PERGAMON

EJC Supplements Vol 1 No. 2 (2003) 28–42

EJC Supplements

www.ejconline.com

New imaging techniques in oncology

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Received 10 December 2002; received in revised form 25 March 2003; accepted 23 May 2003

Abstract

Techniques that have evolved as a result, such as helical computed tomography (CT), intra-operative magnetic resonance imaging (MRI), clinical positron emission tomography (PET) and fusion and functional imaging, will provide oncological physicians with more flexibility and accuracy in the diagnosis and assessment of tumors.

1. Helical computed tomography

The word 'tomography' is derived from the Greek words *tomos*, meaning to slice, and *graphein*, meaning to write. Tomography was computerized during the 1970s. A narrow beam of X-rays sweeps across an area of the body and is recorded, not on film, but with a radiation detector as a pattern of electrical impulses. Data from many sweeps are integrated by a computer, which uses the radiation absorption figures to assess the density of tissues at thousands of points. Helical scanning is a breakthrough technology that has changed the medical community's approach to computed tomography (CT) procedures. Helical CT can improve lesion detection and cancer staging because it improves image quality. With helical CT, the pitch is defined as radio between table speed and collimator width (Pitch = Table speed (mm/s)/Collimator width (mm)). Increasing the pitch allows a greater volume of tissue to be scanned per unit time. Additionally, a pitch greater than one enables narrower collimation, which ultimately results in improved resolution. Another benefit of helical CT is the ability to obtain more consistent opacification of vessels with smaller volumes of contrast, primarily because of the shorter imaging times. Four new techniques, fast imaging for mass screening, virtual endoscopy (and three- dimensional reconstructions), clinical measurement of volumes and perfusion imaging, put this new level of precision to good use in the clinical setting.

1.1. Applications for the mass screening

The Early Lung Cancer Action Project (ELCAP) [1] is designed to evaluate baseline and annual repeat screening by low-radiation dose CT (low-dose CT) (Fig. 1) in persons at high risk for lung cancer, developed by C.I. Henschke of Cornell University of New York. Since starting in 1993, the ELCAP has enrolled 1000 asymptomatic persons, 60 years of age or older, with at least 10 pack-years of cigarette smoking, non-prior cancer, and medically fit to undergo thoracic surgery. After a structured interview and informed consent, baseline chest radiographs (CXR) and low-dose CT were obtained on each subject. Low-dose CT was repeated on an annual basis as long as no malignancy was found. The diagnostic work-up of screen-detected non-calcified pulmonary nodules (NCNs) was guided by ELCAP recommendations which included short-term high-resolution CT follow-up for the smallest NCNs.

The baseline screening results are on low-dose CT at baseline as compared to CXR, NCNs were detected 3 times as commonly (23 versus 7%), malignancies 4 times as commonly (2.7 versus 0.7%), Stage I malignancies 6 times as commonly (2.3 versus 0.4%). Of the

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1359-6349/03/$ - see front matter
doi:10.1016/S1359-6349(03)00012-0

27 CT-detected cancers, 96% (26/27) were resectable; 85% (23/27) were Stage I, 19 (83%) of the 23 were not seen on CXR. Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCNs; 27 had a malignant NCN and 1 had a benign one. Another three individuals underwent biopsy outside of the ELCAP recommendations, all had benign NCNs. No one had thoracotomy for a benign nodule. Concerning the annual Repeat Screening Results: in the repeat screenings, the test result was positive in 30 (2.5%). In 2 of these 30 instances, the subject died (of unrelated cause) before diagnostic work-up; the nodule(s) resolved in another 12; and absence of further growth was documented by repeat CT in 8 of the remaining 16. Further growth was documented in all of the remaining 8; all 8 were biopsied and malignancy was diagnosed in 7 of them. Six of the seven malignancies were non-small cell carcinomas, 5 of Stage IA and one of Stage IIA, and the one small-cell carcinoma was of limited stage. The median diameter of these malignancies was 8 mm. In another two subjects, symptoms prompted interim diagnosis of lung cancer, neither one of these nodule-associated (but endobronchial instead); 1 was a non-small cell carcinoma of Stage IIB and the other a small-cell carcinoma of limited stage.

Thus annual CT screening for lung cancer provides for detecting the disease at earlier and presumably more commonly curable stages in a cost-effective manner.

The ELCAP report, in turn, inadvertently led to considerable public and professional interest in the practice of CT-based screening for lung cancer; and within Cornell it led to two carefully-considered initiatives: the planning and fund-raising for a project experimentally to screen 10 000 high-risk persons in what got to be called the New York ELCAP (NY-ELCAP), and the International Conferences on Screening for Lung Cancer [1].

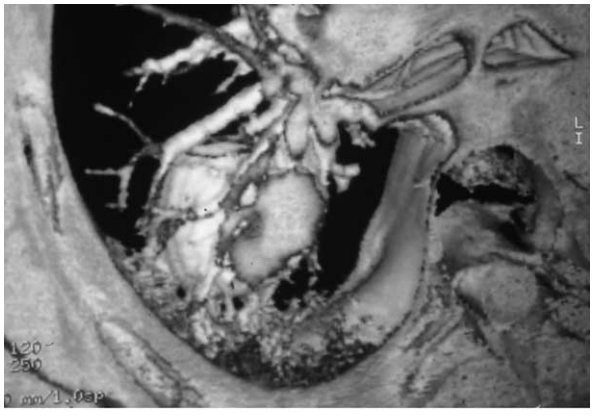


Fig. 1. Low-radiation dose computed tomography (low-dose CT) showing, in 3-D reconstruction, a right lung distal carcinoma with uphill lymphagitis.

1.2. Virtual endoscopy (and 3-D reconstructions) [2]

1.2.1. Acquisition techniques and parameters

Helical CT is particularly suitable for the study of anatomical cavities. New methods of image processing can produce virtual endoscopic images without the use of an endoscope. By combining contiguous table movement at a constant velocity during data collection with concomitant rotation of the tube and detectors at a constant speed and direction, helical CT enables the performance of single volumetric breath-hold acquisition of images of the thorax. Further calculation or interpolation reduces artefacts caused by patient movement. Similarly, respiratory motion artefacts can be eliminated. A high-quality three-dimensional (3-D) image can be reconstructed from the contiguous slices. These reconstructions can be made volumetric by using a slice thickness formed by the summation of several adjacent sections, a technique known as multiprojection volume reconstruction (MPVR). It is also possible to select minimum intensity or maximum intensity algorithms to obtain image projections of the cavities from their outside surface. So-called surface reconstructions appear in relief.

1.2.2. Virtual colonoscopy [3] (Figs. 2 and 3)

Polyps of the colon appear in virtual colonoscopy as in a barium enema or at colonoscopy. They are tissue nodules arising from the colon wall which protrude into the colonic lumen. These nodules may be pedunculated or sessile, with a smooth or irregular surface and a circular or, in contrast a multilobular outline. They may be single or multiple. It is possible to recognise a lipoma by measuring the density (negative) and to identify a vascular lesion (varices or angiomas) by and injection of contraste. A calcification evidencing an angiomatous lesion is easily identified with the scanner.

Colonic carcinomas are evidenced by a persistently undistended segment, combined with an asymmetric

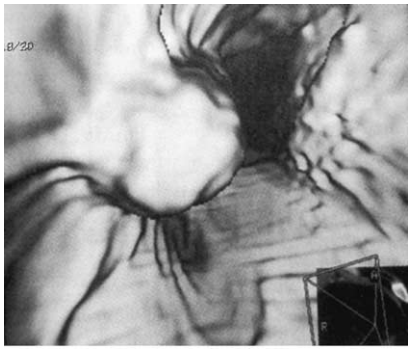


Fig. 2. Virtual colonoscopy showing large sessil polyp carcinoma of the left colon.

parietal thickening, either circumferential or with a large endoluminal polypoid mass. The parietal colonic thickening has sharp boundaries and the haustrations are deformed. The outlines of the parietal thickening are irregular, sometimes with dense streaks in the pericolic fat. An intraperitoneal effusion, adenopathies, mesenteric masses and hepatic metastases are evidence of spread of the disease. In the strictly endoluminal views, it is difficult to differentiate a tumoral narrowing from defective gas distension of the colonic lumen. However, the 2D images (bidimentionnal images in coronal and sagittal planes) readily demonstrate a parietal thickening greater than 1 mm in a distended colonic segment. A tumoral luminal narrowing is irregular, asymmetric, creviced and abrupt and thereby differs from narrowing due to spasm or defective insufflation. Moreover, a tumoral narrowing is constant in the acquisitions in the prone and supine positions. In cases of diverticulosis, the colonic wall is already thickened and therefore the diagnosis of an added tumor is difficult. Only the abrupt nature of the thickening can aid the diagnosis.

Diverticula appear as gaseous clear areas transgressing on the colonic lumen. In the endoluminal views, these are manifested as dark patches with a parietal defect. False images of diverticula are sometimes produced by the adhesion of two bowel segments distended by air.

When the interface is smaller than the contact zone, the wall between the two segments disappears completely or partially. Ulcerations are not clearly identified since the colour is also virtual. They appear as parietal depressions surrounded by a rim or by nodular folds (pseudopolyps) [3].

Colonic pseudolesions are essentially represented by folds, haustrations and colonic plications. Colonic folds and haustrations are narrow transverse bands 1–2 mm thick which bar the lumen. They predominate in the sigmoid and transverse colon, where they assume the triangular appearance of a bar of Toblerone chocolate. Their thickness is regular but they assume a nodular aspect which simulates a polyp when seen in oblique view or when they are curved. These complex folds are commoner near the angles. These false polyps may be seen during endoluminal inspection but also in the 2-D images. In order to relate these images to the folds and haustrations from which they originate, the multiplanar reconstruction for the 2-D images must be displaced in space. For the endoluminal view, it is the virtual endoscope which must be so displaced. It is also possible to access the relevant fold by a descending and then an ascending route [4].

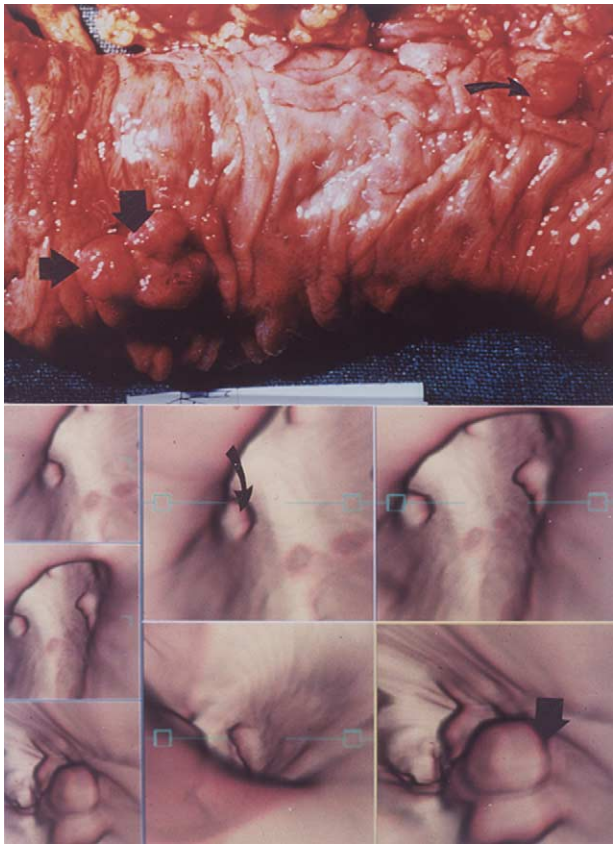


Fig. 3. Colonic polyps: at virtual endoscopy (lower image), multiple polyps are detected in the left colon, of which three are small and one larger. The operative specimen confirms these images (upper image, arrows) (courtesy of G. Schmutz, Springer [3]).

1.2.2.1. Reliability [3]. This technique has been evaluated by *in vitro* studies [5] but especially in a series of patients with colonic carcinomas and polyps. These preliminary studies, dealing with over 2000 patients, demonstrated a sensitivity of more than 75% and a specificity exceeding 90% for colonic carcinomas and polyps larger than 10 mm. The sensitivity fell to 70% for polyps between 5 and 10 mm and to 28% for polyps smaller than 5 mm. The sensitivity rose to 85% if double acquisition in both the prone and supine positions was used. Recent larger prospective studies (100 patients) reveal, per patient, a total sensitivity of 82% and a specificity of 84%, with a positive predictive value of 82% and a negative value of 84% [6]. For polyps larger than 10 mm, the sensitivity, specificity, positive predictive value and negative predictive value were 96%. Moreover, these studies reveal certain particular advantages of virtual colonoscopy compared with conventional colonoscopy. Thus, virtual colonoscopy can study the colon above an obstructive lesion [7] and can analyse the margins of the haustrations in both an antegrade and retrograde manner to reveal lesions that may be missed at conventional colonoscopy.

1.2.2.2. Limitations [3]. The main diagnostic difficulties are represented by solid or fluid residues within the internal lumen [8]. Anomalies are easier to identify in the 2-D sections than the 3-D endoluminal images,

appearing as formations with endoluminal relief and thus resembling true polyps. Nevertheless, the projecting appearance of the lesions is often less marked and less regular. The use of two helices in different positions allows mobilisation of fluid residues. Thus, this double study, which increases the irradiation, markedly improves the detection of polyps of 10 mm, increasing the detection rate from 75 to 85%. In order to eliminate this difficulty while reducing the burden of preparation for the patient, studies are under way to label the stools with barium sulfate or gadolinium for MRI colonoscopy by giving the patient contrast medium to drink 1–2 days before the examination [9]. The result appear inconclusive for the barium, and for gadolinium the cost is quite an obstacle and the effectiveness of the procedure has not yet been demonstrated. However, by thus labelling the stools, their simultaneous automatic electronic effacement may become possible.

The endoluminal study requires good distension of the colonic lumen since the virtual endoscope must be at a distance from the endoluminal lesion to permit its better assessment. Further, the parietal colonic thickening cannot be confirmed unless luminal distension is optimal. For a satisfactory endoluminal view, it is necessary to have a volume of at least 2 cm around the lumen [3].

Artefacts exist which are linked to characteristics of the reconstruction, as is notably the case for the scanning artefact, which produces concentric circles on the colonic walls. This is easily treated by smoothing the image. By decreasing the thickness of the section and reducing the 'pitch', these concentric circles are reduced. Artefacts of movement give rise to a linear image seen in relief in the endoluminal images. The colonic outlines also appear fuzzy. Barium and metallic bodies (hip prostheses) which drastically modify the attenuation of the X-rays produce artefacts on the colonic contours.

During analysis of the images obtained, the study of the 2-D and 3-D reconstructions is made simultaneously. An anomaly detected in an axial 2-D view is immediately monitored by an endoluminal view. The parietal colonic thickening can also be monitored and studied by simple tilting or rotation of the colonic lumen, according to the modes of multiplanar reconstructions. A study comparing the input of the 2-D and 3-D images confirms their essential complementarity, with a similar sensitivity for each analysis [10].

The current limitations of virtual colonoscopy are those of inadequate colonic preparation [11]. Defective insufflation and colonic distension both limit virtual endoluminal evaluation. Clinical tolerance is generally good, better than for colonoscopy, but the irradiation (similar to that of a double-contrast barium enema) is a factor to be considered, especially in the context of screening in young subjects. The medical time at the work console required to perform virtual endoscopy, with four successive complete colonic studies, i.e. antegrade and retrograde displacement in both the prone and supine positions, is a major limiting factor [12].

1.2.2.3. Place and prospects [3]. Its qualities permit virtual colonoscopy to be envisaged as a method for detecting colonic polyps. Conventional colonoscopy might then be reserved for patients suspected of having polyps at virtual colonoscopy. It is difficult at this time, with the number of scanners available, to envisage replacing all screening colonoscopies by virtual colonoscopy. Nevertheless, the results of current comparative studies allow consideration of this possibility, especially if developments in information technology shorten data treatment times and allow the development of automatic virtual endoscopy, possibly also with automatic detection of polyps by an advanced system.

Actually, the objective is to reduce the number of patients at risk who currently escape all methods of detection. By its simplicity and ease of performance, virtual colonoscopy may perhaps reach these patients.

Apart from the detection of polyps, in which the United States seems widely involved [13,14], the other applications of virtual colonoscopy that may be envisaged are the failures and inadequacies of endoscopy for anatomic or lesional anomalies. Stenosing lesions make colonic emptying above the lesion more difficult; nevertheless, in 75% of cases a virtual proximal endoscopic study is possible. Virtual colonoscopy may also be envisaged as supplementary to endoscopy in the case of endoluminal lesions detected at colonoscopy but whose exact etiology remains undecided: whether a mucosal, subucosal or parietal lesion. Complete analysis of the colonic wall may facilitate the diagnosis. Thus, it is possible to assess pericolic lesions such as abscesses and fistulae. Unlike bronchoscopy, where virtual transgression of the bronchial wall allows placement of the virtual endoscope in an identical aerial environment [15,16], crossing the colonic wall does no allow a real endoscopic study of the pericolic space. Virtual colonoscopy, or rather scanographic study of the colon, may also be envisaged in unfit elderly persons where colonoscopy or opaque enemas are difficult to perform. In this situation, 2D images are then essential in the search for a malignant thickening. Moreover, in the precise location of colonic lesions and, if need be, integrating the different layers (cutaneous, muscular, peritoneal, etc.), the scanner can facilitate the surgical procedure, especially for laparoscopic resections.

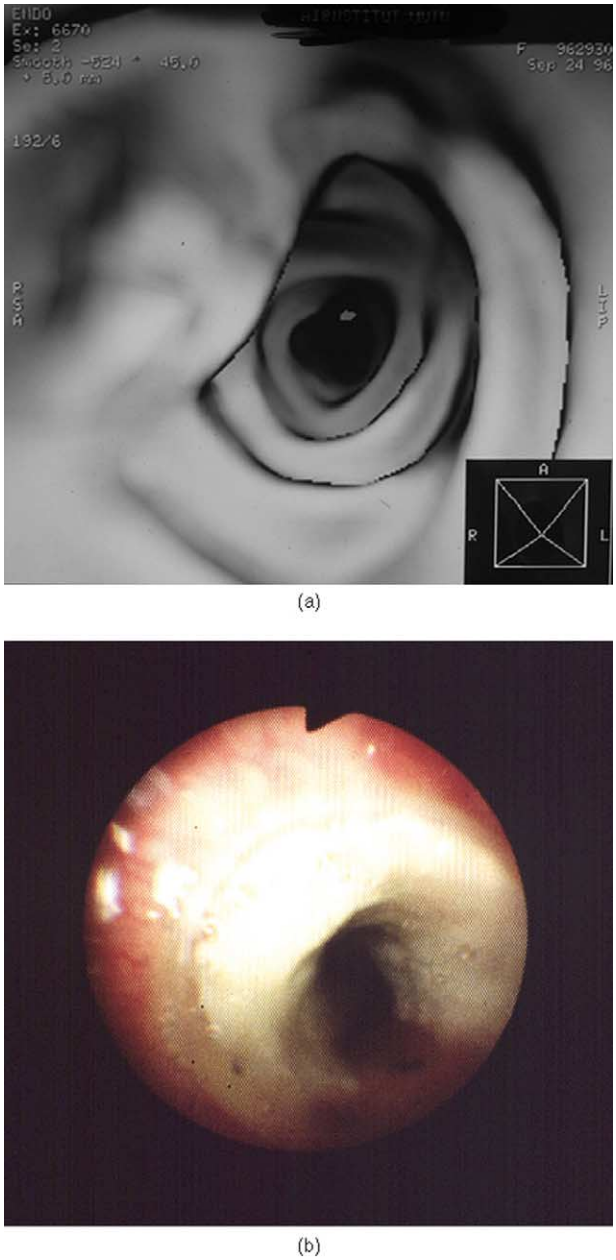
Lastly, looking to the future, it is possible to envisage that virtual colonoscopy will become the mode of training for endoscopists and perhaps even that it will permit the automatic teleguidance of actual colonoscopy for the resection of polyps.

Virtual colonoscopy remains a technique that is still under evaluation. The first studies, especially in America,

confirm the hopes invested in this technique for the detection of polyps, but larger series remain necessary. Apart from this important contribution to cancer management, virtual colonoscopy already allows improvement of the quality of colonic studies by scanner.

1.2.3. Virtual bronchoscopy (VB) [17] (Fig. 4)

Virtual reality has been applied to the bronchial tree since 1994 [18]. Assessment of VB for various clinical and educational applications [19] is still under investigation. However, fields of potential applications of this new technique are numerous. VB can play a rôle in the diagnosis and staging of lung cancer, for preoperative planning of bronchoscopy or surgery, for intra-operative guiding of interventional bronchoscopy procedures, for assessing non-invasively the results of various treatments.



(a)

(b)

Fig. 4. Partial blocking of a wall stent in virtual bronchoscopy (a) and in standard endoscopy (b) (courtesy of D. Buthiau [42]).

Bronchoscopy and CT are complementary modalities for evaluation of the central airways [20]. Diagnosis of centrally located lung cancer is usually based on cytological and/or histological examination of samples obtained with fibre optic bronchoscopy (FOB). FOB is a minimally invasive technique that has a very low rate of severe complications (0% mortality rate and 0.8% morbidity rate) [21]. Although the false-positive rate of biopsies is very low (less than 1%), the false-negative rate is dependent on the location of the tumor, ranging from 8% in case of visible tumors to up to 90% in the case of peripherally located tumor [21]. Progression of FOB is limited by the diameter of the fibroscope (5–6 mm) to segmental bronchi. Severe stenoses of the airways preclude progression of a bronchoscope. Abnormalities that are located behind the bronchial wall and that do not modify its appearance are overlooked.

Axial CT offers high positive and negative predictive values for the presence of endobronchial diseases up to a segmental level [22,23]. However, the interpretation of complex airway anatomy is sometimes difficult when using only axial CT images. Helical CT has enhanced the accuracy of CT examinations because of volume acquisition, optimisation of contrast enhancement, selection of smaller section thickness, and generation of non-axial reconstructions. However, axial CT is not able to delineate mucosal abnormalities. Therefore, CT is the primary technique for assessing the extraluminal extension of the cancer and the extension to thoracic lymph nodes while bronchoscopy is the technique of reference to detect and diagnose central bronchogenic carconima.

May we expect any improvement from VB?

1.2.3.1. Detection of lung cancer [17]. The signs of bronchogenic carconima at VB are derived from the signs observed at real bronchoscopy. However, VB does not show the mucosa of the tachea and bronchi. Therefore, VB analysis of the airways is limited to the qualitative evaluation of the gross morphology of the airways and search for alteration of the relief of the air/wall interface. Bronchogenic carcinomas appear at VB as stenoses of the airways that are usually asymmetric, due to endoluminal mass, infiltration of the wall of the bronchi or trachea, and extrinsic compression. Total occlusion of the bronchi may be seen. VB images should always be interpreted along with axial CT or 2-D reformations of the bronchi in order to avoid mesinterpretation.

Important information given by FOB concerning the vascularisation of the mucosa, its colour, or the dynamic of the bronchi is not accessible by using VB, and constitutes its main drawbacks. Many authors have reported the excellent correlation between VB and real

images concerning the location, shape, and size of space occupying tumors. Estimating the degree of stenosis can be done visualising only one VB image, whereas several contiguous axial CT images or MPR images MPR images were usually needed [24].

One of the possible benefits of VB is examining the airways situated peripherally to severe stenoses or an obstructions because VB could pass high-grade stenoses, which is not possible using real bronchoscopy. However, one should emphasize that false positive results can be created by viscous secretions or coagulated blood within the bronchi.

An interesting way of research has been proposed by Summers and colleagues [25], who developed a computer algorithm for automatic detection of polypoid lesions of the airways from surface-rendered VB reconstructions. The ultimate goal of this technique is to shorten the time devoted to review VB images and to reduce incorrect diagnoses. In fact, sensitivity increased significantly when only lesions larger than 5 mm in diameter were considered.

1.2.3.2. Characterisation of endobronchial lesions [17]. Once detected, endobronchial lesions must be quantified. Using surface-rendering VB software, Summers and colleagues [26] have evaluated the effects of HCT parameters on the detection and size measurement of simulated round endobronchial lesions ranging from 3 to 10 mm in diameter. They have demonstrated that the apparent size and shape of endobronchial lesions were highly dependent of the choice of HCT parameters (collimation, pitch, reconstruction filter, and level of thresholding). Increasing slice collimation decreased the apparent size of lesions. The choice of the threshold value was of great importance: as the threshold was more negative, the apparent size of lesions increased artificially. An optimal threshold was around −500 HU. Spherical lesions seemed elongated along the *z*-axis under certain parameters. This distortion increased when using larger section thickness, larger pitch, and larger interval reconstruction. Moreover, the size of endobronchial lesions was dependent of the distance between the mass and the objective of the virtual endoscope, because of perspective projection artifacts. Summers and colleagues concluded that measuring endobronchial masses from perspective surface rendering can be unreliable and that measurements should be made from standard axial CT images or by using multiplanar reformatted images [26].

Although VB is able to show external compression of the airways as smooth and regular reduction in diameter of the trachea or bronchi, analysis of the origin of the compression requires displaying axial CT or multiplanar reconstruction. The main causes are thyroid goiter, aortic aneurysm, mediastinal tumors or adenopathy.

Although VB gives realistic reproduction of space occupying lesions of the central airways, VB could not replace FOB for evaluation of patients suspected of lung cancer because FOB allows precise assessment of the mucosa as well as obtaining histological and cytological samples. VB provides an alternative for patients in whom real bronchoscopy is refused or contra-indicated.

1.2.3.3. Staging lung cancer [17]. The prognosis of patients with lung carcinoma depends on both the histopathological cell-type, i.e. non-small cell carcinoma (NSCC) and small-cell carcinoma (SCC), and the extent of the disease as evaluated using the TNM system [27]. In patients with NSCC, surgery is the only hope of a cure. However, approximately 50% of patients with NSCC have unresectable tumors at the time of diagnosis. Therefore, imaging should ideally differentiate preoperatively patients who may benefit from surgical resection because the disease is localised, from those with unresectable cancers because of local, nodal or distant extensions. CT is used in most institutions as a standard part of the initial work-up of patients with known or suspected lung cancer although CT disagrees with postoperative TNM staging in about 40% of patients [28].

1.2.3.4. Lymph-node staging [17]. Ideally, imaging techniques should be able to separate metastatic from normal lymph nodes. The only CT sign of tumoral spreading to lymph nodes is nodal enlargement. Using a 10-mm short-axis diameter cut-off figure and a gold standard consisting of extensive mediastinal dissection, recent studies have reported a low accuracy for CT scanning, with both a low sensitivity and a specificity ranging from 50 to 65% [29,30]. In practice, mediastinoscopy or alternative biopsy techniques of the mediastinal nodes are recommended in patients with enlarged mediastinal lymph nodes shown on CT images, to prove nodal metastasis that could preclude surgical resection [31].

Trans-bronchial needle biopsy (TBNA) is a minimally invasive and cost-effective bronchoscopic procedure for diagnosis and staging lung cancer. TBNA allows sampling of mediastinal and hilar nodes, i.e. nodes in sites 2D, 2G, 4D, 4G, 7, 10, 11, 12 of the AJCC classification [32]. Therefore, TBNA can possibly avoid mediastinoscopy. However, this technique is underutilised (11% of practising pneumonologists in the US [33]) despite its good clinical efficacy in trained hands [34]. The sensitivity of TBNA for malignancy varies from 34% to more than 90%. One of the main difficulties in performing TBNA is to define the site of puncture according to axial CT findings [34]. VB has the capability to demonstrate enlarged lymph nodes adjacent to the trachea and bronchi in rendering semi-transparent the wall of the airways [35]. Simultaneous display in a bronchoscopic

format of endobronchial landmarks, mediastinal nodes to sample, and great vessels to avoid could play a dramatic rôle in stimulating the diffusion of TBNA. McAdams and colleagues [36] conducted a preliminary study of VB as a guide for TBNA. Using the volume-rendering technique, they included 17 patients with mediastinal adenopathy. TBNA were conducted by a trained fibroscopist used to practise TBNA. In this series, the sensitivity of TBNA was 88% on a per node basis analysis. Bronchoscopists involved in the study mentioned several reasons that may have produce such good results: (a) VB helped them to evaluate node location and angle of approach for biopsy; (b) VB increased their confidence so that they aspirated smaller nodes at more difficult locations; (c) VB shortened the time spent preparing bronchoscopy as well as duration of bronchoscopy. Despite these promising results, the real impact of VB on the diagnostic yield of TBNA has to be evaluating in prospective randomised studies. Haponik and colleagues [37] emphasised that the rôle of VB in guiding TBNA is likely to vary with each fibroscopist yield. VB may enhance the yield of TBNA in a fibroscopist with little or no experience of the technique.

TBNA may be monitored using a miniature sensor attached to the extremity of the bronchoscope [38]. The sensor gives the exact position of the tip of the bronchoscope within the airways and is reported in real time in the virtual airways.

Bricault and colleagues [39] developed a computer-assisted transbronchial biopsy system. Registration of the position of the tip of the endoscope is obtained without any external localisation device. The technique requires the registration of a preoperative helical CT of the thorax and an intra-operative endoscopic 2-D image sequence. Matching of the two kinds of images is realised in real time during the procedure, thanks to algorithms able to localise the fiberoptic camera position inside the CT data coordinate system. Simulations showed a localisation accuracy of 1.1 mm.

1.2.3.5. Monitoring interventional bronchoscopic procedures [17]. Interventional bronchoscopy, including placement of bronchial stents, laser photocoagulation, endobronchial cryotherapy, and brachytherapy has an increasing role in the minimally invasive management of tracheobronchial diseases in selected patients. These procedures require careful preoperative planning and postoperative assessment of abnormal bronchial segments. To our knowledge, the exact rôle of VB in planning these procedures has not been extensively evaluated.

VB may help fibroscopists in showing, in a familiar format, abnormalities that are not visible using real fibroscopy, i.e., the bronchial tree below bronchial stenoses or recurrent views. In patients with stenoses of the airways, VB should be used along with axial CT images and multiplanar reconstruction in order to accurately measure the length of stenoses. VB could also be associated with 3-D surface shaded reconstructions as this technique of visualisation has been shown to be of value to demonstrate and assess stenoses. Helical CT with reconstructions can be used for non-invasive follow-up after endobronchial procedures such as bronchial stenting. After stenting, the lumen of the bronchi should recover its normal size. The stent should cover the narrowed bronchial segment but should spare the orifice of bronchi located above and under the stenosis. Depending on the type of the stent, the bronchial lumen appears smooth or irregular. VB is useful for the follow-up of bronchial stents to detect stent migration or stent fracture. In case of stent misplacement or migration, VB shows persistent stenosis of the bronchus at one of its extremities. Real bronchoscopy is therefore indicated in order to reposition the stent properly. Diagnosis of stent migration to the mediastinum or lung parenchyma requires the reading of axial CT images along with VB. Insertion of a stent smaller in diameter than the bronchus results in creating a recess between the stent and the bronchus. Secretions will accumulate in the recess, creating conditions for bronchial and parenchymal infections. When the stent diameter is equal or even larger than the bronchial lumen, one classical complication is the development of granulomatous reaction at the extremity of the stent, which narrows the lumen of the airway. VB and 2-D reconstructions in the axis of the bronchi are useful to depict stents that are larger than the bronchial diameter.

1.2.3.6. In summary [40–49]. VB is a new way to visualise CT data in an endoscopic format that allows depicting major endobronchial abnormalities. However, VB does not add any information to that provided by axial CT images. As VB does not show mucosal detail of the airways and, does not provide any samples, VB will probably not replace real bronchoscopy. Potential diagnostic applications are numerous but more clinical word has to be done to prove the advantage of VB as compared to axial CT images and other 2-D and 3-D reconstructions. It can be employed to visualise semi-distal lesions that can be only seen with a thinner endoscope. It can also be applied as an aid in brachytherapy. Virtual tracheobronchial endoscopy permits follow-up endoprostheses (Fig. 4) (sensitivity 95%; specificity 79%) without additional risk to the patient, and it permits the surgeon to check on suture stability.

1.2.4. Virtual cystoscopy [50]

1.2.4.1. Bladder tumors [50–52]. Today, endoscopic inspection remains the most valuable procedure for the diagnosis of bladder tumors. The classification of tumors of the urinary bladder is based on two essential criteria: Histological differentiation and degree of

cytologic abnormalities will grade the tumor (G: I, II, III); however, morphologic pattern with papillary or non-papillary aspect, pedonculated or sessile attachment and tumor confined to the epithelium or infiltrating the bladder wall will stage the tumor (T: Tis, Ta, T1, T2, T3, T4). The vast majority of bladder tumors are transitional cell carcinoma (up to 90%) with near papillary appearance. Squamous cell carcinoma accounts for less than 5% while adenocarcinoma, representing less than 2% of the total number of bladders are even less frequent. Whatever the type of the bladder tumors, they vary widely in their endoscopic appearance but their form correlates well with the grade and often the stage of the tumor. Papillary lesions with well-defined fronds are usually low grade and low stage as well. These papillary tumors (Fig. 5) can be solitary or multiple. They are often located just lateral to the ureteral orifice but can be found any where within the bladder. The variety in appearance from a papillary to a sessile tumor represents a spectrum of morphology, and various patterns and combinations may be seen within the same tumors. Assessment of all the characteristics can be correctly achieved by the 3D CT cystoscopy. This tool is certainly able to provide a good assessment in number, size and morphological appearance of all type of tumors of the bladder. In the same manner as for the clinical cystoscopy, bladder tumors can be ranged from flat to exophytic, with broad sessile or pedonculate attachment and with solid or papillary appearance. Typical papillary tumors represent up to 90% of all the tumors of the urinary bladder. These tumors correspond to nearly spherical masses of tumor fronds responsible of their 'sea anemone-like' configuration (Fig. 5). They are solitary, or more often, multiples in the case of diffuse papillary disease. These small or voluminous tumors with a pedonculated or a sessile base have been proved to be low-stage and low-grade tumors. Diffuse papillary disease of the urinary bladder corresponds to a condition in which multiple low-grade and low-stage transitional cell carcinomas have circumscribed papillary configuration and appear as 'mulberries' on the inner bladder surface. On virtual cystoscopy, while papillary aspects are correctly assessed with the largest tumors, small tumors show always a near polypoid solid configuration. A more solid-appearing mass tumor, possibly with a wide base, is much more likely to be high-grade and high-stage than pedonculated and papillary tumors. In the course of cystoscopy an experienced endoscopist on inspecting the bladder knows immediately that he is dealing with an aggressive, high-grade and probably high-stage tumor. In the same way, a solid-appearing aspect of a tumor can be assessed with confidence by 3-D CT cystoscopy. 2-D axial and reformated views are complementary tools with virtual cystoscopy and should be used together for accurate tumor identification and assessment of the stretching through the bladder wall.

1.2.4.2. Tumors of the upper urinary tract. Because benign and malignant tumors of the upper urinary tract usually present with similar symptoms, their differential diagnosis is often difficult. Papillomas, fibroepithelial polyps, inverted papillomas, cholesteatomas, malacoplakia, endometriosis and others may present with obstruction and when the maximal contrast–tissue interface is obtained, the virtual endoscopy could find the same mucosal or parietal abnormalities as for the urinary bladder.

1.2.4.3. In summary [50]. In patients with bladder tumors, it is well understood that virtual endoscopy is less effective than traditional endoscopy cystoscopy because it will never perform biopsies or resections which remain unavoidable. However, some conditions such as screening for recurrent diseases, technical difficulties in fatty patients or specific abnormalities like strictures, may represent a good indication for this new technique. With the added advantage that it is less invasive and thus has fewer complications and reduced inconvenience, time and discomfort for the patient than clinical cystoscopy, virtual cystoscopy permits not only the diagnosis of the presence or absence of a bladder

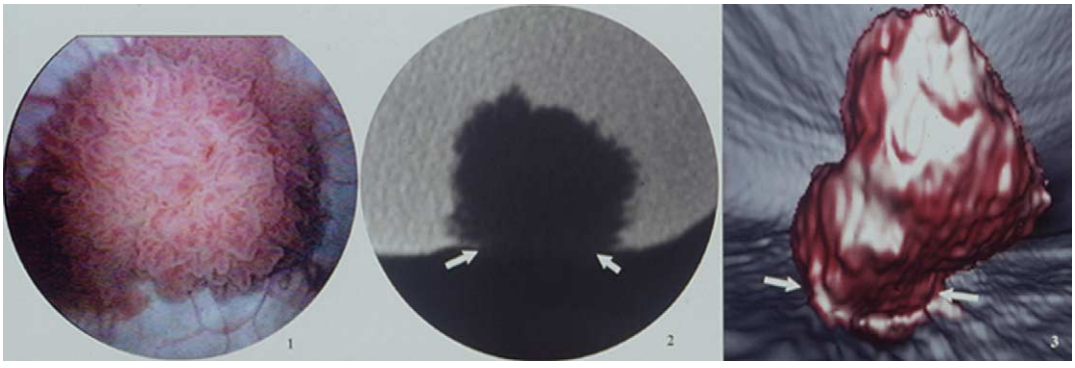


Fig. 5. Typical papilloma: 3-D CT cystoscopy (right image), axial-CT section (middle image) and cystoscopy (left image) show a large villous papillary tumor (sea anemone-like tumor) with numerous short folds and quite large base proven to be a T1 stage (courtesy of R. Palau [50]).

tumor, but it is also useful in the assessment of the number and position of the tumors. Moreover, 3-D CT cystoscopy allows in the same time an evaluation of the adjacent extravesical structures. Inspection of the lesion will also offer some evidence of the stage and often the grade of the tumor. However, grading the tumor remains a great challenge but, although the specificity was low concerning the mural stretching, it is obviously improved when combined with 2-D axial and reformated CT section. In this way, virtual cystoscopy may yield important clinical and public health benefits, particularly in patients with repeated surveillance cystoscopy. Moreover, virtual endoscopy of the urinary tract and especially of the bladder may be a valuable toolin training and teaching.

1.2.5. Virtual endoscopy in ENT [53] (Fig. 6)

Virtual endoscopy is recent and was, we must admit, initially disappointing. The comparison of real endoscopic images with reconstituted virtual images encountered great difficulties, sometimes aberrations, and rendered the technique of little value.

It should also be noted that, at the very beginning, the technique was often used to visualise zones easily visualized by other means (e.g. the nasal cavity) which, in view of the poor results obtained, devalued the technique.

Actually, it is used in ENT with several aims:

- More convenient images for clinicians.
- Educational value in a teaching context.
- Recent applications before operations in specific areas: a preoperative example is in the surgery of the sphenoid with simultaneous visualisation of the carotid and the sinus cavity. During the operation, the surgery can be computer-assisted, the systems of peroperative guidance providing the surgeon at each moment in real time with the position of his instrument in the images derived from the operative zone or with images of the cavities and surrounding tissues in a 3-D virtual model.

These navigational systems are developing rapidly and their precision has improved. Nevertheless their high cost remains a barrier to their development, as does the need for supplementary training comprising an apprenticeship in specific visual strategies.

1.3. Clinical measurements in vivo *[54,55] (Fig. 7)*

According to the World Health Organization (WHO) criteria for therapeutic evaluation of the response to treatment, chemotherapy, radiotherapy or immunotherapy should be assessed using clinical findings and 1D or 2-D (surface) measurements. These measurements are subject to interpretation biases and other factors that influence accuracy. Helical CT adds a third dimension to cases to which the traditional bidimensional modalities are applied. The primary application of this more precise and direct measurement of volumes is the anatomical sizing of the volume of an organ (whole or part) or other specific structures. The chief clinical application relative to oncology is the evaluation of a tumor mass. The benefits of volumetric measurements are optimal before treatment, when knowledge regarding the tumor's size and position will influence prognosis. In fact, more accurate assessment of the tumor volume will be useful when predicting the tumor's response to treatment. The measurement of volume may also permit improved assessment of

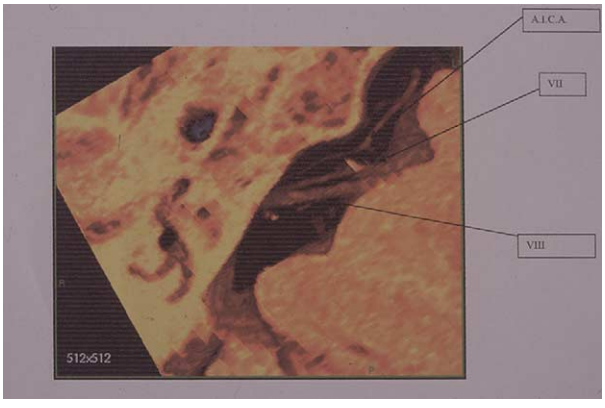


Fig. 6. Endoscopy of right cerebellopontine angle superior view. Visualisation of VII and VIII in their cisternal course and relation with antero-inferior cerebellar artery (AICA) (courtesy of J.L. Bensimon) [53]).

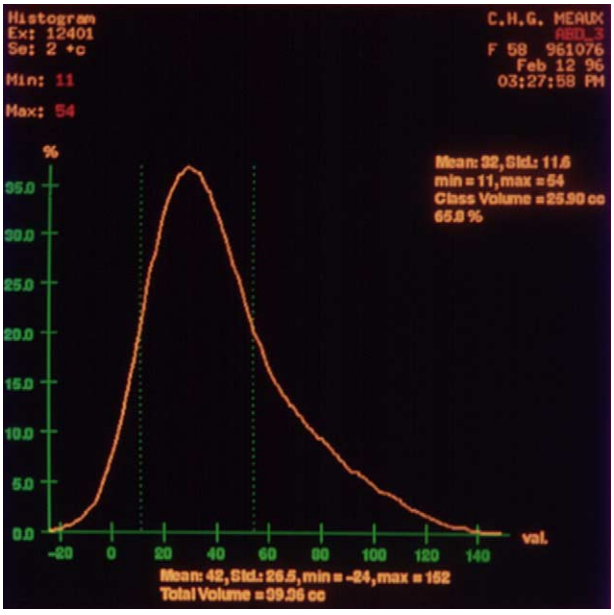


Fig. 7. Statistics of densitometric distribution of nodal studies (histogram) and follow-up of the densities of a treated lesion during the time (courtesy of D. Buthiau [54]).

operability or determinable lesion volume before radiotherapy.

1.4. Perfusion imaging [2,41,55]

The advent of helical scanners now makes it possible to track a bolus of iodinated contrast medium through tissue. In reference to drug development, the study of blood flow in the tumor could be useful in measuring the impact of anti-angiogenesis inhibitors. Ongoing research at the Imaging Center RMX and SOMPS (Paris) [55] has made more practical use of this new capability with the development of quantitative imaging of blood flow in tumors. We have optimised the method for application in cancer patients so that it can easily be incorporated into routine CT imaging protocols. The perfusion study protocol requires intravenous injections of 300 mg/ml non-ionic contrast agent at the dosage of 0.5 ml/kg body weight and 45 s of continuous CT scanning. Within minutes of the completion of the perfusion study, a map of tumor blood flow can be generated from the acquired images. This information on the development of blood flow in tumors can be applied to diagnosis, prognosis and the evaluation of treatment response.

2. Magnetic resonance imaging (MRI)

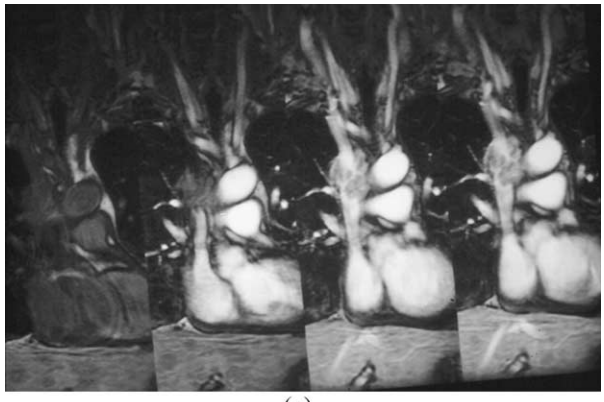
2.1. Nuclear MRI

This is more commonly referred to as magnetic resonance imaging (MRI). MRI developed into an important clinical modality between 1978 and 1985. The modality capitalises on the fact that magnetic nuclei in a static magnetic field exhibit a characteristic resonance frequency that is proportional to the field strength and unique to nuclei of the same type and same environment. The net magnetisation of the sample when irradiated by a radio wave at the resonance frequency could thus be manipulated to produce an induced MRI signal. Primarily, clinical MRI systems produce images of the distribution of hydrogen nuclei (mainly water) within the body. Other biologically important nuclei (carbon, nitrogen and phosporus), as well, as the imaging of hyperpolarised inert gases (helium and xenon), are under investigation. Recent developments in MRI have included chemical shift imaging (hydrogen-containing metabolites), blood-flow imaging (MR angiography), ultra-high-speed imaging (Echo Planar), and imaging of brain function based upon magnetic susceptibility differences resulting from blood oxygenation changes during brain activity.

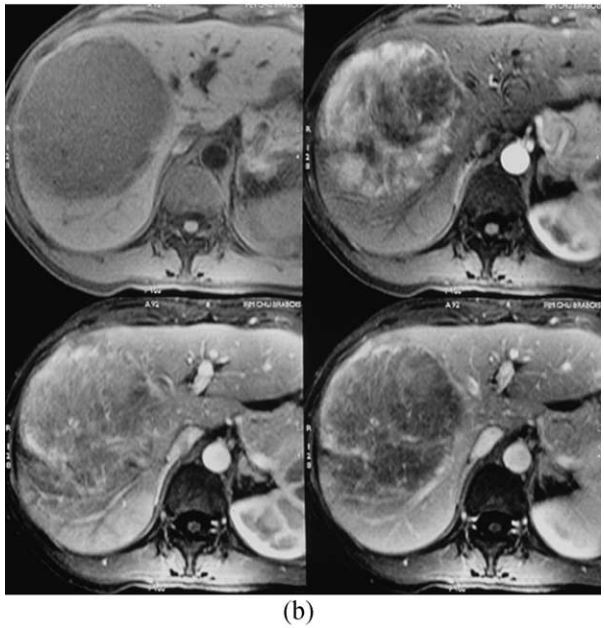
For a long time, oncologists have valued MRI's unique ability to image soft tissue and to differentiate benign and malignant tissue. As a result, it has become a major component of oncological diagnosis and therapy staging.

Dynamic imaging of extracellular fluid space contrast media after bolus injection may currently be the single most important component of an MR examination for the liver (Fig. 8). This is true in a number of circumstances, particularly the detection and characterisation of tumors. Practical imaging strategies can be applied in three different clinical situations: the characterisation of incidental liver lesions, detection and characterisation of hepatocellular carcinoma in cirrhosis and detection of liver metastasis before surgical resection.

While MRI has been highly utilised for staging and prognosis, before now it has not been suitable for intraoperative guidance. This can be attributed to many factors including patient access. Advances in magnetics,



(a)



(b)

Fig. 8. (a) Superior venacava tumor in cardiac-gated MRI before (left image) and after injection of Gadolinium, at different times of injection (following images from left to right) (courtesy of D. Buthiau on a Signa 1,5 T from G.E.M.S); (b) Hepatocarcinoma before and after injection of Gadolinium, in perfusion MRI, defining consistency, vascularity, extension, infiltration and vascular atypies and spread.

like the development of the Signa SP (a vertical gap magnet) and the increasing speed at which modern systems can obtain images has made it possible to use MRI intraoperatively. Surgeons can view MRI images in real time while operating. Such technology is likely to improve a surgeon's ability to better distinguish between malignant and benign tissue and to remove tissue accordingly.

As mentioned earlier, MRI provides excellent soft-tissue resolution but poor source definition and CT provides excellent source localisation but poor soft-tissue visualisation. The two fused together can generate a useful datatset that provides both source tissue resolution and source definition.

CT combined with MRI can provide anatomical answers by better defining tumor volume and its evolution under treatment. It might also increase the accuracy of radiotherapy by helping physicians to distinguish between the residual tumor and inflammatory or scar tissue. Because it requires good visualisation of patient anatomy and localization of sources for dose calculations, CT-MRI fusion images can help to assure the quality of permanent brachytherapy implants.

2.2. New acquisitions of MRI [2,41,55,56] (Figs. 8–10)

2.2.1. Anatomical and functional imaging [57]

2.2.1.1. 3-D imaging. Visualisation of the brain parenchyma and blood vessels in three dimensions supplies the neurosurgeon with a more realistic view of internal CNS pathology and its relationship to surrounding structures. Precise localisation of lesion with respect to extrinsic and intrinsic landmarks enables the neurosurgeon to correlate the surface topographical anatomy in vivo to that represented on MRI and thus to precisely plan the operative approach.

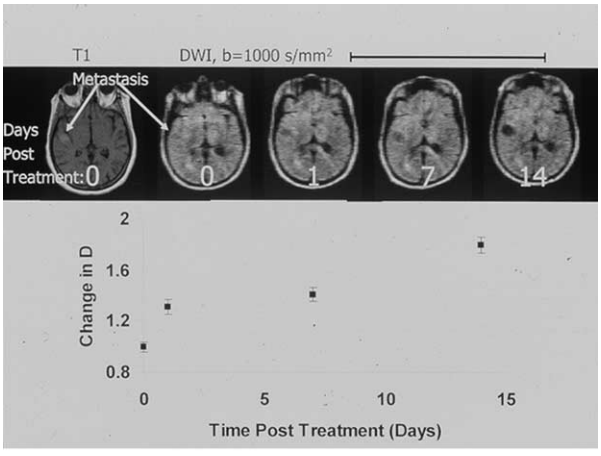


Fig. 9. Diffusion imaging by diffusion weighted MRI (DW MRI): non-invasive characterisation of brain metastasis, sensitive to the diffusion of water molecules in the tissue, showing early changes in morphology and physiology of the metastasis 15 days after treatment: the lesion (arrows) starts from bright signal (slow water = metastatic tissue) to dark signal (fast water due to necrosis within the lesion) (courtesy of Y. Mardor, Israel [58]).

2.2.1.2. Peritumoral changes [57]. The extension of the tumor is often difficult to determine. The difference between tumor expansion that compresses normal structures and frank infiltration is obscure. Peritumoral changes may represent edema, ischemia, necrosis, tumor infiltration along white matter tracts, perturbation of deep venous drainage, or other yet unknown etiologies. In the majority of cases, the usually T2-hyperintese changes do not correlate with malignancy in several biopsy-proven specimens of correlative material. It remains for newer MR techniques to clarify this in conjunction with pathological proof.

2.2.1.3. MR spectroscopy [57] (Fig. 10). *In vivo* MR spectroscopy is a technique that allows non-invasive monitoring of metabolites within the tissue of interest, and has the potential for providing information about a lesion's composition and response to therapy. A number of water-suppressed proton (^{1}H) MRS techniques have been developed for obtaining spectra from selected regions within the brain. These provide either a single-spectrum (single-voxel MRS) or a multidimensional array of spectra from the region of interest (multivoxel MRS imaging). It has been shown that tissues appearing similar on conventional MR images may have different spectral characteristics. In patients with brain tumors, the presence of elevated choline and decreased NAA levels correlated with tumor histological findings and can thus be used to distinguish regions of viable cancer from normal and other non-cancerous tissue, such as necrosis and astrogliosis.

2.2.1.4. Perfusion MRI [57] (Fig. 8). The sensitivity of MRI in localising pathology is truly impressive, yet the lack of pathological specificity has been a disappointment. The clinical history and examination are, and will remain, vital discriminators in narrowing the differential diagnosis. The pathology of the tumor and its functional effects are important considerations that must be integrated in the synthesis of the final surgical strategy. For many tumors, the specific MR parameters that precisely define pathology (consistency, vascularity, adherence and extension or infiltration) cannot be determined by anatomical imaging alone. Newer techniques like perfusion MRI can provide estimates of tumor vascularisation and thus provide hints on the pathology of the tumor.

2.2.1.5. Cortical activation (functional MRI-fMRI) [57]. Although the mechanisms that couple neuronal activity with haemodynamic and metabolic changes are not completely known, it is well established that neuro-

nal activity induces focal changes in cerebral blood volume, cerebral blood flow, blood oxygenation and metabolism. MR imaging techniques have been developed that exploit each of these changes as functional mapping signals. The most widely used MR method for *in vivo* mapping of brain activity is the BOLD technique which detects functionally-induced changes in blood oxygenation upon neuronal activity. The advantages of fMRI over other well established brain mapping techniques stem from its non-invasiveness, its wide availability, its high spatial and temporal resolution in comparison with other haemodynamic techniques such as positron emission tomography (PET), its ability to provide both anatomical and functional information in the same session so that the anatomic site of the activated region can be determined accurately, and its ability to provide functional information from the whole brain allowing information on the organisation of functional brain systems rather than from superficial cortical areas only.

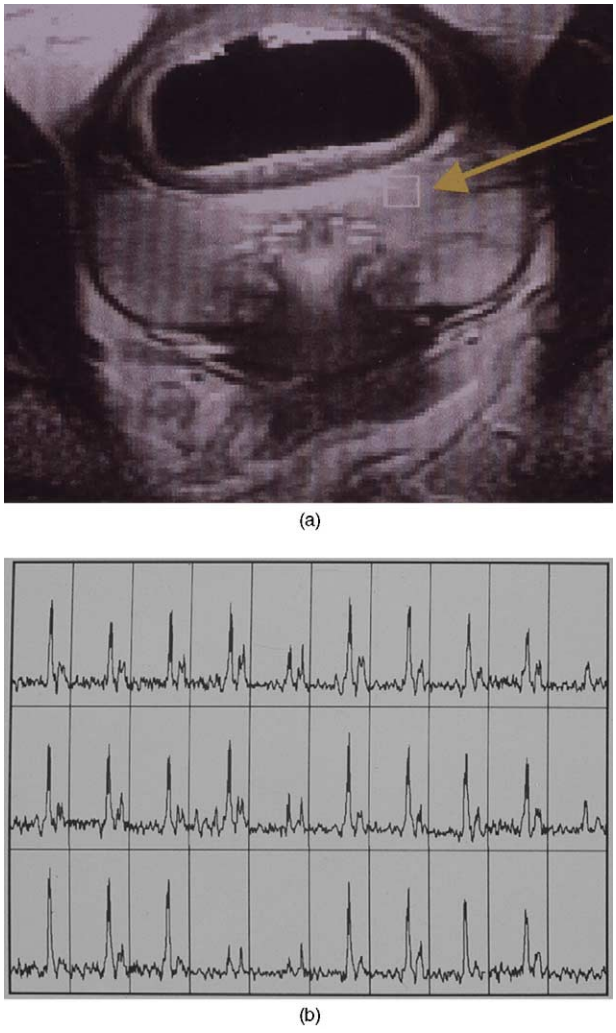


Fig. 10. *In vivo* MR spectroscopy allowing non-invasive monitoring of metabolites (b) within a prostatic cancer (a).

2.2.2. Diffusion imaging [58] (Fig. 9)

In vivo there are two main water populations, a slow water (bound to macromolecules or confined in the cell organelles) and a fast water, mostly free.

Diffusion-weighted MRI (DW MRI) represents a non-invasive characterisation of tissues sensitive to the diffusion of water molecules in the tissue. This technique can detect early changes in morphology and physiology of tissues, and allows early evaluation of response to anticancer therapy.

2.2.3. Surgical applications

Structural and functional imaging is provided for the surgeon for risk management and for determining possible intra-operative trajectories. The combination of various MR techniques proved helpful for guiding surgical resection and for navigation purposes. Individual risks can be assessed preoperatively and different surgical strategies can be discussed.

3. PET-Scanner [59] (Fig. 11)

PET is a unique diagnostic imaging modality that displays the metabolic function of the human body. PET scans produce images of the body that represent the functional rather than anatomical characteristics of disease, resulting in the early detection of many abnormalities that are undetectable using conventional X-rays, CT, or MRI diagnostic imaging systems. PET imaging with F-18 fluorodeoxyglucose (FDG), a metabolic tag, has proven to be a valuable imaging modality over the last few years. Its major indications are grading

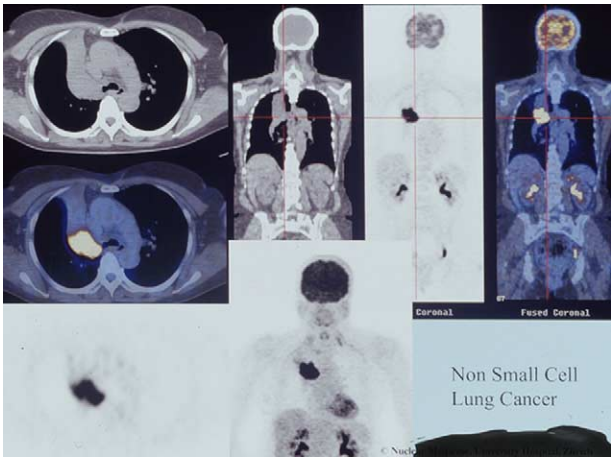


Fig. 11. PET scanner of a non-small cell lung cancer (axial views, left images; coronal views, middle and right images) the FDG uptake (appearing in yellow) corresponds to the tumor itself, with a good discrimination between the tumour itself and the obstructive consequence, with an increase in specificity by this combined technic (courtesy of G.K. von Schulthess [59]).

and staging of tumors, identification of epileptic foci and the evaluation of three-vessel coronary disease.

PET imaging can be used to stage many common tumors such as bronchial carcinoma and lymphoma but, for these indications, whole-body PET capabilities are necessary. Whole-body imaging requires the higher level of efficiency, and the detection systems that have been developed over the past few decades can provide it. The newer systems are capable of producing tomographic whole-body PET scans in less than an hour.

Our investigation with a relatively large series of patients showed PET was superior to the morphological picture modalities for tumor staging. These results concurred with studies conducted by other groups. PET's superiority can be explained by two reasons. By detecting pathological FDG uptake, PET imaging can detect lesions smaller than 1 cm which morphology cannot clearly classify as benign or malignant. The high, external S/N ration lights lesions up like light bulbs. This makes reading the scans easier and reduces the chances of making an error.

The realisation of PET imaging has created a multitude of clinical indications and the high cost of PET imaging machinery and installation has created a new consideration for health-policy makers. Careful planning of the installation site and the logistics of radiopharmaceutical delivery is critical. For any public institution that wishes to introduce the technology costs efficiently, the optimisation of funding resources and national consensus of where strategically to place the equipment will need to be considered. von Schulthess [59] says:

> ''Pet imaging has become a important modality in the staging of many tumors, and control of therapy response using PET is rapidly growing in importance. This is due to the fact, that the glucose analogue Fluorodeoxyglucose is taken up strongly by many aggressive malignant tumors, but hardly by any normal physiological structures of the human body. This results in excellent lesion to background contrast and makes identifying pathological foci relatively easy in many situations. The specificity of lesions is not as good because inflammatory disease also accumulates FDG. Because of the high negative predictive value, PET scans—particularly if it is known that the primary tumor site takes up FDG—are excellent predictors of the absence of lymph node involvement or metastatic disease. One approach to improve specificity, is to have better information on lesion location and morphological appearance. For this, high resolution morphological imaging, afforded by CT or MR imaging, is required, and in tumor staging, CT is mostly used, because with the new multi-detector techniques, extensive body regions can be surveyed in a matter of seconds. Experience with combining images from separate PET and CT scanners suggests improvements, but in a number of situations software fusion of images is inaccurate in addition to always being cumbersome. Integration of a PET and CT scanner into a single unit therefore makes much sense.

Since every PET scanner contains a 'low-end CT' (typically a Germanium source circling the patient) to permit correction of the emission images by a transmission scan, integration of PET and CT is synergistic in more than one respect. Fast CT scanning provides high resolution transmission correction data; thus the transmission correction of the PET images introduces hardly any additional image degradation over the PET emission image. Furthermore, image acquisition of the transmission scan is so much faster with CT that substantial increases in patient throughput can be achieved in the PET scanner of 25% or more. In the past 11 months, we have scanned over 1100 patients with such an integrated system. Preliminary conclusions from the wealth of data accumulated are:

- there are few technical problems;
- The most critical issue in 'hardware' fusion is respiration and good protocols have to be designed;
- low dose CT data (40–60 mAs) provide adequate information for lesion specification;
- FDG acts as a 'contrast agent' in CT. In many situations, ionic contrast may be unnecessary;
- a number of interesting pitfalls have been observed due to precise anatomic co-registration;
- it is advantageous to give iodine containing contrast media for bowel enhancement;
- there is a substantial decrease in the number of lesions not assignable to a class (tumor versus inflammation versus other);
- the two last points lead to an increase in specificity;
- in addition to an increase in specificity (Fig. 11), there may also be an increase in sensitivity because lesions not noted on PET may still show on the CT scan.

Thus, integration of PET and CT into a single modality makes sense from a clinical and a technical perspective. We already have good understanding of how to use the system in oncological patients, but applications are not limited to this disease entity. Applications in infection imaging, cardiac imaging and possibly neuro imaging can be envisioned. The use of a high end PET scanner is mandatory and using a very fast CT scanner is excellent because it helps in acquiring patient data in a single 'breath hold'.''

4. Other technologies [2,41,55]

The oncologist's imaging tool kit has become a lot fuller and its depth and width continues to expand. Teleradiology is another the next medical application derived from coupling physical sciences with computer applications. Teleradiology involves transmitting high-resolution medical images from one remote site to another and displaying the images effectively so that radiologist can perform the proper diagnosis.

The ability to electronically transmit radiologic images from one location to another provides convenience. Thus, teleradiology can be of benefit in many situations, not the least of which is the increased availability of radiological expertise in remote areas.

The process of remotely displaying radiological (X-ray) and other imaging studies for interpretation, consultation or both requires use of a local area networks (LANS), wide area networks (WANS), picture archival and communication systems (PACS) and compression digital imaging and communication in medicine (DICOM).

DICOM has allowed teleradiology to expand from a point-to-point technology to an Internet-like network. Recent developments in computer technologies have made it possible to store images digitally therefore they can be transmitted digitally over telephone lines.

PACS is the central component of any digital imaging distribution system. It forms the basis for distributing information throughout an enterprise, regardless of its size; it can range from an enterprise-wide, high-performance network to a single workstation connected to the acquisition device by telephone. The heart of a PACS-teleradiology system is its archive, the place where all the images can be stored and retrieved.

Another innovation in the optical sciences that may eventually find an application in the clinic is the construction of a table-top laser capable of generating a coherent beam of X-rays. It has long been possible to generate X-rays with lasers but, in the past, long physical distances were necessary to manipulate the light source in an appropriate manner.

As the intense light passes through a hollow glass tube filled with gas, electrons pull away from their atoms then snap back when their field is reversed. These electrons emit energy in the form of X-ray photons, a particle form of X-ray light. The work currently enables any researcher with a short-pulse laser to use the techniques to improve their view of biological processes. Attempts to alter and improve upon the way X-rays are obtained in the clinic are probably not far behind.

In conclusion, technology is changing the ways of diagnosis and therapy [60]. This combination of macro- and micro-informations leads to a more accurate and personalised treatment.

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