NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 6 • 616–620

Invited review

Impact of imaging on treatment choice for localised tumours

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The effective management of patients with cancer requires a multidisciplinary team approach with regular dialogue between the specialist cancer surgeon, oncologist, diagnostic radiologist and histopathologist to decide on the choice of treatment for each individual patient. The diagnostic radiologist plays an extremely important role in that team in advising on the role of imaging for each particular tumour site and for a proper evaluation of images for staging of the local tumour and lymph nodes and distant metastases. This guest lecture will focus on the impact of imaging on the treatment choice for localised tumours, looking first at the significance of the findings of a radiological investigation and then the impact of imaging on management of lung cancer and breast, prostate and cervical cancer as illustrations.

Znaczenie diagnostyki obrazowej dla wyboru metody leczenia w przypadku nowotworów o zaawansowaniu miejscowym

Skuteczne leczenie chorego z nowotworem wymaga podejścia wielodyscyplinarnego. W toku postępowania konieczna jest stała wymiana informacji pomiędzy chirurgiem onkologiem, radiologiem i histopatologiem. Umożliwia to indywidualne dobranie postępowania - inne pod kątem każdego przypadku. Radiolog - specjalista w zakresie diagnostyki obrazowej pełni bardzo istotną funkcję; doradza techniki obrazowania optymalne przy danej lokalizacji guza i pomaga ocenić uzyskane obrazy, co z kolei ułatwia określenie stopnia zaawansowania nowotworu, stan węzłów chłonnych i ewentualną obecność odległych przerzutów. Poniższa praca poświęcona jest znaczeniu metod obrazujących w diagnostyce zmian nowotworowych. Omówione zostały możliwości diagnostyczne oraz wpływ wyników uzyskanych dzięki technikom obrazującym na postępowanie terapeutyczne na przykładzie chorych z rakiem płuca, piersi, prostaty i szyjki macicy.

Key words: imaging, oncological imaging, choice of cancer treatment
Słowa kluczowe: obrazowanie, obrazowanie w onkologii, leczenie przeciwnowotworowe – wybór metody

Imaging may be used in the diagnosis of a tumour, staging both local disease, lymph node involvement and distant metastases and may be requested in order to answer a specific clinical question in an individual patient. It is also used to measure therapeutic response to radiotherapy and chemotherapy and in the detection of tumour relapse. One important impact of the use of sophisticated imaging techniques to stage patients with cancer is the apparent continuous improvement in cancer survival rates reported over the last 25 years. Although this is easily attributable to earlier diagnosis and new and more effective treatments, the effect of more accurate staging may to some extent explain these improved results [1, 2]). These authors showed that improved survival rates were mainly an artefact of better staging; patients in the lower stages with clinically occult (usually nodal) disease were being identified with better imaging and were being placed in a more advanced stage (stage 'migration'). This improved staging led to benefit to all groups; in the lower stages patients with occult metastases would be removed with benefit to those stages; in the higher stages those patients with a lower tumour burden would be added to those with a higher one with improvement in survival rates. Thus, while individual prognosis did not change overall, survival in each stage improved. The stage migration phenomenon occurs when comparisons are made between groups of patients who have undergone less or more thorough staging techniques and therefore occurs when comparisons are made over a time period during which new imaging technology has been introduced.

In order for a local treatment such as surgery or radiation therapy to be effective and result in a cure the tumour must be truly localised without any spread to lymph nodes or distant organs. One of the key issues which therefore occupies both clinician and radiologists together is which imaging modality provides the best diagnostic performance in detecting local invasion and metastatic disease for an individual tumour site.

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The choice of imaging modality will depend on the diagnostic performance of a particular technique to identify the disease correctly. This diagnostic performance is a measure of sensitivity (the ability of an investigation to identify correctly those patients who have the disease), and specificity (the ability of an investigation to identify correctly those patients who do not have the disease), both of which are independent of disease prevalence and called the 'intrinsic operating characteristics' of the test. In contrast, the positive predictive value (the probability of whether the disease is actually present if the test is positive) and the negative predictive value (whether the disease is likely to be absent if the result is negative) and accuracy (combined sensitivity and specificity) are highly dependent on the prevalence of the disease. Reports of sensitivity and specificity of an imaging modality are therefore more reliable than PPV and accuracy, which are greatly influenced by regional variation of disease prevalence. However, in spite of knowledge of the best diagnostic performance of an imaging modality, other practical variables such as availability and cost of equipment, expertise and workload of an imaging team and department and patient compliance, may mean that the optimum imaging practice may not always be feasible in an individual patient situation.

A receiver-operator characteristic (ROC) curve is a plot showing a relationship between sensitivity and specificity for different cut-off points of a particular test. As the criteria for calling a test positive become more stringent specificity improves and sensitivity decreases. As the criteria are relaxed, sensitivity improves while specificity diminishes. The fundamental principle illustrated by the ROC curve is that there is an inherent limit to the diagnostic efficacy of the test. Once this limit has been reached, the interpreter can only improve sensitivity at the expense of specificity and vice versa. The ROC curve can therefore be used to select the 'best' cut-off criteria for positivity taking the positive predictive value and the relative costs in terms of patient outcome of false positive and false negative test results into account. Close collaboration between radiologist and oncologist is therefore essential to interpret the results of imaging in staging cancer, the choice of imaging for different tumour types, protocols and timing of imaging in relation to treatment and protocols for follow up of treatment.

Lung Cancer

Computed tomography has become the imaging modality of choice in the evaluation of patients with lung cancer and is useful for detecting metastases in the liver and adrenal glands, as well as determining the local extent of the primary tumour as a guide to surgical management and radiotherapy target volume (GTV). The technical resectability of the primary tumour is determined by the T stage. T3 tumours may cross the pleural space to involve the parietal pleura or may invade the chest wall or extend in limited fashion within the mediastinum, but remain operable using more complex techniques. Conventionally T4 tumours are irresectable because of the invasion of critical mediastinal structures such as the heart, major vessels, oesophagus or carina. The distinction therefore between T3 and T4 disease is critical reflecting the dividing line between conventional surgical and non-surgical management.

There are several pitfalls in the interpretation of CT images in determining the extent of the primary tumour. Firstly, separating the tumour from peripheral consolidation in the lung can be difficult. Distal collapsed lung has been shown to enhance more than central tumour [3]. A tumour mass results in expansion and a convex shape configuration whereas atelectasis produces contraction and a concave configuration; consolidation produces no change [4]. Caldwell et al in Toronto have studied the impact of PET scanning information on the inter-observer variation in GTV delineation and have shown that PET reduces this variability, partly due to its ability to distinguish tumour from adjacent atelectasis [5].

The value of CT in the determination of chest wall invasion is somewhat limited. Only the presence of rib destruction or tumour extending outside the chest wall are reliable signs of chest wall invasion [6]. Hence, both CT and MRI can predict resectable tumours but may fail to distinguish inflammatory chest wall adherence from early invasion. Extensive chest wall disease is readily identified by either modality but may not imply inoperability. Glazer et al correlated three features of lung tumour with operative findings and showed that (i) less than 3cm of mediastinal contact (ii) maintained fat plane of separation from the mediastinum (iii) less than 90° of circumferential aortic contact are key features [7]. The presence of at least one of these features predicted resectability in 36 out of 37 cases with mediastinal contact. However, criteria for non-resectability are harder to identify and this is unfortunately the information required by the surgeon.

MRI is of undoubted benefit in the special situation of superior sulcus tumours where it can not only diagnose chest wall invasion but also show extension into the root of the neck with visualisation of vascular and neural structures [8].

The appearance of the CT image used for delineation of the GTV can be varied by the CT window display settings. Soft tissue window settings are most appropriate for imaging of central structures such as mediastinal nodes. However, it has been shown that for pulmonary nodules the lung settings are the most accurate as shown in one study by Harris et al which used lung settings of width 850HU and level -750HU [9]. The detection of lymph node involvement using CT relies on the criteria of size and a short axis greater than 1cm is usually taken as the cut-off for positive tumour involvement. However, moderate enlargement may be due to reactive hyperplasia or distal infection or other inflammatory lung conditions

and one study has shown that 37% of mediastinal nodes in the range 2-4cm were tumour free from lung cancer [10].

CT is the standard method for diagnosing nodal enlargement and has been extensively evaluated. Pitfalls in diagnosis for the clinician include partial volume effect and mistaking vascular structures such as the azygos vein for mediastinal lymph nodes. The value of CT is that if it shows extensive nodal metastases then inappropriate surgery can be avoided. If the CT scan is negative for mediastinal adenopathy then either a PET scan should be performed or mediastinoscopy performed prior to surgery or nodal sampling at surgery. If CT shows enlarged lymph nodes only then a biopsy is essential to obtain histological tissue before the patient is denied the chance of surgical cure because of the preponderance of enlarged reactive nodes.

Positron Emission Tomography (PET) with FDG has become a useful imaging modality in evaluating patients with lung cancer. It takes advantage of increased glucose metabolism by malignant cells so that tumour masses take up increased amounts of FDG relative to normal lung tissue. Several studies have shown that up to 18% of patients considered to be resectable by conventional imaging will have more advanced disease demonstrated by PET scanning and become non-resectable. PET scanning is particularly helpful in staging lymph node disease where it has a sensitivity of 79% and specificity of 91%, much increased over CT scanning. With a negative predictive value of 95% the surgeon knows that if the PET scan is clear the patient is likely to be operable. However, the positive predictive value is only 80% which means that mediastinoscopy and biopsy is still necessary in case PET scan has created a false positive result due to inflammation. Biopsy is essential in order to ensure that the patient is not denied curative surgery due to a false positive result [11]. Kalff et al have prospectively studied the impact of PET on the changing stage of 59 patients with lung cancer and have shown that it not only up-stages patients with stage I, II and III disease, but also down-stages patients with stage III and IV disease leading to more appropriate choice of patients for curative surgery [12].

In summary, the impact of imaging for lung cancer is that CT is the imaging modality of choice and can be used to predict resectable tumours but is unreliable for identifying inoperable mediastinal invasion. MRI is comparable with CT but is reserved for problem solving situations such as superior sulcus tumours. PET scanning improves lymph node staging but where it is unavailable CT with mediastinoscopy can provide similar information. The liver and adrenal glands can be conveniently imaged at the same time as chest CT for the detection of asymptomatic metastases. Further imaging studies in the asymptomatic patient depends on patient selection.

Van de Steene et al have shown a large inter-observer variation in definition of GTV for lung cancer in a recent study where five clinicians were asked to define the GTV on planning CT scans of 8 patients [13]. A further study by Giraud et al looked at the inter-observer variability of GTV in 10 patients with lung cancer shown between radiation oncologists and radiologists [14]. Significant differences in site and size of the GTV were observed with radiologists delineating smaller GTVs than oncologists and experiencing less difficulty with difficult cases. The reasons for discrepancy were failure to identify atelectasis and pleural thickening correctly and poor knowledge of radiological anatomy. Multidisciplinary co-operation and teaching of ICRU definitions and interpretation of CT scan images would all improve GTV delineation. Joint delineation of the GTV with radiologists and senior and junior clinicians would be an advantage. The role of PET/CT fusion remains under evaluation.

Breast Cancer

Mammography is still the most widely used method for diagnosing breast cancer supplemented by ultrasound. However, it has a false negative rate of 4-34%. Recently rapid progress has been made with MRI in its diagnostic potential, including the use of dynamic MRI. MRI is still in a state of development and indications for MRI imaging are still unclear and protocols vary considerably between different institutions. Image interpretation is also under development and at present there are not internationally accepted criteria for the interpretation of breast MRI images. There have been two major approaches: evaluation of lesion morphology and assessment of dynamic contrast enhancement patterns. Using dynamic contrast enhanced sequences the sensitivity for tumour detection has been reported between 90 and 100%. However, specificity has not been as impressive with reported rates of 37-85%. It is likely that a combination of dynamic and morphological sequences will improve on this specificity. The main role of MRI is in delineating multicentric disease but whilst MRI is sensitive in detecting invasive cancer, lobular tumours are less well defined. It is less sensitive for detecting DCIS than for invasive cancer and microcalcification is poorly seen with MRI.

MRI is better at defining the size of the primary tumour than mammography (95% versus 75%) and this may have a role in the selection of patients for breast conserving surgery where the upper limit is 4cm. The ability of MRI to detect multicentric disease leads to the selection of patients for mastectomy but, at the moment, biopsy under MRI control remains difficult. MRI is also good for assessing suspected local recurrence in the breast following radiotherapy but false positives may occur within the first nine months after treatment.

Prostate Cancer

The aim of local staging is to select out those patients with organ confined prostate cancer for radical prosta-

tectomy, brachytherapy or external beam radiotherapy as curative treatment from those in whom the cancer is no longer contained within the prostate gland. Magnetic resonance imaging has become the most accurate method for evaluating the prostate gland with reported staging accuracies of 80-90%. Either phased array, pelvic coils or dedicated endorectal coils can be used and MRI scanning should preferably be avoided for two to three weeks after prostatic biopsy. Prostate cancers are best identified on T2 weighted scans with the normal peripheral gland shown as high signal intensity and cancers shown as areas of low signal intensity. MRI is the best imaging method for diagnosing seminal vesicle involvement with accuracy rates of 65-90%. Accuracy rates of 58-90% are reported for diagnosis of T3 disease with extension "through the capsule" of the prostate. Future developments in MRI such as dynamic contrast enhancement and MR spectroscopy will further refine the areas of active tumour within the prostate gland and help to improve GTV definition. MRI and CT offer similar levels of accuracy in the detection of pelvic lymphadenopathy with CT having the advantage that fine needle aspiration cytology can be performed more easily for confirmation of disease.

Evaluation of regional nodes is performed as part of the staging process and is particularly important in patients who are candidates for radical prostatectomy, since positive nodes make surgery inappropriate. Laparoscopic pelvic lymph node dissection is less invasive than open pelvic surgery and almost as accurate in sampling lymph nodes (90%). However, this method requires skill and experience and if no lymph nodes metastases are found a second operation is necessary unless frozen section or FNA interpretation is highly reliable. Computed tomography scanning of the prostate is not diagnostically useful because it does not show internal prostate anatomy nor tumour within the gland. It also over-estimates the volume of the prostate gland compared with MRI and studies are on-going to provide CT-MR image fusion for more accurate delineation of the GTV [15]. Modern ultrasound equipment used for transrectal ultrasound provides excellent images of the prostate and its internal architecture. Its main application is in prostate brachytherapy where it can be used for CTV definition and to guide the treatment process itself. The entire prostate gland is the CTV for planning purposes and where the tumour is visualised this information can be taken into account for dosimetry.

Cervical Cancer

The most important aspect of staging in cervical cancer is an assessment of the possibility of parametrial invasion. Patients without evidence of parametrial invasion are treated with radical hysterectomy whereas when there is radiological evidence that parametrial invasion is present patients are treated with radiotherapy. The identification of disease less than or equal to stage IIA is therefore critical. The overall accuracy of MRI in staging cervical cancer is 76-83%, compared with 70% for clinical staging and 63% for CT [16]. Comparative studies reported that the accuracy for parametrial invasion was 78% for clinical evaluation, 70% for CT and 92% for MRI [17]. Using MRI 95% of stage IB tumours can be identified. Preservation of the outer low signal intensity ring of the cervical stroma on T2 weighted images reliably indicates that tumour is confined to the cervix and no parametrial spread has occurred. However, disruption of the outer ring does not always indicate tumour extension into the parametrium and false positive results occur, particularly with large exophytic tumours and in the presence of peritumoural inflammation. The sensitivity of MRI in detecting vaginal invasion (stage IIA disease) is excellent with an accuracy of up to 93%. In stage IIB disease there is extension of tumour into the parametrium best seen on axial T2 weighted images. Preservation of the hypodense stromal ring is a reliable sign of intact parametrium. This sign has a very high specificity, almost 100%, and is of great value in the exclusion of parametrial invasion. The clinical value of MRI in staging carcinoma of the cervix lies in its extremely high negative predictive value for parametrial invasion on which the decision regarding the need for hysterectomy can be based. The loss of the low signal intensity ring has a lower specificity and positive predictive value of about 85% for parametrial invasion.

In patients with early stage carcinoma of the cervix the standard treatment of hysterectomy results in sterility. However, a new surgical procedure called a trachelectomy preserves the uterine body with excision of tumour within the cervix and maintenance of fertility. The key to determining the operability for this procedure is assessing the proximal extent of the tumour into the uterine body. MRI is able to predict the proximal extent of the cervical cancer into the myometrium and its relationship to the internal os ([18].

As MRI has been showed to provide such an accurate depiction of the size and extent of cervical tumours it follows that it is widely suited to planning radiotherapy treatment. Two large studies have shown that the introduction of MRI led to a change in position of portals in 50-70% of patients [19-21]. Both studies conclude that when treating carcinoma of the cervix standard protocols do not exist and the design of lateral fields has to be based on tumour anatomy as delineated using MRI. Individually shaped fields based on MRI scans could better encompass the PTV and spare avoidable radiation to normal tissues. No study has yet been reported on the implementation of MR images in a planning system in the design of radiation treatment of carcinoma of the uterine cervix.

There is no doubt that regular multidisciplinary team meetings with review of imaging and histopathology and discussion with colleagues of individual patient's tumour presentations is the best way to provide optimum management of patients with cancer. These discussions

not only clarify decision making for the individual patient but act as stimulus to areas of research and education for all members of the team.

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References

1. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *New Engl J Med* 1985; 312: 1604-8.
2. Bosi GJ, Geller NL, Chan EY. Stage migrations and increasing proportion of complete responders in patients with advanced germ cell tumours. *Cancer Research* 1988; 48: 3524-7.
3. Onitsuka H, Tsukuda M, Araki M et al. Differentiation of central lung tumour from post-obstructive lobar collapse by rapid sequence computed tomography. *J Thorac Imaging* 1991; 6: 28-31
4. Bourgouin PM, McCloud TC, Fitzgibbon JF et al. Differentiation of bronchogenic carcinoma from post-obstructive pneumonitis by *MRI. J Thorac Imaging* 1991; 6: 22-7.
5. Caldwell CB, Mah K, Ung YC et al. Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT. The impact of 18FDG-hybrid PET fusion. *Int J Radiat Oncol Biol Phys* 2001; 51: 923-31.
6. Webb WR, Gatsonis C, Zerhouni E et al. CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiology Diagnostic Oncology Group. *Radiology* 1991; 178: 705-13.
7. Glazer GM, Oringer MB, Gross BH et al. The mediastinum in non-small cell cancer: CT-surgical correlation. *Am J Radiol* 1984; 142: 1101-5.
8. McLoud TC, Filion RB, Edelman RR et al. MR imaging of superior sulcus carcinoma. *J Comput Assist Tomogr* 1989: 13: 233-9.
9. Harris K, Adams H, Lloyd D. and Harvey D. The effect on apparent size of simulated pulmonary nodules of using three standard CT window settings. *Clin Radiol* 1993: 47: 241 -
10. McLoud TC, Bourgouin PM, Greenberg RW et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 1992; 182: 319-23.
11. Dwamena BA, Sonnad SS, Angobaldo JO et al. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s – meta-analytic comparison of PET and CT. *Radiology* 1999; 213: 530-6.
12. Kalff V, Hicks R, MacManus M et al. Clinical impact of 18F Fluoro-deoxygluscose positron emission tomography in patients with non-small-call cancer: a prospective study. *J Clin Oncol* 2001; 19: 111-8.
13. Van de Steene J, Linthout N, de Mey J et al. Definition of gross tumor volume in lung cancer: inter-observer variability. *Radiat & Oncology* 2002; 62: 37-49.
14. Giraud P, Elles S, Helfre S et al. Conformal Radiotherapy for Lung Cancer: Different delineation of the gross volume (GTV) by radiologists and radiation oncologists. *Radiother & Oncol* 2002; 62: 27-36.
15. Rasch C, Barillot I, Remeijer P et al. Definition of the prostate in CT and MRI: a multi-observer study. *Int J Radiat Oncol Biol Phys* 1999; 43: 57-66.
16. Kim SH, Choi BI, Lee HP et al. Uterine cervical carcinoma: comparison of CT and MRI findings. *Radiology* 1990; 175: 45-51.
17. Kim SH, Choi BI, Han JK et al. Preoperative staging of uterine cervical carcinoma: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr* 1993; 17: 633-40.
18. Peppercorn PD, Jeyarajah AR, Woolas R et al. Role of MR imaging in the selection of patients with early cervical carcinoma for fertility-preserving surgery: initial experience. *Radiology* 1999; 212: 395-9.
19. Zunino S, Rosao O, Lucino S et al. Anatomic study of the pelvis in carcinoma of the uterine as related to the box technique. *Int J Radiation Oncol Biol Phys* 1999; 44: 53-9.
20. Thomas L, Chacon B, Kind M et al. Magnetic resonance imaging in the treatment planning of radiation therapy in carcinoma of the cervix treated with the four-field pelvic technique. *Int J Radia Oncol Biol Phys* 1997; 37: 827-32.
21. Ahed S, Nutting CM, Reznek R et al. The impact of MRI in radiotherapy planning for cervix cancer. *Clin Oncol* 2001; 13: 318-9.

Paper received and accepted 23 June 2003