Radiological Assessment of Clinical Staging of Lung Cancer

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Abstract

Technical details of volumetric spiral CT and high resolution CT are presented. The role of CT scan in lung cancer is discussed: confirmation of a suspected lesion, identification of an unknown one, clinical staging, planning bioptical procedures and follow-up. In clinical staging, CT scan measures tumor diameter and relationship with surrounding structures (T factor) as well as investigates about nodal status (N factor) at the hilum or in the mediastinum but the limitation is due to the difficulty of distinguish between nodal inflammatory enlargement and metastatic involvement. Moreover, CT can be extended to the upper abdomen aimed of assessing adrenals, kidneys and liver (M factor).
Key words: CT, volumetric spiral CT, high resolution CT, lung cancer, clinical staging.

Riassunto

Vengono inizialmente presentate le premesse tecniche delle metodiche TC volumetrica spirale e TC ad alta risoluzione. Viene successivamente discusso il ruolo della TC nei pazienti affetti da carcinoma del polmone: conferma di una lesione polmonare sospetta, identificazione di una lesione misconosciuta alla diagnostica tradizionale, staging clinico, pianificazione delle procedure bioptiche, follow-up postchirurgico o monitoraggio della terapia radio/antiblastica. Nelle procedure di staging, la TC è apparsa in grado di misurare il diametro del tumore ed i rapporti con le strutture adiacenti (fattore T) come pure di indagare sullo stato linfonodale (fattore N) ilare e mediastinico ma la sua limitazione è dovuta alla difficoltà nel distinguere tra linfoadenopatia infiammatoria e coinvolgimento metastatico. D'altra parte, l'estensione all'addome superiore delle scansioni TC consente l'esame di reni, surreni e fegato e la valutazione, pertanto, del fattore M.
Parole chiave: TC, TC volumetrica spirale, TC ad alta risoluzione, carcinoma del polmone, staging clinico.

Preoperative diagnosis and staging of lung cancer is based on several techniques including radiological assessment of tumour and its extent. Standard chest X-ray is still considered the first imaging method in lung disease, while computed tomography (CT) is commonly used as a second step technique. However no patient usually undergoes further diagnostic or therapeutic procedure without a preliminary CT scan, because of its accurate anatomic evaluation. In addition CT can obviate or suggest the use of more complex and expensive imaging methods, like magnetic resonance (MR) or positron emission tomography (PET), that are in our experience mainly employed as problem solving techniques.

Recent developments of CT technology are volumetric acquisition and high resolution computed tomography (HRCT). Volumetric CT is performed with slip-ring scanners that allow continuous emission of X-rays during continuous rotation of the tube-detector assembly and continuous movement of the patient table at a constant speed[1, 2]. Since the x-ray tube focal spot locus defines a spiral or helix with regard to patient axis this technique is known as spiral or helical CT. Advantages of spiral CT are mainly related to the speed and to the spatial contiguity of the acquisition. Volumetric acquisition allows to scan the entire volume of the thorax during breath-holding, without respiratory misregistration: modern sub-second scanners are able to perform a thoracic acquisition in 20 seconds; scanners with multiple detector arrays are already commercially available, allowing a high quality thoracic scan in less than 10 seconds. Furthermore it is possible to reconstruct images at arbitrary levels in order to have overlapping images at short intervals that are suitable for multiplanar and 3D reformations. These "tricks" allow a different spatial approach to thoracic CT[3], that is no more limited to axial images but can rely on coronal, sagittal and oblique views and possibly on 3D images of vessels, thoracic wall and bronchi (virtual bronchoscopy).

High resolution CT involves obtaining 1- to 2-mm-thick sections and using a high-spatial-frequency reconstruction algorithm to enhance spatial resolution[4, 5]. It provides detailed images of the lung parenchyma comparable to.

gross tissue inspection, allowing detection of disease at an earlier stage. In lung cancer evaluation it is used to better depict nodule borders, to detect fissure involvement, to investigate the relationship between lesion, vessels and bronchi in order to predict the results of a transbronchial biopsy and finally to early diagnose potential cause that can avoid surgery, like diffuse or localised emphysema, interstitial disease and lymphangitic carcinomatosis. Volumetric acquisition and HRCT may be employed together in selected cases to visualise at a better advantage small details in short volumes (small nodules, relationship between nodule and fissure).

The role of CT in lung cancer evaluation is complex. It is used to confirm the presence of a suspected lesion; to identify a lesion not detected with the standard chest X-ray; to evaluate a hilar or mediastinal mass; to complete a bronchoscopic diagnosis; to depict the local extension of the tumour (clinical staging); to characterise the nature of a small nodule; to plan the most useful bioptical procedure (bronchoscopical, transthoracic, surgical); to follow-up surgical and non surgical patients; to define possible obstructive or interstitial associated disease. Future applications that must be clinically validated are virtual bronchoscopy and low-dose spiral CT for mass screening of lung cancer.

Standard chest X-ray has well known limitations in detecting lung cancer. It can miss peripheral lesions smaller than 6 mm and larger lesions located posterior to the heart or the sternum, in the lung hilum or apex (superior sulcus tumours). Nodules adjacent to the pleural surface or the diaphragm can also be difficult to detect. For these reasons mass screening protocols based on standard chest X-ray were abandoned in most institutions. On the contrary CT is able to detect with high sensitivity even 2-3 mm peripheral nodules and 5 mm central and hilar cancer. While conventional CT can occasionally miss nodules up to 1 cm because of respiratory misregistration in uncooperative patients[6] spiral CT usually performs better than conventional CT also in cooperative patients by single-breath-hold scanning of the whole lung parenchyma[7]. Small lesion detection must be optimised using overlapping reconstructions at 4-5 mm intervals[8]; moreover nodules smaller than 5 mm are better detected by means of real-time cine-viewing on a workstation than by simply looking at the images reported on the film[9].

Commonly, CT is first performed to confirm or further assess an abnormality seen on the chest roentgenogram. In approximately 20% of patients referred to tertiary care institutions CT can demonstrate that the questioned or suspected abnormal opacity represents an inconsequential or benign lesion[10]. Some of these pseudonodules are due to pleural disease, fibrosis or an extrapulmonary lesion (ribs, ostephytes, vessel abnormality) that can mimic lung masses on the plain film but can be correctly assessed at CT. In other cases a benign aetiology (granuloma, hamartoma, arteriovenous malformation) may be confidently distinguished from a suspected primary malignant neoplasm at CT, and either further work up obviated or different investigation and management directed.

CT can also help in predicting the nature of the detected lesion by means of morphological, densitometric and dynamic analysis. However the initial evaluation of a suspicious nodule should begin with a comparison of any obtainable previous chest radiographs. Even if absence of growth for two years generally is considered indicative of a benign lesion, the possibility of slow growing malignant and benign lesions must be remembered. Morphological analysis is based on the evaluation of nodule borders[11]. An outer margin that has a spiculated interface with lung or is hazy and less dense than centrally due to lepidic growth is indicative of a malignant lesion; an endobronchial component, convergence with a peripheral pulmonary vein, focal pleural retraction (pleural tag) and the evidence of small central areas of necrosis are additional signs supporting the diagnosis of carcinoma. The presence of small air bronchograms or focal bubble lucencies in a poorly marginated nodule must be considered with suspicion because they may be present in bronchioloalveolar carcinoma, adenocarcinoma and sometimes lymphoma as well as in benign inflammatory mass[12]. Benign nodules usually are well circumscribed with sharp and smooth margins. The basic assumption underlying the use of CT densitometry is that the presence of calcification in a well-circumscribed pulmonary nodule is a strong indicator of a benign lesion because granulomas contain greater amounts of calcium much more frequently than malignant neoplasms. Moreover hamartomas often contain calcium deposits mixed with fatty areas. CT has a great sensitivity in evaluating even small calcium deposits not detectable on the plain film[13]. The demonstration at high resolution volumetric CT of diffuse or central or lamellar calcifications within a well-circumscribed nodule is indicative of a benign lesion and no further evaluation is necessary. However eccentric and stippled calcifications may be present also in primary bronchogenic carcinomas and carcinoid tumours and must be considered with suspicion. The theoretical basis of dynamic analysis of pulmonary nodules is that the vascularity of healed granuloma is minimal. Nodules that enhance < 15 HU in the central portion after intravenous administration of 420 mgI/kg of 300 mgI/ml uroangiographic contrast medium at a flow rate of 2 ml/sec are most likely benign, whereas those that enhance > 25 HU usually are neoplastic. According to Swensen[14] this protocol of dynamic analysis, performed with thin collimated spiral acquisition, has a positive predictive value of 96% and a negative predictive value of 94 % in differentiating cancerous lesions.

An equivalent or even superior efficacy in separating a benign from a malignant nodule may be obtained by assessing the metabolic activity of the nodule by means of FDG-PET (fluoro-deoxy-glucose positron emission

tomography): nodules with active metabolism show significant uptake of FDG and are considered malignant[15]. However active infectious granulomatous disease may also show increased metabolism (false positive result) and some cases of low-metabolism tumours (mainly bronchioloalveolar cell type) may not show significant FDG uptake (false negative result).

Depending on the clinical situation, any nodule that remains indeterminate may be biopsied with a bronchoscopic direct or transbronchial approach, biopsied via a percutaneous needle or surgically removed. In all cases CT can be extremely helpful in planning the best management. Central or even peripheral nodules with a close relationship with a bronchus shown on high resolution CT (bronchus sign), may be best managed by the bronchoscopist and multiplanar or endoscopic reconstruction of CT images (virtual bronchoscopy) may be very useful prior to bronchoscopic biopsies. Percutaneous transthoracic biopsy is usually performed with CT guidance. Fluoroscopic guidance is now performed in few institutions due to the difficulty in assessing the correct position of the needle inside the nodule and to the availability of modern fast CT scanners that can minimise the procedural time and the complication rate. Peripheral, mediastinal and even centrally located lesions can be safely and quickly biopsied with CT guidance. Depending on the experience of the radiologist and the pathologist, needle biopsy may be performed with fine aspirating needle in order to obtain a cytological sample or with fine or large cutting needle in order to obtain small histologic samples. Many authors report different results with both techniques[16, 17] with sensitivity from 74% to 87% but the most interesting results are the very high positive predictive value of 100% and the low negative predictive value of 65% that can be extrapolated from the literature. It means that a biopsy showing neoplastic cells must be considered always positive for cancer but a biopsy in which there aren't neoplastic cells have a good chance of being a false negative result. Consequently is a good practice to repeat the biopsy in all cases where clinical and morphological suspicion of malignancy is high in order to exclude a false negative result. The typical complication of a transthoracic needle biopsy is the occurrence of a pneumothorax in 15 to 25% of the patients; it is usually uneventful but occasionally (3-5%) requires tube drainage, mainly in patients with advanced emphysema. An interesting feature of the bioptical procedure is that in many cases a skilled pathologist can differentiate among the different citotype of lung cancer in order to detect preoperatively the small cell type that can be treated with chemotherapy. CT can be useful also in cases in which a surgical biopsy is performed. With CT guidance is possible to localise small lung nodules for thoracoscopic resection[18] by positioning an hookwire inside the nodule or marking the pleural surface and the tract to the lesion with methylene blue dye.

Promising applications of spiral CT are mass screening of lung cancer and virtual bronchoscopy. Mass screening has been tested in Japan by means of spiral CT performed on mobile scanners at low doses (50 milliampere tube current) by Sone et al[19] on 5483 individuals from the general population aged between 40 and 74 years. Their lung cancer detection rate was 0.48% with a mean lesion size of 17 mm (range 6-47) and their conclusion was that spiral CT led to early detection and an accurate diagnosis of lung cancer and should be considered in future health plans. Virtual bronchoscopy is the possibility to reconstruct from a set of thin collimated axial volumetric CT images a view from the inner surface of the airways. By means of special algorithms and software it is possible to navigate in real-time through the trachea and bronchi and to visualise alterations of their morphology obtaining views that are very similar to real bronchoscopy[20]. Potential applications of this technique are the morphological evaluation of the airways prior to an operative bronchoscopy (laser, transbronchial biopsy, stenting), the identification of small endobronchial tumours in difficult patients, the identification of the extraluminal causes of lumen compression on the native axial images and the visualisation of the areas beyond even high-grade stenosis. However it is not possible to detect initial mucosal alterations and small infiltrations.

Computed tomographic staging of the thorax and upper abdomen has a high accuracy in helping predict the possibility of curative surgical resection and is indicated in the vast majority of patients in whom surgery is contemplated. But its role is not by itself to determine operability or establish prognosis because it depicts gross anatomic abnormalities but has definite histologic limitations and high specificity may not be possible. Thus the detection of an enlarged mediastinal node or adrenal gland or focal liver lesion should not constitute sufficient evidence for inoperability before histologic confirmation. Based on CT localisation of suspected disease, the appropriate biopsy procedure and access route can be determined. CT should not be used to replace invasive staging techniques such as mediastinoscopy but to optimise more selective use of these techniques.

Extent of the primary tumour: the T factor

CT can easily measure tumour diameter and relationship with surrounding structures, thus differentiating T1 tumours located in the peripheral parenchyma without any contact with visceral or mediastinal pleura. It also can evaluate T2 tumours with associated lobar atelectasis or obstructive pneumonitis: sometimes it can be difficult to define tumour burdens from atelectatic lung parenchyma; usually contrast medium administration can help in this task, demonstrating the high and homogenous contrast enhancement of the atelectasis. On CT, mediastinal invasion should be absent if a preserved fat plane or

portion of the lung is demonstrated between the neoplasm and the mediastinal structures, but it should be noted that a simple contact with the mediastinal pleura, with the lack of a well-defined fat plane, does not indicate mediastinal invasion[21]. A low probability of invasion exists if the tumour merely touches the mediastinum over a very short distance with an angle less than 90°. Relatively central tumours, especially adenocarcinomas, frequently extend proximally in the submucosa of the bronchi for a considerable length: peribronchial, soft-tissue thickening may be depicted on CT and should indicate that a deep biopsy at bronchoscopy is needed. Peripheral tumours may directly invade the adjacent pleura: thin-section CT provides more useful information than thick-section CT with an accuracy of 93%[22]. CT can also show a small pleural effusion not detected on conventional radiographs and can guide fluid aspiration for cytological evaluation. The value of CT in the determination of chest wall invasion is controversial[23]. The presence or rib destruction or a soft-tissue mass external to the ribs infiltrating the fat and muscles are absolute signs of chest wall invasion, but are detected only with advanced tumours. CT findings of long contact with the pleura, an adjacent pleural thickening and an obtuse angle between the mass and the pleural surface may suggest parietal pleura invasion but are neither sensitive nor specific. The loss of the extrapleural fat layer is suggestive of invasion and may be more easily recognised on MRI because of its superior contrast resolution in soft tissue evaluation. Magnetic resonance is for this reason mandatory when possible chest wall invasion can alter the management, especially in superior sulcus carcinomas, in which sagittal and coronal planes are very important to detect the extension of the tumour through the apical fat and the relationship with the subclavian vessels and the brachial plexus[24]. Axial CT images usually have limitations in assessing the cephalad extension of these tumours and multiplanar reconstruction obtained from a collimated spiral CT scanning can only partially obviate this problem. However involvement of the ribs and vertebral bodies may be depicted at better advantage by CT. Infiltration of the pericardium, the diaphragm and the heart can be suspected on CT but may require confirmation with multiplanar MR, with cardiac and or respiratory synchronisation in order to differentiate between simple adhesion and true invasion. Trachea, carina, great vessels and oesophagus are usually infiltrated when CT demonstrates that the tumour extends around them and substantially distorts their lumen. MR is generally superimposable to CT in their evaluation.

Summarising a crucial role of the radiologist is to determine whether an advanced T3 or T4 clinical stage is based on unequivocal CT or MRI findings in order to exclude from surgical consideration only non-resectable patients. However it is often not possible to distinguish T3 from T4 lesions: even with an accurate and appropriate technique and modern CT and MR scanners an indeterminate category would occur, when some obliteration of the mediastinal fat is present or vessel and airway distortion is minimal. In most instances these patients remain candidates for an accurate surgical exploration.

Mediastinal lymph node status: the N factor

CT can provide important information about the nodal status in patients with bronchogenic carcinoma. Both CT and MRI can detect lymph node 5 mm or larger in the hilum or in the mediastinum and can correctly attribute them to the various nodal stations. Really the limitation of CT and MR is not represented simply by the detection of lymph nodes but by the difficulty to differentiate between nodal enlargement due to inflammatory disease (infection, reactive hyperplasia, pneumoconiosis) or metastatic involvement[25]. Pragmatically the larger the lymph node appears on CT, the greater the chance it will be neoplastic. However metastases can occur in normal size nodes (microscopic metastases) in up to 15% of patients, concurring to a false negative result of CT nodal evaluation. Moreover occasionally large nodes can be simply reactive causing a CT nodal overstaging. Because of this lack of specificity in detecting the nature of lymph node enlargement, usually a biopsy is needed for confirmation of disseminated disease: a patient should not be denied a potentially curative resection based solely on radiological size criteria of mediastinal lymph node involvement. Usually diagnostic criteria on CT and MR scan, largely chosen to maximise sensitivity, are that any mediastinal node < 1 cm in long axis diameter is considered non neoplastic; nodes between 1 and 2 cm in diameter must be considered suspicious and nodes > 2 cm in diameter are considered metastatic. The reported sensitivity and specificity in predicting nodal metastases from lung cancer are extremely variable, even when using apparently the same criteria and recent equipment with accurate technique. False positive rate varies from 20% to 45% with false negative results ranging from 7% to 39%. An overall sensitivity and accuracy of about 65% seems reasonable with state of the art CT and MR scanners. Even if these results seems to be discouraging CT still plays an important role by aiding in the selection of the most appropriate procedure for further staging (mediastinoscopy, transbronchial nodal sampling), by guiding biopsy and by providing important anatomic information for visual correlation with FDG-PET. At present, anatomic MR imaging has no advantage in evaluating mediastinal node involvement with the exception of the aortopulmonary window nodes that are best imaged in the coronal plane. Future trend in MR research is physiologic MR imaging with iron oxide contrast medium infusion. Uptake of iron oxide particles by normal lymph node has the potential to change their signal intensity helping in differentiating from metastatic

lymph nodes, unable to uptake the contrast medium.
Advances in physiologic imaging of mediastinal lymph nodes with FDG-PET have resulted in improved diagnostic accuracy in determination of nodal status[26]. PET is reported to have better results than anatomic imaging with a sensitivity range between 90% and 95%. Because of its poor anatomic resolution, PET images must be correlated with corresponding CT sections by means of visual correlation or computed generated fusion images (anatomometabolic PET-CT fusion imaging).

Evaluation of distant metastase: the M factor

The adrenals and the liver are the most frequent site of occult extrathoracic metastases and CT staging for lung cancer must be extended to the abdomen to assess these sites. Usually CT can easily demonstrate metastatic deposits in the liver. Suspicious lesions may be confirmed and biopsied with ultrasound if histologic confirmation is needed. MR can be used to differentiate hemangiomas or to clarify pseudolesions due to its superior contrast resolution and the introduction of organospecific contrast media (superparamagnetic iron oxide particles).
CT is very sensitive in detecting adrenal masses but it's to underline that an adrenal mass is not synonymous with metastasis: incidental benign non hyperfunctioning adenomas occur with a similar frequency as that of metastases in patients with lung cancer[27]. Small, well-circumscribed adrenal mass with a low attenuation value (< 20 HU) due to high lipid content is almost certainly benign adenomas. Inhomogeneous enhancing lesions > 3 cm are usually metastases. Lesions with low enhancement at late scan are also usually benign. If the mass is still equivocal after CT scan with appropriate technique and densitometry, MR can be useful[28]. Relatively low signal intensity on both T1- and T2-weighted images, no enhancement after gadolinium injection and signal dropout on opposed phase gradient-echo images (chemical shift imaging), are reliable indicators of a benign adenoma. Percutaneous CT-guided needle biopsy should be planned to confirm adrenal metastases if the patient is otherwise deemed operable of if surgical adrenal removal is considered.
Kidney metastases are easily detected with CT while percutaneous biopsy with ultrasound or CT guidance may provide histologic confirmation.
Cerebral metastatic deposits are usually indagated in selected cases with cranial CT and confirmed by MR, that has a higher sensitivity and specificity.
Bone lesions are occasionally seen during CT scan of the thorax and superior abdomen but they are usually investigated with radionuclide bone scan. Areas of uptake must be confirmed and differentiated from benign or degenerative bone disease by means of dedicated thin collimated CT or MR of the region of interest because of the relatively low specificity of radionuclide imaging.
FDG-PET scanning has an expanding role also in assessing extrathoracic disease when a total body PET scanner is available. It has the potential to detect with a single examination metastatic deposits in the liver, adrenals, bone, kidneys, brain and spleen[15, 29].

Conclusions

There are mainly two different policies in imaging patients with a suspected lung cancer. The more traditional approach is based on CT that has good chances of discovering true lesions and characterising nodules by means of morphological, densitometric and dynamic high-resolution analysis. At the same time it can help in the planning of the best approach to obtain a histologic sample and provide precious information about the likelihood of local and distant metastases. Modern fast spiral scanners are available in many institutions and can provide all this information in a small amount of time.
A second strategy is based on the potential of PET in determining the nature of a solitary pulmonary nodule and in detecting nodal and extranodal disease at the same time. Potential drawbacks of the latter strategy are the high cost and the limited availability of PET scanners; moreover, physiologic information of PET is somewhat limited without anatomic correlation of CT that further increases costs. In a recent decision analysis study regarding cost-effectiveness of FDG-PET for staging non-small cell lung cancer Scott et al.[30] reported that a strategy that uses PET only after a negative CT study is shown to be a cost-effective alternative to the CT-alone strategy. Probably a compromise should be found in which greater use of PET for diagnostic and staging purposes is warranted, provided that CT has obtained an initial selection of benign, other inconsequential lesions and of really advanced cases.

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