple addition to the – widespread utilised – CT for detection of liver and extrahepatic diseases and this presumably explains this inconsistency between evidence and daily practice/guidelines. This difference in viewpoints is reflected in the results of this survey where both chest CT as well as conventional chest X-ray are used to a comparable extent. In addition, some responders noted that chest CT was predominantly used for staging of rectal cancer which is in line with the USA guideline. As the prevalence of lung metastases is higher in rectal cancer compared with colon cancer,[27] the role of chest CT should be more clearly defined in the Dutch guidelines and differentiating between patients with colon cancer and rectal cancer might be a sensible approach.

For the evaluation of extrahepatic abdominal disease, no recommendations were made in the Dutch guidelines.[1,20,21] In international guidelines CT is preferred as is also seen in our survey. This may be different between patients with rectal and colon cancer, where in the former MRI is used for local staging and might be extended as an abdominal MRI.[24-26]

The Dutch guidelines lag behind in following current insights into the role of FDG-PET and FDG-PET/CT.[28,29] In USA guidelines these modalities are already playing a major role[24] and this is also seen in clinical practice to some extent. However, the role of FDG-PET and FDG-PET/CT as routine investigation in staging CRC is not well established and is primarily used in specific groups of patients.[30]

In summary, the present Dutch guidelines on staging of patients with colorectal cancer are only partly in line with recent international guidelines and on some aspects there is considerable discrepancy between the guideline and the findings of the survey. A potentially important reason for this discrepancy between guideline and daily practice – as well as between guidelines – is the lack of cost-effectiveness studies comparing different strategies. Hospitals will therefore either use a commonly used established strategy or develop a different strategy based on variable weighting of different issues, including evidence, availability and costs. This leads to variation in work-up with either over- or under-utilisation of imaging techniques. Research into the optimal strategy of staging of patients with CRC is therefore mandatory.

There is only one German study comparing the costs of whole body MRI with the costs of a conventional diagnostic algorithm for the staging of rectal cancer, consisting of abdominal ultrasound and chest X-ray (chest/abdominal CT in the case of positive findings at abdominal ultrasound or chest X-ray).[19] They reported substantial savings when whole-body MRI was used for the preoperative TNM staging of patients with rectal cancer; however, no data on the effectiveness in terms of diagnostic accuracy have been reported.

We therefore propose to perform cost-effectiveness studies for the comparisons of different staging strategies for colon and rectal cancer separately, including comparing a strategy of CT liver/abdomen versus MRI liver/abdomen for the evaluation of liver and extrahepatic disease and chest X-ray or chest CT for lung metastases and studying the additional role of FDG-PET and FDG-PET/CT. Based on these data well-founded adjustments can be made to the present guidelines

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CASE REPORT

Therapeutic challenges in elderly patients with symptomatic hypercalcaemia caused by primary hyperparathyroidism

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ABSTRACT

Background: Hypercalcaemia resulting from primary hyperparathyroidism (PHPT) can cause a wide range of symptoms, including cognitive disorders, psychiatric symptoms and muscle weakness. Parathyroid surgery is the only definite cure for PHPT. When surgery is contraindicated or patients decide against it, several non-surgical treatment options are available.

Objective: To illustrate the treatment options of symptomatic hypercalcaemia caused by PHPT in the elderly and discuss these options in consideration of the available evidence.

Design: Consecutive case series.

Setting: University hospital.

Patients: Four older patients aged 79-87 years with symptomatic hypercalcaemia resulting from PHPT.

Results: Three patients had a parathyroid adenoma shown on a sestamibi scan. Normocalcaemia and resolution of symptoms was achieved by different treatment scenarios encompassing forced saline hydration, forced diuresis, intravenous pamidronate and cinacalcet, a calcimimetic drug. In one patient, no parathyroid abnormalities were revealed with imaging. Treatment with cinacalcet resulted in normocalcaemia and a strong improvement of symptoms.

Conclusion: In clinical practice, different treatment scenarios are chosen for the treatment of elderly patients with symptomatic hypercalcaemia caused by PHPT. The introduction of cinacalcet offers a new treatment paradigm. We propose to apply cinacalcet preceding elective surgery as an alternative option to standard therapy or as maintenance dose when surgery is not possible.

KEYWORDS

Calcimimetics, drug therapy, elderly, hypercalcaemia, hyperparathyroidism

INTRODUCTION

Hypercalcaemia resulting from primary hyperparathyroidism (PHPT) is one of the reversible causes of cognitive disorders in the elderly.[1] Apart from cognitive disorders, a wide range of other symptoms can occur, including psychiatric symptoms and muscle weakness.[2-4] Associated complications of PHPT include nephrolithiasis and osteoporosis.[3,4] Consequently, these symptoms and complications can cause a significant impairment in cognitive and functional status, and wellbeing. Efficient diagnosing and adequate treatment can prevent and resolve these problems. In most patients (99%), the cause of PHPT is benign, particularly a single adenoma (85%).[3,5] Different advanced imaging techniques are available, including CT imaging and sestamibi scanning, but in practice results are not always conclusive. A DEXA scan for diagnosing osteoporosis as an adverse effect of hyperparathyroidism is only necessary if certain other risk factors are present, such as a previous fracture, low body weight, etc., in accordance with the CBO guideline for osteoporosis and fracture prevention 2011.[6] Once PHPT is diagnosed, there are several treatment options, all with their specific advantages and disadvantages.[2,5] To illustrate these therapeutic challenges in clinical practice, we present four elderly patients with symptomatic hypercalcaemia caused by PHPT with their specific treatment scenarios.

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Furthermore, we discuss the treatment options of symptomatic hypercalcaemia in elderly PHPT patients in consideration of the available evidence.

METHODS

Case series of four elderly patients with hypercalcaemia resulting from PHPT admitted to the University Medical Center Utrecht, between November 2008 and July 2009.

ILLUSTRATIVE CASE REPORTS

An 84-year-old woman was admitted because of low back pain, nausea, cognitive disorders including confusion, a failing short-term memory and hallucinations, muscle weakness and a depressed mood. She had a history of a hip fracture and osteoporosis. Investigations included a raised ionised calcium of 1.46 mmol/l (reference values 1.15 to 1.32 mmol/l), parathormone of 14 pmol/l (1-6 pmol/l) and 1,25-di-OH-vitamin D of 267 pmol/l (47.0 to 130.3 pmol/l). The calcium and vitamin D suppletion were stopped. Spinal MR imaging showed old wedge fractures (Th10-12, L5), while CT imaging and a sestamibi scan revealed a sub-aortic mediastinal parathyroid adenoma. Symptomatic treatment with the calcimimetic drug cinacalcet was started. After consultation with a surgeon, elective parathyroidectomy was planned and the patient was discharged in a relatively good condition. Within three weeks, acute readmission was necessary because of progressive nausea, probably a side effect of cinacalcet. After uncomplicated parathyroidectomy, calcium and parathormone levels normalised and symptoms largely attenuated.

A 79-year-old woman with a history of coeliac disease, secondary osteoporosis, hyperparathyroidism and a hip fracture was admitted because of a persisting ionised hypercalcaemia (1.48 mmol/l) and raised parathormone (19 pmol/l) with a normal 25-OH-vitamin D (31 nmol/l). Symptoms were progressive confusion, muscle weakness and under eating. Calcium and vitamin D suppletion had already been stopped six months before admission. CT imaging and a sestamibi scan revealed no parathyroid abnormalities. Treatment with cinacalcet resulted in normalisation of the ionised calcium (1.16 mmol/l) and a strong improvement of the cognitive and mobility problems. Surgical treatment was not performed.

An 80-year-old woman with known diabetes mellitus and hypertension was admitted because of symmetrical muscle weakness and fluctuating confusion. Laboratory investigations revealed a raised ionised calcium (1.65 mmol/l) and parathormone (19 pmol/l) with a normal 25-OH-vitamin D (53 nmol/l). Evidence for a parathyroid adenoma located caudodorsally to the thyroid gland was found on a sestamibi scan. Echography and a CT scan did not reveal parathyroid pathology. Treatment with forced saline hydration, forced diuresis and intravenous pamidronate resulted in normalised calcium with total resolution of symptoms. Two months later, uncomplicated parathyroidectomy was performed.

An 87-year-old woman was admitted because of confusion and repeated falls. She had an extended history with multiple bone fractures caused by falls since the age of 50, osteoarthritis, osteoporosis and a transient ischaemic attack. A sestamibi scan was performed because of an increased ionised calcium (1.56 mmol/l) and parathormone (9.6 pmol/l). This revealed a parathyroid adenoma located caudodorsally to the thyroid gland. Forced saline hydration did not result in sufficient reduction of the calcium level. Subsequent treatment with cinacalcet resulted in normalisation of the calcium with disappearance of symptoms. Two weeks later, successful parathyroidectomy was performed.

DISCUSSION

This case series illustrates different therapeutic scenarios in elderly patients with symptomatic hypercalcaemia caused by PHPT applied in clinical practice.
Recently, several reviews have focused on the current available treatment options in the management of patients with PHPT.[1,2,5] Sims *et al.*[1] report that the indications for parathyroid surgery, encompassing hypercalcaemia, renal disease, bone disease, abdominal or neuropsychiatric symptoms, are not changed by advancing age. Parathyroid surgery is the only definite cure for PHPT, but the risks and benefits of surgery need to be extensively considered in the elderly given their more fragile status and comorbidity. Preoperative imaging with echography, CT and sestamibi scans may help in the decision to offer surgery.[7] When surgery is contraindicated or patients decide against it, different non-surgical alternatives are available.[1,2] For acute treatment of severe hypercalcaemia, intravenous saline solution loop, diuresis and bisphosphonates are recommended.[2] Subcutaneous calcitonin is also an option, but its efficacy is limited to the first two days.[2] Cinacalcet, a calcimimetic drug, lowers PTH secretion by enhancing receptor sensitivity to extracellular calcium. Normocalcaemia can be achieved after one day of treatment, the response to cinacalcet can be persistent and cinacalcet is generally well tolerated.[4,8,9] The most common adverse events are nausea, vomiting and paresthesias.[10] Raloxifene and oestrogen therapy are

not recommended as first-choice treatment for elderly women because of the marginal effects on hypercalcaemia and the associated adverse events and risks.[1,4] General recommendations include avoidance of calcium-enhancing drugs (e.g. thiazide diuretics and lithium carbonate), of volume depletion by encouraging patients to drink sufficiently, and of vitamin D insufficiency.[5] Vitamin D deficiency stimulates PTH secretion and bone resorption. A low calcium diet may lead to further increases in PTH secretion and could aggravate bone disease. Moderate calcium restriction (<800 mg/day) is probably warranted when the serum vitamin D levels are high. In cases of resistant, life-threatening hypocalcaemia (>4.5 mmol/l or >18 mg/dl) haemodialysis against a low-calcium dialysate is necessary.

Given the available evidence and recommendations, our case series illustrates that different scenarios are chosen in clinical practice for the treatment of elderly patients with symptomatic hypercalcaemia caused by PHPT. However, little literature is available about medical treatment of symptomatic hypercalcaemia specifically in the elderly. No evidence-based recommendations have been made concerning the alternative treatment options besides surgery for this patient group. Conroy *et al.* (2003),[11] Boonen *et al.* (2004)[12] and Sims *et al.* (2004)[1] discussed the nonsurgical management of primary hyperparathyroidism in older patients, but the best treatment of symptomatic hypercalcaemia remained unclear and no algorithm was presented which encompasses current medical treatment options for elderly patients. The authors concluded more randomised controlled studies are necessary to provide recommendations concerning treatment of PHPT in the elderly, mainly for calcimimetics. Nowadays, cinacalcet seems a promising and relatively safe drug for the management of hypercalcaemia, as recent randomised double-blind placebo-controlled trials showed that cinacalcet normalises calcium and lowers serum PTH with similar rates of adverse events between treatment and placebo groups, but no effect on bone mineral density.[8-10] Recently, Aw[13] reviewed surgical and nonsurgical treatment options in the elderly and presented a short summary algorithm without focus on treatment options before elective surgery. However, a stepwise algorithm combining the treatment options of symptomatic hypercalcaemia in elderly patients before elective surgery as well as the treatment options when surgery is contraindicated is useful in clinical practice. Thus, we present a stepwise therapeutic algorithm for the management of elderly patients with symptomatic hypercalcaemia caused by PHPT (*figure 1*). In this algorithm, the introduction of calcimimetics offers a new treatment paradigm given the relatively fast mode of action and infrequent undesired effects. We propose to apply cinacalcet in symptomatic hypercalcaemia preceding elective surgery as an alternative option to the standard therapeutic strategies or as maintenance dose when surgery is contraindicated or decided against. Definite determination of the most appropriate treatment regimen for cinacalcet in elderly patients with symptomatic hypercalcaemia caused by PHPT, however, is not yet completed,[5,14-16] as more evidence is needed concerning both its short- and long-term efficacy and adverse events.

Figure 1. *Therapeutic algorithm for the management of elderly patients with symptomatic hypercalcaemia caused by primary hyperparathyroidism (PHPT)*

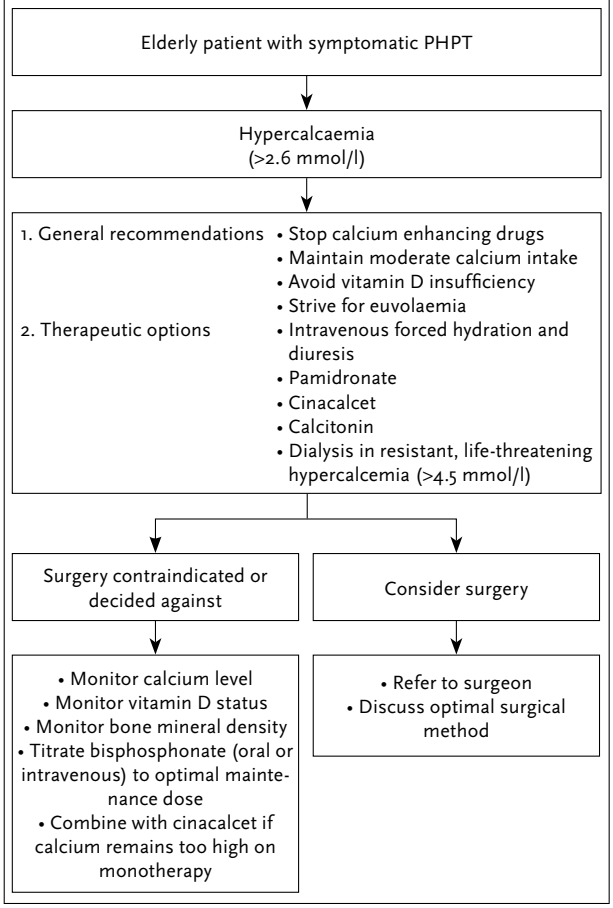

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PHOTO QUIZ

An unusual complication of a central venous catheter placement

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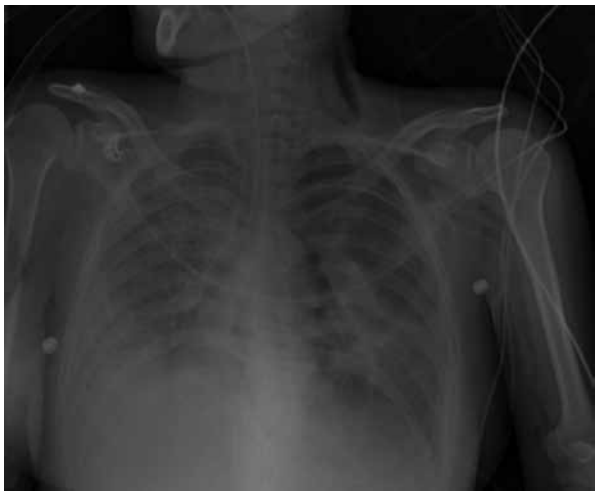
CASE REPORT

A 46-year-old woman was admitted to the intensive care unit with progressive liver failure. She was put on mechanical ventilation because of progressive respiratory failure and adult respiratory distress syndrome (ARDS). A central venous catheter was inserted in the left subclavian vein. During the procedure, air was aspired and a pneumothorax was suspected. Afterwards, plain radiography of the chest was taken (*figure 1*).

Figure 1. *X-ray of the thorax after placement of a central venous catheter in the left subclavian vein*



WHAT IS YOUR DIAGNOSIS?

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PHOTO QUIZ

An unusual cause of hyperandrogenism

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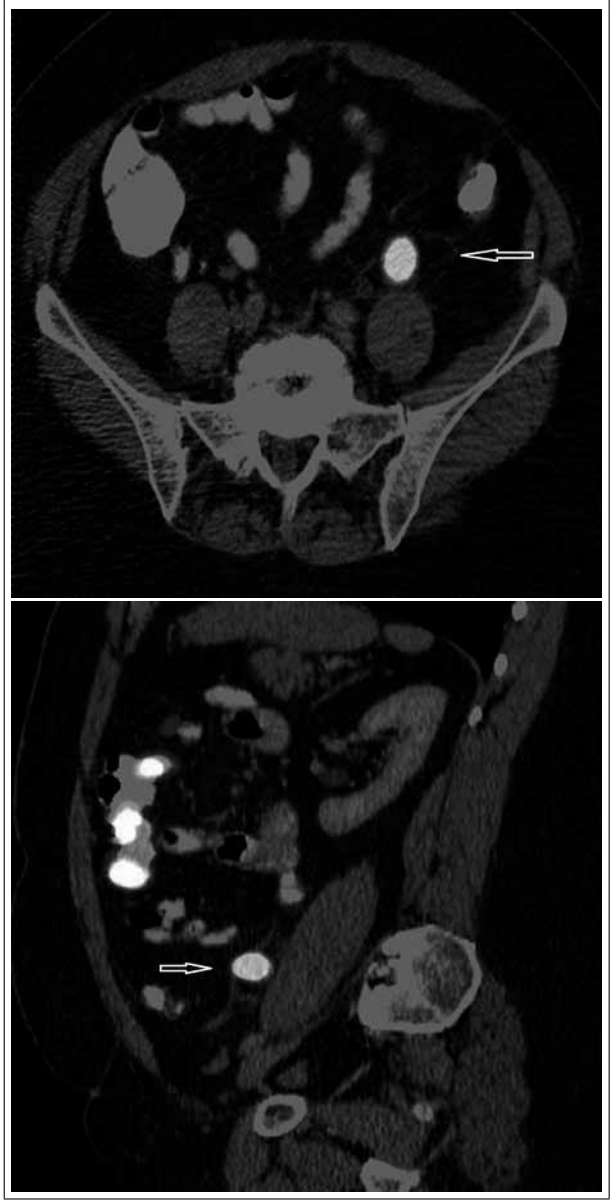
CASE REPORT

A 66-year-old woman was referred with complaints of increased libido and clitoral hypertrophy. Her medical history showed a caesarean section, and 19 years before, in 1992, she was diagnosed with cancer of the left breast (T3N3M0 adenocarcinoma). For this she underwent mastectomy, followed by chemotherapy.

She complained of an increase in libido in the last 18 months as well as an increase in facial hair. She had noted clitoral hypertrophy, which had been present for 1.5 years. Physical examination revealed a masculine, overweight woman. The abdomen showed a few dark hairs on the linea alba, but no other signs of hirsutism. At inspection the clitoral hypertrophy was evident. Further physical examination was unremarkable. There were no clinical signs of Cushing's syndrome. Routine laboratory results were unremarkable. The specific laboratory results showed a serum testosterone level of 24.6 nmol/l (normal 0.2 to 3.0 nmol/l), dehydroepiandrosterone sulphate (DHEAS) of 2.9 μmol/l (normal 1.3 to 3.9 μmol/l) and androstenedione was 7.4 nmol/l (normal 0.0 to 5.4 nmol/l). Computed tomography of the abdomen showed no abnormalities in the adrenal region, but a 2 cm large lesion in the region of the left ovary was reported. Bilateral ovariectomy was advised and performed. The surgical procedure was uneventful, but the ovaries were not enlarged. Pathological examination showed normal ovarian tissue. After surgery, all clinical signs persisted and testosterone level remained elevated. Therefore additional investigations were performed. A five-day dexamethasone suppression test showed a cortisol suppression to <55 nmol/l, but no suppression of the androgens. Single photon emission computer tomography (SPECT) with ^{131}I-6β-iodomethyl-19-norcholesterol was performed, which revealed a lesion located in the mesosigmoid shown in *figures 1* and *2*.

Figure 1 and 2. *Three days after injection of ^{131}I-6β-iodomethyl-19-norcholesterol there is a hotspot shown on the SPECT in the lower abdomen*



WHAT IS YOUR DIAGNOSIS?

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PHOTO QUIZ

Bubbles in the urinary bladder

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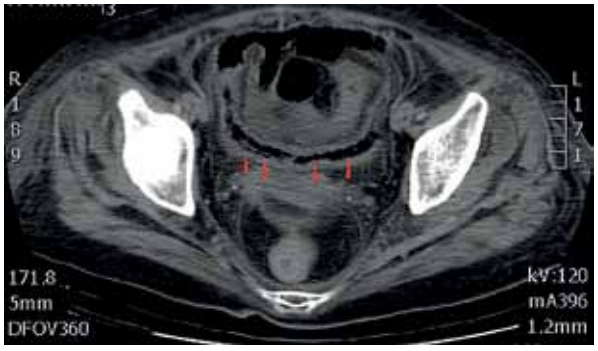
A 51-year-old woman with a recent history of intestinal strongyloidiasis, hyperthyroidism, and diabetes mellitus presented with consciousness disturbances and septic shock. At our intensive care unit, palpation of the lower abdominal area revealed a firm baseball-like mass. Acute urinary retention was considered, and the patient was catheterised with a Foley catheter. The effluent consisted of bloody urine with a large amount of air inside the drain bag. The results of laboratory evaluation revealed a white blood cell (WBC) count of 24,570 cells/mm^3 made up of 63% segmented and 28.5% band neutrophils, a haemoglobin level of 9.7 g/dl, and serum creatinine level of 1.1 mg/dl. Urinalysis showed numerous red blood cells and 5 to 10 WBCs/µl. Computed tomography (CT) images showed multiple air densities within the urinary bladder wall (*figure 1*).

Figure 1. *After Foley catheterisation, abdomino-pelvic CT images revealed both intravesicular gas formation and a characteristic mottled 'cobblestone' appearance of radiolucency within the thickened urinary bladder wall (arrowheads)*



What is your diagnosis?

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Netherlands
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Maculopapular rash and fever

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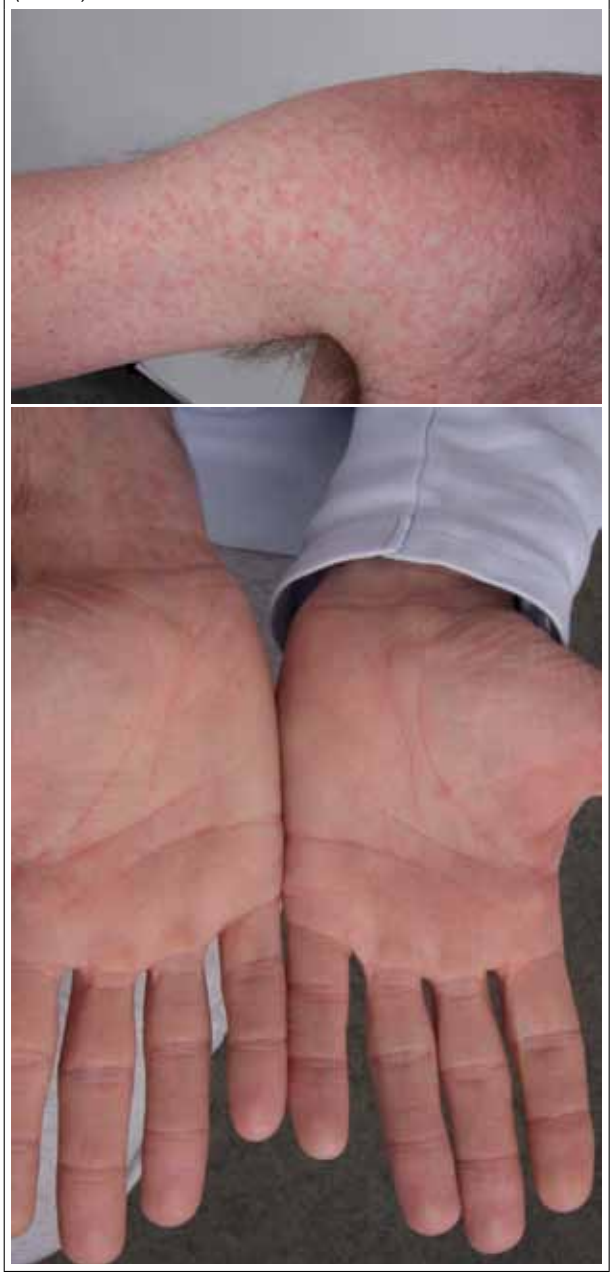
A 38-year-old man with no relevant previous medical history presented at our outpatient clinic with fever, malaise, dry cough and sore throat for six days. The day before presentation he had developed a non-itching rash on his face, trunk and arms. He had returned from Crete seven days earlier where he had stayed in an all-inclusive resort for two weeks with his wife and children (aged 2, 4 and 6 years). Two of his children had complained of aphthous lesions in the mouth but had otherwise not been ill. He had not been in contact with animals or insects and was not on any medication at the time of presentation.

On physical examination the patient was febrile with a temperature rising to 40.2 °C. An erythematous and maculopapular rash was apparent on the torso, face and to a lesser extent on the extremities and hand palms (*figure 1*). Furthermore, he had pharyngitis and the cervical, post-auricular and inguinal lymph nodes were slightly enlarged. Blood analysis results showed an elevated C-reactive protein (12.8 mg/l), leukopenia of 2.0 giga/l with a lymphopenia (0.3 giga/l) and 28% rods and a mild thrombocytopenia (146 giga/l). Chest X-ray showed no abnormalities.

Figure 1. *An erythematous and maculopapular rash on the torso (above) and the extremities and hand palms (below)*



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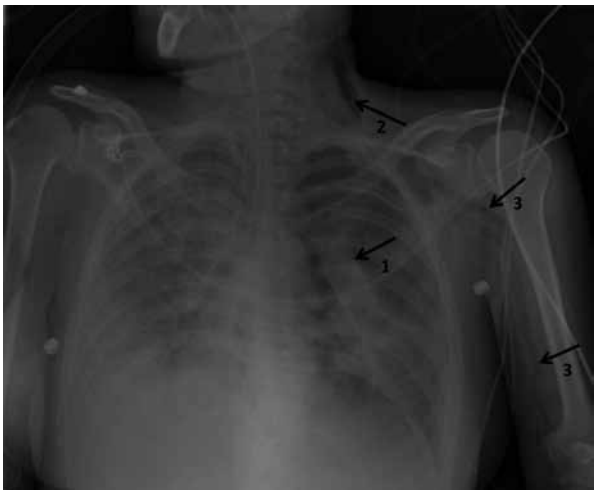
ANSWER TO PHOTO QUIZ (PAGE 40)

AN UNUSUAL COMPLICATION OF A CENTRAL VENOUS CATHETER PLACEMENT

Besides alveolar oedema in both lungs, a pneumothorax is shown on the left as was suspected. Also, subcutaneous emphysema is shown in between the lateral neck musculature together with a pneumovenogram of the veins of the left upper arm. Air embolism is a rare complication of insertion or removal of central venous catheters but can lead to cardiac arrhythmias, obstruction of the pulmonary outflow tract, acute cor pulmonale and asystole, depending on its volume. Also, when moving to the arterial circulation via patent foramen ovale, it can lead to ischaemic events. Gas embolism complicates 2.65 of 100,000 hospital admissions and is associated with high morbidity and mortality.[1] Treatment varies from putting the patient in the Trendelenburg position, 100% oxygen flow or hyperbaric oxygen treatment in order to reduce the volume of the embolus by diffusion of oxygen to the plasma. Luckily, our patient did not have any of the complications mentioned above and a chest tube was inserted to treat the pneumothorax. After a few weeks she was discharged from the ICU.

Figure 2. *Intubated patient with a central venous catheter in the left subclavian vein.*



Arrow 1 shows a pneumothorax on the left with a shift of the mediastinum to the right and pulmonary oedema of the right lung. Arrow 2 shows subcutaneous emphysema and arrow 3 a pneumovenogram of the upper left arm.

Conclusion: Pneumovenogram of the arm after placement of a central venous catheter.

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ANSWER TO PHOTO QUIZ (PAGE 41)

AN UNUSUAL CAUSE OF HYPERANDROGENISM

DISCUSSION

A SPECT with ^{131}I-6β-iodomethyl-19-norcholesterol demonstrated a left-sided lesion, which appeared on the fusion CT to be located in the mesosigmoid, ventral of the iliopsoas muscle. The lesion was metabolically active, which was suggestive of ectopic steroid-producing tissue. After removal of this ectopic adenoma, all symptoms resolved and the androgen levels normalised. Pathological examination revealed that the lesion was an adenoma of ectopic adrenal tissue.

Virilising adrenal tumours are a rare cause of hyperandrogenism, and they are typically associated with high serum levels of DHEAS. However, testosterone-secreting adrenal adenomas with normal levels of DHEAS and androstenedione have been described in a few cases, showing a hormone profile that is similar to that of virilising ovarian tumours.[1]

Ectopic adrenal tissue is usually found in close proximity to the adrenal glands, and along the path of descent or in association with the gonads.[2] However, adrenal tissue has been found in other locations such as the liver, uterus, gallbladder and even the central nervous system, and usually produces cortisol.

To our knowledge there are two reported cases of strictly androgen-producing ectopic adrenal masses, one case localised in the thorax[3] and one case behind the iliopsoas muscle.[4] Initially the hormonal profile and CT scan suggested an ovarian origin. In this case a SPECT with ^{131}I-6β-iodomethyl-19-norcholesterol revealed the real location. Therefore one should consider this investigation when the location of the androgen-producing tumour is unclear or when the ovaries are excluded from the differential diagnosis.

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ANSWER TO PHOTO QUIZ (PAGE 42)

BUBBLES IN THE URINARY BLADDER

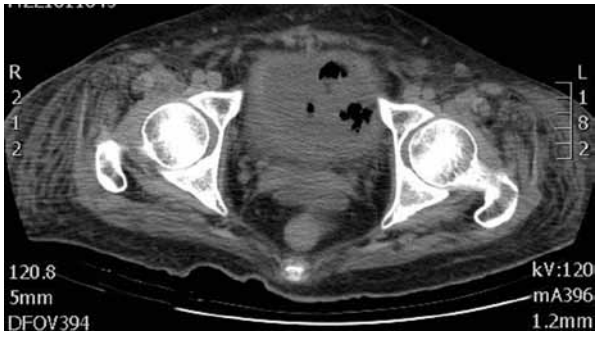
DIAGNOSIS

To treat the septic shock, empirical antibiotics, namely, piperacillin with tazobactam, were immediately administered. Both blood and urine cultures eventually yielded *Escherichia coli*. Ten days later, the residual air was found to have diminished dramatically on follow-up abdominopelvic CT (*figure 2*). Considering the initial presentation and the entire therapeutic course, emphysematous cystitis was diagnosed. The Foley catheter was then removed successfully, and the patient subsequently regained normal urinary function.

Emphysematous cystitis, first described by Bailey in 1961,[1] is a rare clinical condition in which pockets of gas are formed in and around the bladder wall by gas-forming organisms.[2] Patients with diabetes,[3] neurogenic bladder, compromised immune status, and chronic urinary infection are predisposed to the disease, especially if there is an obstruction of the urethra or cervix. Women are affected twice as often as men.[4] The pathological mechanisms of gas formation in emphysematous cystitis are a matter of debate, and bacterial fermentation of either glucose (in diabetic patients) or albumin (in non-diabetic patients) to carbon dioxide is widely hypothesised.[5] Among the organisms reported in the recent literature, *E. coli* is the most prevalent pathogen.[4] The main symptoms of emphysematous cystitis vary widely, ranging from painless gross haematuria to fulminant sepsis. Pneumaturia is rarely observed, but its presence in such patients effectively facilitates the diagnosis of emphysematous cystitis.[6]

First-line imaging modalities, including intravenous urography or abdominal plain films, can usually confirm the diagnosis, which characteristically shows curvilinear or mottled areas of increased radiolucency in the region of the urinary bladder, separate from the more posterior rectal gas.[7] Intraluminal gas presents as an air-fluid level that changes with the patient's position and, when adjacent to the nondependent mucosal surface, may have a cobblestone or 'beaded necklace' appearance.[8] This finding reflects the irregular thickening produced by submucosal blebs as seen by direct cystoscopy.[9] On the other hand, bladder sonography commonly demonstrates diffuse bladder wall thickening with increased echogenicity. CT provides the advantage of early detection of intraluminal or intramural gas[10] and a more accurate delineation of the extent and severity of emphysematous cystitis. Other causes of intraluminal gas can also be differentiated by CT, such as enterovesical fistula formation from adjacent bowel carcinoma or inflammatory disease.[11] Cystoscopy is useful for differentiating gas in the bladder secondary to an enterovesical fistula; however, it is rarely necessary for the diagnosis of emphysematous cystitis. If gas is identified in the bladder, the differential diagnosis should include the following: enterovesical fistula (caused by diverticulitis, Crohn's disease, or rectosigmoid carcinoma) and recent urinary tract instrumentation.[12]

Figure 2. *Ten days later, a follow-up CT image showed disappearance of the intramural air and dramatically diminished air density within the urinary bladder*



Treatment of emphysematous cystitis depends on early broad-spectrum antibiotics, drainage of the bladder, and glycaemic control.[2] The initial antibiotic choice should focus on aerobic and anaerobic pathogens — even including potential fungal infections. Urinary drainage with a urethral catheter usually suffices to reduce the pathogen burden directly within the bladder. Rarely, surgical debridement is needed if an abscess develops outside the bladder.[2] Treatment of hyperglycaemia will decrease glycosuria — the bacterial substrate for gas formation. Although the prognosis in patients diagnosed and treated early in the disease process is usually favourable, this disease is potentially fatal.[4] The development of emphysematous ureteritis, nephritis, or adrenalitis heralds a poor prognosis.[2] In patients with uncontrollable necrotising infections, combined medical and surgical interventions are warranted, such as partial or total cystectomy and nephrectomy for emphysematous pyelonephritis.

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ANSWER TO PHOTO QUIZ (PAGE 43)

MACULOPAPULAR RASH AND FEVER

DIAGNOSIS

Our differential diagnosis included rickettsiosis, measles, lues, rubella and acute HIV infection. Antibiotic treatment with doxycycline was started. Serological analyses showed high titres of anti-measles IgM (8.03; reference <1.1) whereas IgG titres were merely elevated (0.84; reference: >0.7). Additionally, measles DNA was detected in urine and saliva samples using polymerase chain reaction, confirming the diagnosis of measles. The antibiotics were stopped and the patient was treated with supportive care. After discharge he also developed a measles-related keratitis from which he recovered completely.

Measles is a very contagious disease caused by measles virus, which usually presents with high fever followed by a characteristic rash. It rarely occurs in the Netherlands since the introduction of a single-dose vaccine in 1976. The vaccination coverage has been >95% since the introduction of a two-dose regimen of MMR vaccine in 1986. The last outbreak was reported in 2008 and included 99 measles cases, mainly amongst unvaccinated patients.[1,2] In March 2011 there were 14 reports of measles infections in the Netherlands. Also this year there have been outbreaks and a marked increase in the numbers of cases reported in several other European countries.[3,4]

Our patient was born before 1976 when the vaccine was introduced in the National vaccination programme and had therefore not been vaccinated. His wife and children were vaccinated. Most adults who grew up before 1976 have been in contact with the virus as a child and have therefore developed natural immunity. It seems that adults born between 1970 and 1976 are less likely to have natural immunity and are therefore at risk. Clinicians should be aware of measles as a possible cause in patients presenting with a febrile illness with an erythematous and maculopapular rash, especially in patients of this age group.

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Netherlands
The Journal of Medicine

SPECIAL ARTICLE

Displaying chest X-ray by beamer or monitor: comparison of diagnostic accuracy for subtle abnormalities

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ABSTRACT

***Background*: The advent of beamer projection of radiological images raises the issue of whether such projection compromises diagnostic accuracy. The purpose of this study was to evaluate whether beamer projection of chest X-rays is inferior to monitor display.**

***Methods*: We selected 53 chest X-rays with subtle abnormalities and 15 normal X-rays. The images were independently judged by a senior radiologist and a senior pulmonologist with a state-of-art computer monitor. We used their unanimous or consensus judgment as the reference test. Subsequently, four observers (one senior pulmonologist, one senior radiologist and one resident from each speciality) judged these X-rays on a standard clinical computer monitor and with beamer projection. We compared the number of correct results for each method.**

***Results*: Overall, the sensitivity and specificity did not differ between monitor and beamer projection. Separate analyses in senior and junior examiners suggested that senior examiners had a moderate loss of diagnostic accuracy (8% lower sensitivity, p<0.05, and 6% lower specificity, p=ns) associated with the use of beamer projection, whereas juniors showed similar performance on both imaging modalities.**

***Conclusion*: These initial data suggest that beamer projection may be associated with a small loss of diagnostic accuracy in specific subgroups of physicians. This finding illustrates the need for more extensive studies.**

KEYWORDS

Chest X-ray, projection, monitor, beamer, diagnostic accuracy

INTRODUCTION

Nowadays, computer-generated images are commonly used for displaying chest X-rays. Monitors are frequently employed, but beamer projection is also used for presentation and evaluation of X-rays during clinical rounds and conferences. There are differences in optical characteristics between beamer projection and monitors. In particular, beamers have inferior performance in terms of contrast and resolution, and sensitivity to ambient light intensity.[1-7] This may pose a problem in the interpretation of more subtle abnormalities.

We set out to investigate whether beamer projection of chest X-rays is inferior to monitor display. Our hypothesis is that beamer projection results in underdiagnosis of relatively subtle abnormalities.

MATERIALS AND METHODS

A senior pulmonologist and radiologist collected 53 chest X-rays which they judged unanimously to show subtle abnormalities. They also collected 15 normal chest X-rays. The X-rays were reviewed by both physicians independently on a state-of-the-art radiological computer monitor (NEC md213mc or similar type). They reached consensus either directly or after brief deliberation. We used this consensus judgment as the reference standard.

Four observers (one senior pulmonologist, one senior radiologist, both with over five years of clinical experience, and one junior resident of each speciality) participated in the observer study. They independently judged the set of images on a computer monitor and with beamer projection. The interval between these sessions was two weeks, the order of cases was randomised for each

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projection session to prevent recognition and avoid learning bias. They were asked to record the nature and location of each abnormality they observed.

During the viewing sessions, we used standard computer monitors and beamers that are commonly used in hospitals. The monitors that were (randomly) used were: Dell 1908 WFP (brightness: 300 cd/m²; contrast: 1000:1), Dell 1708 FPT (brightness: 300 cd/m²; contrast: 800:1), Dell 1704 FPT (brightness: 300 cd/m²; contrast: 500:1) and Philips MCL 1801 (brightness: 270 cd/m²; contrast: 400:1). The beamer projectors that we used were: ASK C170 (brightness: 2000 lumen; contrast 1000:1), ASK 460 (brightness: 3500 lumen; contrast 750:1), ASK 200 (brightness: 2500 lumen; contrast 800:1) and ASK 160 (brightness: 1700 lumen; contrast 400:1). The viewing time per chest X-ray was limited to 60 seconds. If less than 60 seconds were used, the time was recorded. During the reading sessions, observers were allowed to use the image manipulation functions (brightness, contrast, magnification). Ambient light intensity in the room was standardised to around 100 lux.

Data analysis

Data were analysed overall as well as in five separate categories: 1) discrete/solid abnormalities in lung parenchyma, 2) diffuse intrapulmonary abnormalities, 3) pleural/thoracic wall, 4) mediastinum/heart/hilus and 5) remaining (*table 1*). We compared correct diagnostic classifications for each imaging modality, and used the Z-test for proportions to compare sensitivities and specificities between visualisation modalities.

RESULTS

The first two rows of *table 2* show if the observers identified identical abnormalities compared with the reference standard. The sensitivities and specificities are essentially identical (60% against 58% and 53% against 53%).

Also displayed in *table 2* is the time observers took for reviewing the X-rays, which did not differ between monitor en beamer projection (49 seconds for both).

Table 3 summarises the mean sensitivities for the diagnosis categories 1 and 2. The remaining categories were not analysed separately because the number of X-rays in these groups was too small (13, 9 and 9 respectively). The mean sensitivities are essentially identical between categories. *Table 3* also specifies sensitivities divided by specialists and residents. In terms of sensitivity, specialists performed moderately better on the monitor, and the resident did moderately better on the beamer (not significant). Overall, diagnostic sensitivity on the beamer is 53% for specialists and 71% for residents, which is a significant difference ($p<0.05$ by *Z*-test for proportions).

Table 4 summarises mean specificities for the diagnosis categories 1 and 2. As was the case for sensitivities, mean specificities are essentially identical between categories. Also in line with *table 3*, the specialists perform slightly worse on the beamer projection than on the monitor (not significant), while there is no similar difference among residents. The higher overall specificity among residents compared with specialists is not statistically significant.

Table 1. *Categories of chest X-ray abnormalities*

Category	Common abnormalities
1. Discrete/solid abnormality in lung parenchyma	Solid mass Bullae
2. Diffuse intrapulmonary abnormality	Infiltrate Diffuse consolidations Redistribution of blood flow Emphysema Bronchiectasis
3. Pleural/thoracic wall	Pleural effusion
4. Mediastinum/ heart/hilum	Expanded mediastinum Aorta abnormalities Hilar abnormalities Peribronchial cuffing Abnormal cardiac silhouette
5. Remaining	Corpus alienum Intravenous catheter Elevated diaphragm Prosthetic heart valve Clavicular fracture

Table 2. *Sensitivity and specificity (95% CI) of monitor versus beamer visualisation of subtle chest X-ray abnormalities*

	Monitor	Beamer
Sensitivity	61% (56-66%)	57% (56-62%)
Specificity	53% (41-65%)	53% (40-65%)
Time used for judging X-rays	49 seconds	49 seconds

Table 3. *Sensitivity (mean, 95% CI) per diagnosis category and per observer experience*

Category	1	2	1+2
Monitor	63%	64%	64% (57-69%)
Beamer	60%	63%	62% (55-68%)
Specialists monitor	59%	63%	61% (52-69%)
Residents monitor	68%	65%	66% (58-74%)
Specialists beamer	49%	57%	53% (44-61%)
Residents beamer	72%	70%	71% (62-78%)*

1: Discrete/solid intrapulmonary abnormalities; 2: Diffuse intrapulmonary abnormalities; *significantly ($p<0.05$) different from 'mean specialist beamer' sensitivity.

Table 4. *Specificity (mean, 95% CI) per diagnose category*

Category	1	2	1+2
Monitor	58%	58%	58% (54-62%)
Beamer	55%	55%	55% (51-59%)
Specialists monitor	58%	57%	58% (52-63%)
Residents monitor	58%	60%	59% (54-65%)
Specialists beamer	54%	51%	52% (46-58%)
Residents beamer	57%	59%	58% (52-63%)

1: Discrete/solid intrapulmonary abnormalities; 2: Diffuse intrapulmonary abnormalities.

DISCUSSION

This study shows no convincing difference in diagnostic accuracy between beamer projection and computer monitors. The time needed for assessing the X-rays does not differ on beamer projection and computer monitor. Separate analyses in senior and junior examiners suggested that senior examiners had a moderate loss of diagnostic accuracy associated with use of beamer projection, particularly in terms of sensitivity. Whether or not this could be related to a higher degree of educational exposure to beamer projection in juniors cannot be concluded from this study, but clearly is a possible explanation.
This is the first study to address this issue. Furthermore, an important feature of our design is that we exclusively used X-rays with a subtle abnormality or normal X-rays. This explains the limited overall diagnostic accuracy, but we feel a similar study using images with very clearly identifiable abnormalities is not likely to reveal a difference between treatment modalities, and would thus be irrelevant from a practical perspective.

Our study has a few limitations. Although the total number of observations is substantial, only 68 X-rays were used. We divided these X-rays into five different categories, three of which were too small for separate analysis. If indeed the diagnostic accuracy were to be lower for a particular type of abnormality, much larger sets of X-rays would be needed. Also, future studies should include more observers. Our preliminary data provide useful information on the basis of which the required numbers of images and observers for similar future studies can be estimated.

In conclusion, the use of beamer projection does not appear to be associated with a marked loss of diagnostic accuracy. Senior examiners, however, who may have had little exposure to beamer projection during their early professional training, are at risk for missing subtle abnormalities during beamer projection.

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LETTER TO THE EDITOR

Comment on summary of the updated Dutch guidelines for the management of hypertensive crisis

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Dear editor,

In the May issue of this journal, Van den Born and colleagues present the essentials of the updated Dutch guideline for the management of hypertensive crisis.[1] The guideline committee is to be commended for their work, as several aspects of the guideline have clearly been improved, compared with the previous 2003 version.[2] In a number of respects, however, the new guideline is unclear, and important changes in recommendations are neither evidence-based nor appropriately motivated. Our main concerns are as follows:

- In the 2003 guideline, hypertensive crises were distinguished in *emergencies* and *urgencies*. Both were characterised by acute organ damage, the difference between an *emergency* and an *urgency* being the time available for intervention (minutes in an *emergency*, hours in an *urgency*). In the updated guideline, a crisis is still defined by the presence of 'acute target organ damage', but the definition of urgency is 'severe hypertension *without* evidence of acute hypertensive organ damage'.[1] This is confusing at least, if not impossible. It suggests that *urgencies* are basically non-existent as part of hypertensive crises.
  Strange as the implicate abolishment of the hypertensive *urgency* may be, another choice that was made is actually compatible with this: all forms of acute organ damage now suddenly require intravenous therapy. This is advocated not only for retinopathy, but also for microangiopathy and acute renal failure. Nonetheless, the updated guidelines state that effective therapy in these conditions may take up to a few hours. Hence, as opposed to the 2003 guidelines, we now appear to define two types of *emergencies*: 'emergency *emergencies*' and 'urgent *emergencies*'.
- We fail to understand why intravenous therapy is required in all situations where at least several hours are available for blood pressure lowering. Some argue that intravenous therapy is safer in terms of sudden excessive blood pressure drops. Although this may be true theoretically, unstable blood pressure on intravenous drugs is unfortunately a frequent reality. We think that evidence showing that intravenous therapy provides both a safer time course and degree of blood pressure lowering in daily practice is lacking. Also, intravenous therapy necessitates a subsequent transition period to oral drugs, for which no proven safe algorithms are available. Again, unstable blood pressure during this transition period is not infrequent in our clinical experience. Finally, a crucial point to be made is that short-term lowering of blood pressure by >25% should *never* be considered safe. Only in theory is this particularly unsafe in situations of acute organ damage, especially grade III-IV retinopathy and/or encephalopathy.
- What is now defined as a hypertensive *urgency* is basically, as acknowledged by the committee, severe hypertension without acute organ damage. International guidelines on the management of hypertension advocate the use of long-acting antihypertensives in these patients. In fact, in severe hypertension, starting with long-acting combination tablets is recommended.[3] What is the reason for stepping away from these recommendations? Why propose the use of nifedipine-retard tablets? As a result of their shorter half-life, blood pressure instability, particularly after discharge, is a real danger. Also, clinical experience is that moderate doses of long-acting antihypertensives, even as combination tablets, rarely if

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ever cause an excessive drop in blood pressure, which is why international guidelines actually recommend this strategy.[3]

Also, observation for a few hours is advocated in patients with severe hypertension without signs of acute organ damage (i.e. an *urgency*). Although this may be harmless in itself, we do not see the justification for this, let alone for defining an absolute maximum level of blood pressure allowing discharge.

- Finally, the guideline would have been more complete if recommendations had been made for patients who are already on antihypertensives, which is the case for a large proportion of those presenting with severe hypertension. Is nifedipine for example still treatment of choice in those already taking calcium blockers?

In conclusion, the updated guidelines are a step forward in some respects, but a step backward in several others. We contemplated on this when we had to decide what to teach our residents. We decided to recommend they read the guideline carefully, but take terminology and classification with a couple of grains of salt. We teach them that a common mistake is to overestimate the benefit and underestimate the risk of acute lowering of blood pressure. Blood pressure should be lowered as acutely as the associated clinical condition may reasonably be expected to deteriorate. When the acute benefit is less clear, such as in the case of grade III/IV retinopathy without visual disturbance, they should proceed with the attitude of 'first, do no harm'. We thus teach that central to the approach to patients with severe hypertension is the question of whether there are signs of acute organ damage and, if so, what degree of hurry is dictated by common sense and epidemiological evidence is leading. We do not encourage routine use of intravenous drugs when acute blood pressure lowering is not called for, nor do we support the use of short-to-medium long acting drugs for severe hypertension without acute organ damage.

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Rebuttal

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Dear editor,

We thank Smulders *et al*. for commenting on several aspects of the recently published guideline on the management of hypertensive crisis.[1] We cannot but agree that not all changes incorporated in the 2010 revision are evidence-based. This is stated as such in the guideline along with the motivation for the recommendation (and the – grade D – level of evidence). Most such changes were incorporated to concur with international guidelines. In the recent summary we have tried to select the most important changes and motivations of the guideline.[2] We welcome the opportunity to respond to the issues raised by Smulders and colleagues, who have some reservations about definitions and recommendations in the revised guideline.

The first issue raised by Smulders *et al*. involves the definitions for hypertensive urgency and emergencies, which -in contrast to the previous guideline- conform to international guidelines and literature. Smulders *et al*. suggest that hypertensive urgencies cannot be considered a hypertensive crisis because acute target organ damage is lacking. As stated in the summary, a hypertensive urgency

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is essentially a diagnosis of exclusion which can only be made after ruling out acute organ damage (e.g. by ECG, funduscopy). However, despite the lack of acute organ damage these patients are still considered urgent because of their severe blood pressure elevation. To prevent acute organ damage, treatment with oral blood pressure lowering medication is recommended along with a brief period of observation. In general further treatment and analysis can take place at the GP's office or outpatient clinic. In the guideline and summary, hypertensive emergencies are not defined by the promptness by which blood pressure should be lowered, but by the recommendation to start intravenous therapy (under haemodynamic monitoring) to lower blood pressure to safe levels and prevent progressive organ damage. This definition is in line with international literature and guidelines and also includes hypertensive crisis with advanced retinopathy (with or without microangiopathic haemolysis or acute renal failure).

The second issue concerns the choice for intravenous blood pressure lowering therapy in favour of oral blood pressure lowering medication. The disadvantages of oral medication for the treatment of a hypertensive emergency are discussed in the guideline and include the slower onset of action and unpredictable blood pressure lowering efficacy. As recognised by Smulders *et al.* blood pressure reductions exceeding a MAP of 25% should in general be avoided with the exception of acute aortic dissection. There are no studies showing that this can be reliably achieved by oral medication. The hazard of vigorous lowering of blood pressure in patients with hypertensive encephalopathy and grade III/IV retinopathy is not only theoretical since excess blood pressure lowering has been associated with incident stroke and death (see guideline for references).

The third issue concerns the therapeutic management of a hypertensive urgency, i.e. patients presenting with a severe blood pressure elevation (BP >220/120 mmHg) who are suspected of a hypertensive crisis and lack signs of acute target organ damage. This includes patients with both acute or chronic blood pressure elevations for different reasons (e.g. anxiety, chronic uncontrolled hypertension, substance abuse). These patients are difficult to compare with the average hypertensive patient receiving combination therapy in a controlled trial. The treatment of a hypertensive urgency is not aimed at reaching target blood pressure, but at reducing excess risk associated with severe blood pressure elevations within an acceptable time-frame. Combined with the knowledge that blood pressure may lower spontaneously in a number of these patients the goal is to lower blood pressure without 'doing harm'. The available evidence, summarised in the guideline, shows that nifedipine retard has the most predictable blood pressure lowering efficacy without risk of hypotension in these situations. Because of the heterogeneous causes of a hypertensive urgency and the spontaneous blood pressure changes that occur in these patients in an emergency setting there is reason to recommend a brief period (at least two to three hours) of observation. This will help in making a definitive diagnosis regarding the nature of the blood pressure elevation next to allowing appropriate observations of the initial BP-lowering effect. Finally, in our experience and that of others, most patients presenting with a hypertensive crisis have not received or taken their medication in the weeks prior to their presentation. This suggests that even patients who were prescribed calcium antagonists may respond well to nifedipine retard, although evidence for this is lacking.

To conclude, we fully agree with the general recommendations pointed out by Smulders *et al.* that form the basis of our guideline and clinical practice in general. We look forward to their experiences after using the guideline in their practice.

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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