and management plans after expert review in North American studies[3–5] than in UK series[1] likely reflects greater variation in practice standards in the USA. Review work should ideally occur within the context of a multidisciplinary team (MDT) meeting. Such work is time-consuming and requires the attendance of key radiologists, pathologists, surgeons, physicians and paramedical staff, as well as the support of administrators and clerical staff. Notes, films and slides must all be available and in this forum clinical and pathological information is often brought to light which resolves problems, downgrades the clinical impact of radiological uncertainty or else discussion helps to form management or investigation plans to respond to this. There is little reported research on the value of such meetings but such as it is the data are clear. Clinicians place high value on time spent within such meetings and they are time-effective for radiologists[6,7].

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Ovarian cancer — difficulties in monitoring response

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The imaging of malignant disease involves tumour diagnosis, staging, measurement of response and identification of complications. Increasingly, oncologic radiologists are expected to provide objective assessment of change in masses, on serial studies, in order to validate response or resistance to new chemotherapeutic agents. In some cancer centres follow-up examinations make up over 75% of computed tomography (CT) activity.

Objective assessment on CT depends on a somewhat simplistic assumption that those masses that increase in size define disease progression, whereas reduction in tumour size indicates a favourable therapeutic impact. The 1979 WHO Handbook and the 1981 paper by Miller *et al*.[1] identified criteria for bi-dimensional measurements of tumour masses and established the classification of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD). It has became apparent, however, during the application of these criteria that assessments based on bi-dimensional measurements of one or two marker lesions could result in misleading conclusions, particularly in respect of progressive disease where increasing size of a single lesion might be at variance with favourable change elsewhere. This could lead to an incorrect conclusion that therapy was ineffective. It has also become clear that methods for evaluating change in the size of measurable lesions have not always been universally applied and different observers and even centres could employ different regimes. Husband, Gwyther and Rankin highlighted these features in 1999[2] when they described the problems of bi-dimensional measurements of 3-dimensional masses, as well as the difficulties posed by tumour necrosis and calcification.

In June 1999 a revised version of WHO criteria under the heading 'Response Evaluation Criteria in Solid Tumours (RECIST criteria)'[3] was published, based on the assessment of up to 10 target lesions, the sum of whose longest diameters define the baseline measurement. The stimulus for this finite objective measurement emanates from the licensing authorities, whose requirements define phase II drug assessment protocols for the pharmaceutical industry. RECIST criteria require the identification up to 10 solid, well-marginated nodules and their repeated identification and assessment of

change on serial CT or MRI examinations. The unidimensional measurement of 10 target lesions on sequential examinations is laborious and fraught with potential inaccuracy. The application of these criteria within a busy cancer imaging unit is at best tedious and expensive and for some tumours impractical. Outside well-resourced research units, generously staffed with expert observers, these criteria appear to have achieved little practical relevance.

Neither the original WHO criteria nor RECIST take into account changes in physical characteristics of the tumour such as cystic degeneration or calcification. Serial measurements of the diameter of an involved para-aortic lymph node in metastatic non-seminomatous testicular tumour may well increase during effective response to chemotherapy. This is commonly due to a degree of cystic degeneration within the mass. This phenomenon is well documented[4] and in this situation application of RECIST criteria alone may lead to incorrect conclusions and for individual cases may be dangerous. Other metastases, e.g. in the liver, may also undergo necrosis and sarcomas may also increase in size when necrosis occurs during effective therapy. The occasional development of tumour calcification may have varying implication for the assessment of response but is not considered in these protocols.

Recent discussion[5] has highlighted potential weaknesses in RECIST criteria, particularly in relation to the inability to determine any functional change resulting from effective drug activity. Tumour neo-angiogenesis and cellular metabolic changes require assessment by new dynamic forms of functional imaging such as ^{18}FDG-PET or ^{31}P-magnetic resonance spectroscopy (MRS). In the vast majority of cancer cases, however, assessment of response depends on morphological measurement of appropriate target lesions on serial CT studies.

Problems of reproducibility are encountered when, on the basis of Phase II trials subsequent phase III studies involve several centres and multiple observers. Gwyther[6,7] has reported the impact of independent radiological review of image data sets in studies of Gemcitabine and Topotecan and in both reports showed that response rates were significantly reduced when independently reviewed by an expert panel.

The mechanics of these reviews still rely on application of WHO criteria of bi-dimensional measurement, but this task becomes most difficult when the assessment involves metastatic ovarian cancer. It might be argued that in this particular disease the application of RECIST criteria is so fraught with potential inaccuracy that meaningful objective measurements and conclusions are scientifically impossible, whether performed by single observers or review panel. In response to the promulgation of these new guidelines the Gynecologic Cancer Intergroup have published a recommendation that for the definition of objective disease progression, after first-line therapy, the doubling of CA 125 from the upper limit of normal (or doubling from the post-treatment nadir) predicts disease progression[8].

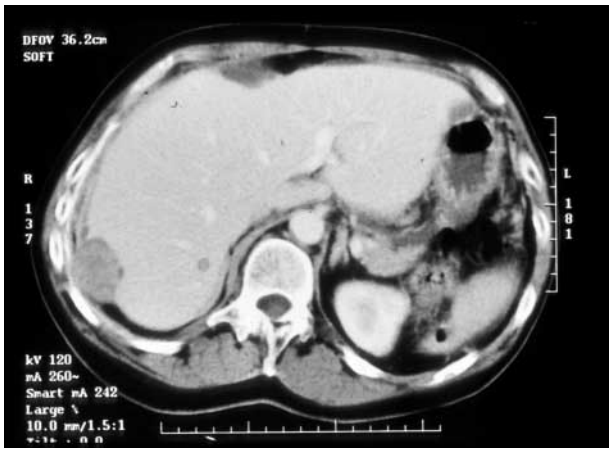

Figure 1

Ovarian cancer is a disease which spreads transcoelomically, and is characterized by the development of abdominal ascites and by widespread peritoneal plaques. Pleural and pericardial effusions together with cystic lesions are considered by RECIST to be non-measurable and these patients are excluded from study populations unless measurable lesions are present. By excluding these patients and including unreliable data based on measurements of ill-defined peritoneal and serosal plaques, the scientific basis for the assessment of therapeutic response must be flawed at the very outset. At the very least the exclusion of a significant percentage of patients because of non-measurable disease skews the study population. Technical improvements in CT with the development of spiral technology, combined with changes in technique and the more widespread use of intravenous contrast enhancement, mean that a small volume plaque as thin as 1–2 mm can be demonstrated and analysed sequentially by an experienced observer but reproducible, accurate measurement is seldom feasible. Whilst discrete tumour nodules may be available in many cases for serial objective measurement (Fig. 1) the identification of disease reactivation or progression can be achieved by recognition of more subtle features such as increasing thickening of wafer-thin enhancing plaques of disease applied to the serosa of the bowel (Fig. 2).

It is argued, therefore, that for studies involving phase II trials in ovarian cancer a more accurate and meaningful method of evaluating therapeutic impact could be afforded by a subjective review of the whole imaging data set performed by an external panel made up of experienced radiologists.

During the observation and attempted measurement of response on serial CT in many cases of ovarian cancer, and becoming increasingly frustrated in so doing, the observation of tumour calcification in association with metastatic ovarian cancer became increasingly obvious. This well-recognized entity has not, hitherto, been subjected to any detailed analysis and in particular its relationship to treatment is unclear. A retrospective study has, therefore, been undertaken examining the temporal relationships of clinical and

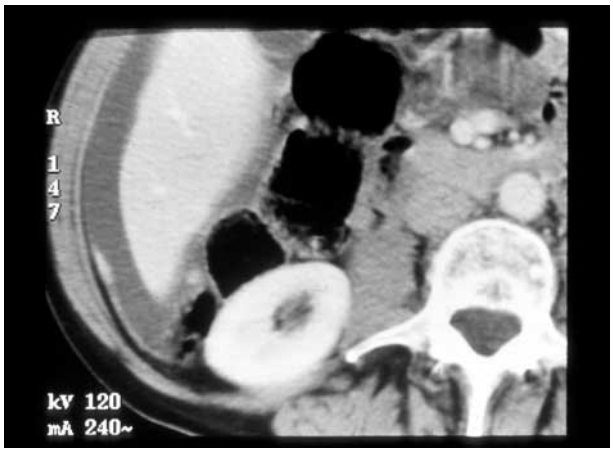

Figure 2

radiological features, together with tumour markers in 122 patients who presented with or developed calcification within metastatic ovarian cancer. Changes in soft tissue lesion size and the development of calcification have been correlated with histopathology and outcome. The study group was compared with a control group of 1577 patients who had a CT scan performed at least once during follow-up. A positive relationship between calcification and tumour sub-type was identified with serous tumours, which represented 60% of the calcified group, against 30% in the control. Patients with calcification were generally higher stage than the control group but lower grade. They also had a poorer survival rate.

There did not seem to be any relationship between the development of calcification and chemotherapy and thus it is unusable as a marker of response. Reliable assessment of metastatic ovarian cancer still remains extremely difficult and it is contended that for this disease trial data should be subjected to external panel review.

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Radiopharmaceuticals in monitoring cancer

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Introduction

Normal cells have three basic outcomes: differentiation, division and death. Cancer cells usually have reduced differentiation, increased division and mechanisms to avoid programmed cell death, apoptosis. These properties can be used to monitor cancer by nuclear medicine imaging.

Differentiation

Thyroid cancer cells show a reduced ability to take up radio-iodine compared with normal cells. Thus, all normal thyroid tissue has to be ablated surgically and with radio-iodine in order that the papillary or follicular thyroid cancers show uptake on radioiodine images and for thyroglobulin, Tg, to be a useful serum marker. Monitoring of thyroid cancer used to be done with a tracer amount of radioiodine ^{131}I. It was found that administration of amounts greater than 185 MBq, 5 mCi may cause stunning, reducing the of effectiveness of the large dose of ^{131}I given for therapy, (5–6 GBq, 150 mCi). However, 185 MBq (or less) ^{131}I gives a poor count rate signal, so that weakly iodine-avid malignant disease may not be detected. If the Tg is raised, some authorities are giving ^{131}I therapy in the absence of proof of iodine uptake. Some 50% of such patients show no uptake