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Clinical Radiology
The Royal College of Radiologists

Recommendations for cross-sectional imaging in cancer management, Second edition

Imaging in the evaluation of cancer

Faculty of Clinical Radiology

Contents

Introduction

Cross-sectional imaging has a central role to play in the management of patients with malignant disease and is used at all points along the patient care pathway:

- In the initial diagnosis and the staging of disease extent
- For monitoring response to treatment
- For evaluation of any residual mass after treatment
- For confirmation of remission of disease
- For recognition of complications of treatment
- When there is concern for disease relapse.

Computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging have well-recognised strengths and weaknesses. At different points along the patient pathway, one or other may be more appropriately used depending on whether treatment intent is curative or palliative, and whether the imaging focus is for local or metastatic disease. There are a number of practical steps which ensure good practice in cancer imaging.

- The provision in the request form of all clinical information relating to histological diagnosis, sites of known disease, previous surgery or other treatment and the specific purpose of the examination. All cross-sectional imaging requests in patients with known or suspected cancer should be vetted by radiologists or experienced radiographers and priorities for examinations should be set in compliance with local and national guidance.
- There are considerations about the timing of staging investigation after surgery. After dissection of the neck, groin or axilla, there may be a complex residual mass. After transurethral resection of a bladder tumour there may be reactive changes which mimic tumour spread. It is vital that the radiologist is fully appraised of the date and nature of surgery performed prior to staging. Where possible, a delay after surgery may allow these changes to resolve.
- All previous radiological investigations should be available or be retrievable in an electronic form for review by the radiologist responsible before the examination.
- Although routine patients should be scanned according to standard protocols, examinations may need to be tailored to answer specific questions. Each department should have written well-defined protocols for standard examinations.
- Where possible, examinations should be reviewed before the patient leaves the department to ensure that the examination is technically satisfactory and to assess the need for additional imaging. Review is aided by preset centre/window functions on the diagnostic console for soft tissue, liver, lung, brain and bone. The final report should be issued only after interrogation of the images on the appropriate window settings and following post-processing of the image data as appropriate.
- Radiologists should be familiar with the normal range of appearances on their equipment as this varies considerably on different machines particularly for MRI.
- Lymph nodes should be measured in the short axis in the axial plane. Normal lymph node sizes (maximum short axis dimensions – MSAD) for different anatomical areas are presented in the section on Lymph nodes.
- Since response to treatment and disease progression are often assessed according to changes in tumour size, follow-up examinations should be performed with comparable technique using the same planes and sequences. Ideally, both sets of examinations should be available to the radiologists ‘side by side’ on the diagnostic console.
- Although there is a great variation in style of reporting, it is good practice to provide a structured report with succinct conclusion statements, paying attention to answering the specific clinical question posed (see the Reporting section below). Recommendations regarding follow-up, biopsy and alternative radiological studies should also be made in the conclusion.

- It should be possible to review all relevant examinations in a multidisciplinary meeting, especially when there is discrepancy between clinical and imaging findings or other diagnostic uncertainty.

Principles of cancer staging

A clinically useful classification scheme for cancer such as the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*[1] encompasses the attributes of the cancer and defines its behaviour. Current schemes are based on the premise that cancers of the same histological type arising in the same anatomical location share similarities in patterns of growth and spread, and have similar outcomes. The process of staging determines how widely a cancer has spread. Clinical staging is performed in patients when there is a reasonable likelihood that a cancer has metastasised. Staging information is used in several ways:

- For selection of the primary and adjuvant therapies
- For estimations of patient prognosis
- To assist in the evaluation of the success of therapy
- To facilitate the exchange of information between providers of healthcare and between treatment centres
- To contribute to the knowledge base of investigations into the behaviour and treatments of cancer.

Key points in cancer staging

- Although clinical examinations, blood tests and simple imaging such as chest radiographs and ultrasound can reveal much useful information, detailed cross-sectional imaging including PET scanning and scintigraphy are the key elements of the staging process.
- ^{18}FDG PET-CT has emerged as a key important technology for staging selected tumours. Recent guidance on the evidence-based indications for the use of PET-CT in the United Kingdom 2013 has been published jointly by the Inter-Collegiate Standing Committee on Nuclear Medicine by members of the Royal College of Physicians and The Royal College of Radiologists (RCR).[2]
- In most patients, staging follows histological diagnosis of the primary tumour, and in some situations there are histological analyses of regional lymph node status and distant sites. In other patients, imaging diagnosis precedes histological confirmation and imaging may replace histological confirmation of the extent of disease spread.
- It should be noted that staging is different for tumours with different histology in the same organ; for example, renal cell cancer and transitional cell cancer of the kidney. Different information is required to plan the different treatment options for the two tumours and their different patterns of metastasis.
- Staging is a process of detection and exclusion. Only those regions of the body which are commonly and predictably involved by the individual tumour should be examined routinely.
- Staging requires the use of the best possible imaging modalities available and should be performed in the fewest steps. This minimises inconvenience for patients and the delay between diagnosis and the beginning of treatment.
- If patients are unfit for radical therapy, only information required to guide palliative therapy should be obtained.
- Staging should be performed according to agreed protocols, but procedures must be flexible to accommodate unusual presentations of disease and individual patient needs (such as patients who are physically or mentally challenged).
- The choice of imaging modalities used may require compromise. Factors to be considered include: local availability and expertise, radiation exposure, tolerance of the staging investigations by the patient, patient renal function and allergies and patient convenience.[3]
- Where possible, a single test is preferred to multiple investigations.[3] The ability to rapidly and reproducibly examine large tissue volumes makes CT the preferred option for staging patients with metastatic soft tissue disease.
- It should be understood that exclusion of metastasis can never be absolute; it is important that all those involved in patient management recognise the limitations of imaging investigations. Radiologists working in multidisciplinary teams (MDTs) are best placed to educate other caregivers on the potential

advantages and limitations of individual techniques for a specific patient indication.

Limitations of staging

Lesion threshold

For every test, there is a threshold above which disease is considered present and below which it is considered absent. These thresholds represent a compromise between sensitivity and specificity and need to be appropriately adjusted for patient management. For example, a threshold for lymph nodes frequently used is 10 mm for maximum short axis dimension (MSAD). Nevertheless, nodes greater than 10 mm are frequently benign and nodes smaller than 10 mm may contain metastases.

The thresholds used may vary according to the implications for treatment (such as to optimise diagnostic accuracy or according to treatment intent). Thus, using a treatment protocol that requires removal of nodes that are definitely considered metastatic, a higher threshold is appropriate (thereby improving specificity by reducing the number of reactive nodes removed) than if using a treatment protocol that requires aggressive removal of all potentially metastatic (which would improve sensitivity – but at the cost of reduced specificity).

Detection and characterisation

There is a difference between detection and characterisation of a lesion. Although chest radiography will reveal most lung nodules of more than 10 mm in diameter, some may be missed in ‘hidden’ lung regions; for example, the lung apex or behind the heart. The technical and diagnostic advantages of CT are its ability to reveal small nodules down to the size of approximately 3 mm and nodules which are invisible on chest radiography.

However, it should be noted that there are also ‘hidden’ areas on CT (particularly in the perihilar regions) which are frequently missed (computer-aided detection software can be helpful here), and that small lesions (less than 5 mm) can be too small to characterise. Indeterminate small lesions are also frequent in other anatomical sites within the body, for example, the liver, kidneys and in the adrenal glands.

Indeterminate lesions; management of uncertainty

Indeterminate lesions should be the subject of clinico-radiological discussion and/or multidisciplinary review, if establishment of their nature would impact upon patient management. If an indeterminate lesion was present on comparable imaging studies prior to the diagnosis, then stability over more than six months usually indicates it is benign. If there is another diagnostic test which is likely to provide a definitive diagnosis, this should be performed. Biopsy is rarely an option for lesions less than 10 mm in size. Sometimes, the only practical option available is to monitor the behaviour of lesions over time. A watch policy is often appropriate particularly when a patient is asymptomatic or when active management would not be prejudiced by a delay in lesion characterisation.

The time interval for a watch policy depends on the primary lesion type, location of abnormality and clinical urgency regarding the need to characterise the indeterminate lesion(s). Many sub-speciality documents can be consulted for appropriate guidance on the follow-up of indeterminate lesions.

Thus the options for resolving uncertainties about staging include (after Spencer 2008):

- Discussion
- Further investigation
- Intervention
- Active monitoring (wait and watch).[4]

Multidisciplinary team meetings

MDT meetings permit a team approach to patient management in which all aspects of the patient's disease are considered to provide individualised therapy. Selection of cases for inclusion and evaluation of responses within clinical trials and provision of a framework for continuing professional development (CPD), audit and multidisciplinary research are also key objectives.

For most patients, the information provided by staging confirms the clinical impression of disease extent. However, in a minority of patients there are discrepancies between the clinical impression and imaging findings or other problems requiring further discussion. Clinicians and radiologists need to identify problem cases which should be reviewed in advance. Following MDT meetings, the results of reviews, including discrepancies with previous findings, must be documented in clinical notes and, if necessary, in addendums to radiology reports. Any further investigations required should be instigated promptly. Feedback should be available to all radiologists within referring cancer units. The time required by radiologists to undertake all these activities should be recognised in job planning.[5] MDT meetings should be supported by appropriate clerical and administrative staff, and all individuals necessary to sanction investigations and to execute treatment plans should attend. Facilities should be available for televisual projection and display of relevant pathology and radiology, as determined by local needs.

Staging systems

A variety of staging systems are used in clinical practice. Staging schemes are based on the premise that cancers arising from the same anatomical locations and sharing similar histological features will have similarities in their patterns of growth and ultimate outcomes. Staging systems define tumour extent which, in turn, determines treatment options and provides a guide to prognosis.

The most widely used system is the TNM system of Union for International Cancer Control (UICC)[5] and this scheme has been wholly adopted by the AJCC.[1] However, other systems have been defined by professional organisations and institutions for specific tumours or groups of tumours which are sometimes used alongside the the TNM staging system (for example, paediatric neoplasms, brain tumours, lymphoma, pleural mesothelioma and myeloma). For local radiological practice, it is important that the staging systems used are well understood and uniformly applied by all in a clinical team.

In the TNM system, an alphanumeric annotation defines the following:

- T stage – the local disease extent with the use of numerical subsets which indicates the progressive extent of the malignant process (T0, T1, T2, T3, T4)
- N stage – nodal status which indicates the presence or absence of regional lymph node metastasis(es) (N0, N1, N2, N3)
- M stage – metastasis stage which defines the presence or absence of distant metastasis (M0, M1).

Description of the general rules for the TNM classification and the documentation of specific classification for individual tumours are beyond the scope of this document. All readers are strongly encouraged to have at the bench side either the *TNM Atlas* of the UICC or the *Cancer Staging Manual* of the AJCC, where the appropriate guidance and definitions can be found readily.[1,6]

Reporting

Oncology patients usually undergo repeated studies often at different institutions and consistent reporting styles are helpful for ensuring quality care for patients regardless of where they are imaged. The structured general oncologic imaging report should comprise the following components.

Indication/clinical details: a statement regarding primary tumour site (second malignancies if relevant), location (example left/right, limb and so on), clinical or surgical staging, pathological type, and tumour marker levels, if relevant and available.

Technique: details of contrast medium administered and imaging parameters used (including sequences in brief) to allow exact replication on follow-up examinations.

When a comparison has been made with previous examinations, the dates and regions scanned on prior studies (and place, if from another institution(s)) should be indicated.

Findings: Generally, oncologic CT reports are structured head to pelvis. As a viable alternative, structuring of reports under headings of primary tumour, lymph nodes and metastases following the pathologic TNM format is being recommended.[7] Such structured reporting can be helpful for communicating imaging findings to oncologic colleagues, while as the same time reminding radiologists to look carefully at the primary site of disease for recurrent disease and to think about common pathways of tumour spread.

Imaging findings should include free text under each heading but should also include measurements of lesions. Unusual sites of suspected disease should be mentioned. Clear identification of marker lesions by anatomic location, size (by measurement) and imaging section(s) (by sequence/slice number(s) or table position) as necessary (tabulated if possible).

A section on other findings should be included as it reminds radiologists to review the scan from head to pelvis ensuring all areas are reviewed. The presence of complications such as bowel obstruction, hydronephrosis or pulmonary embolism should be stated. The more urgent findings, those related to the disease process should be stated first before incidental findings.

If the patient has had a brain study, it can be useful to add this under a separate heading.

Impression or conclusion: if possible, this should provide a staging assessment (TNM status or other) highlighting categories of uncertainty, where appropriate, by the use of the relevant TNM prefix TX, NX, MX. It may not be possible to offer comprehensive staging at the time of report and the remit for formal recording of staging should sit with the MDT meeting. Recommendations regarding follow-up, biopsy and alternative radiological studies should also be made in the conclusion.

Imaging the treated patient

Cross-sectional imaging informs a key part of the overall assessment of patient's response to therapy. Reproducibility of the imaging technique and of the reporting method are key factors in providing accurate assessments of response. Thus, follow-up imaging techniques and protocols should be identical to those used for the initial staging, provided that the initial examination was optimal. Furthermore, the radiologist report should also provide an accurate, objective assessment of disease status that enables oncologists to use the scan information appropriately.

Investigation of suspected relapse should be tailored to the clinical presentation and the anticipated treatment intent. Patients may relapse outside compartments or areas of the body treated initially with surgery or radiotherapy and, therefore, follow-up study protocols may need to be adapted to examine different areas from the initial staging examination. When relapse is suspected, a patient's ability to tolerate the examination may be compromised by symptoms, and it may be helpful to discuss the proposed examination with the clinical team prior to the study. Patients, for instance, with bowel obstruction may not tolerate oral contrast media.

The reporting style of the treated patient should mirror that at baseline. As already noted, structured reports under headings of primary tumour, lymph nodes and metastases following the pathologic TNM format are being recommended.[7] Such structured reporting can be helpful for communicating imaging changes to oncology colleagues while as the same time reminding radiologists to look carefully at the primary site of disease for recurrent disease and to think about changes in common pathways of tumour spread.

Changes in the measurements of marker lesions are an essential part of the objective assessment of the patient's response, often determining clinical decisions regarding therapy continuation. This places extra responsibility on radiologists to provide an accurate and objective report that enable oncologists to use the scan information appropriately. The structured report format can be helpful for promoting uniformity in objective assessment of disease.

There are a number of methods of determining response which rely on radiologists to select and to follow lesions representative of the disease burden. Specific definitions on lesion choice, method of lesion measurement and the assessment of response are discussed briefly in the next section.

Follow-up studies should mention the presence of new disease because that can indicated tumour progression. Summary statements on disease response and complications/squeal of treatment should be noted. Comments on the general trend of change, intermediate lesions and differential responses should be specifically noted.

Documentation of response to treatment

Imaging reports of patients undergoing treatment should document changes in tumour size, using criteria agreed between the radiologist and oncologist and/or as required by clinical trial protocols.

After the year 2000, RECIST (Response Criteria in Solid Tumours) criteria became widely adopted to be used in clinical trials and require the measurement and documentation of multiple sites of cancer.[8] The revised RECIST guideline (version 1.1)[9] was introduced in 2009 to simplify, optimise and standardise the original RECIST criteria. Other tumour-specific guidelines have also begun to emerge including the Cheson/IWV criteria for lymphoma.[10]

RECIST (v1.1) requires that a maximum of five target lesions, with a maximum of two per organ, with a longest diameter of at least 10 mm; in lymph nodes the short axis rather than the long axis should be measured, with normal LN measuring <10 mm, non-target LN ≥10 mm but <15 mm and target LN ≥15 mm; osteolytic lesions with a soft tissue component and cystic tumours may serve as target lesions. Additionally an augmentation of the criteria defining progressive disease of target lesions was introduced to not only include a ≥20% increase in the sum of the longest diameter (SLD) from the nadir but also a ≥5 mm absolute increase in the SLD (the other response categories of target lesion are unchanged from the original RECIST). Additionally within RECIST 1.1, there appeared guidelines for reporting findings of lesions that are too small to measure and for measuring lesions that appear to have fragmented or coalesced at follow-up imaging. Progressive disease (PD) of non-target lesions can only be applied if the increase in non-target lesions is representative of change in overall tumour burden.[11] RECIST v1.1 has the inclusion of PET findings among the indicators of disease response. It is self-evident that this work is highly demanding of radiologists' time and, since its role is primarily to support clinical research, its use (in particular the calculation of % changes) cannot be considered to constitute routine work. Nevertheless, the structured oncologic report should include as far as possible all the key elements for RECIST assessments to be performed by an appropriately trained person. Essential elements within structured reports could include the identification with appropriately terminology of target lesion (their location, size [two dimensions for primary lesions and for nodal disease if for lymphoma, long axis for metastases, short axis for nodal disease for solid tumours]), non-measurable and new disease. Inclusion of such information will minimise errors in response allocation and thus potential patient harms while at the same time can be helpful for minimising secondary reviews of examinations should patients subsequently enter into clinical trials.

There is increasing awareness that anatomical approaches based on measurements of tumour size such as RECIST have significant limitations including the presence of tumours that cannot be measured, poor measurement reproducibility and mass lesions of unknown activity that persist following therapy. Faced with these limitations, more sophisticated measurements (including tumour volume and lesion regression rates) have been applied to the evaluation of tumour response to therapy. Another recent approach is the use of CT density (Hounsfield Units) measurements for the evaluation of gastrointestinal stomal tumours' (GIST) responses following therapy with imatinib[12] and for renal cancer treated with multi-targeted tyrosine kinase receptor inhibitors such as sorafenib, sunitinib and temsirolimus.[13] The increasing clinical use of such cytostatic therapies has further emphasised that anatomic imaging techniques are insensitive to changes that may inform on overall therapeutic success. This later point has been exemplified by the disconnection between progression-free survival (most often anatomically determined) and overall survival for a number of cytostatic therapies including anti-angiogenic drugs.

Recently, more emphasis has been placed on 'functional' molecular imaging techniques that depict physiological and cellular processes within tumours such as altered vascularity or metabolism. It remains to be seen if these new

approaches will become widely validated for routine clinical use.

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