Original article

Focal malignant liver lesions: diagnosis by dynamic incremental CT, early phase

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Abstract. The purpose of our study was to evaluate the accuracy of dynamic incremental bolus-enhanced conventional CT (DICT) with intravenous contrast administration, early phase, in the diagnosis of malignancy of focal liver lesions. A total of 122 lesions were selected in 74 patients considering the following criteria: lesion diameter 10 mm or more; number of lesions less than six per study, except in multiple angiomatosis and the existence of a valid criteria of definitive diagnosis. Lesions were categorized into seven levels of diagnostic confidence of malignancy compared with the definitive diagnosis for acquisition of a receiver-operator-characteristic (ROC) curve analysis and to determine the sensitivity and specificity of the technique. Forty-six and 70 lesions were correctly diagnosed as malignant and benign, respectively; there were 2 false-positive and 4 false-negative diagnoses of malignancy and the sensitivity and specificity obtained were 92 and 97%. The DICT early phase was confirmed as a highly accurate method in the characterization and diagnosis of malignancy of focal liver lesions, requiring an optimal technical performance and judicious analysis of existing semiological data.

Key words: Focal liver lesions – Conventional CT – Liver CT protocol

Introduction

Although MR and spiral CT are possibly superior to dynamic incremental bolus-enhanced conventional CT (DICT) for liver lesion characterization [1–4] and for small lesion detection [5–7], DICT is still the most widely available and the preferred routine technique for detecting liver lesions [8, 9], and several studies have reported improvement of lesion-to-liver contrast with CT

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scans performed within 2–3 min after administering a bolus of contrast medium [10].

With Conventional CT, noncontrast studies are only occasionally useful when intravenous contrast is unsafe, technically difficult or in some hypervascular lesions [9, 11–13] and delayed CT may also be helpful when one deals with technical difficulties, with cholangiocarcinomas and occasionally to define hepatic tumours [14]. Nonincremental single level dynamic CT may be an alternative for isolated lesions, but is not applicable for multiple lesions at different CT slice levels [5].

Because several medical institutions still face the problem of unavailable MR or spiral CT, and the differentiation between a benign and malignant lesion is crucial for the patient prognosis and treatment, a prospective study was done to evaluate the sensibility and specificity of DICT, early phase, in the characterization of focal liver lesions measuring at least 10 mm in diameter, namely for distinguishing malignant from benign lesions.

Materials and methods

From January 1992 to June 1994, 388 of DICT liver survey and lesion characterization with early phase scans were performed with a CT scanner (Philips Tomoscan LX) for prospective characterization of liver lesions. Studies were performed with a volume of contrast material ranging from 100 to 120 cc (mean volume 105 cc); the contrast media used was sodium and meglumine ioxitalamate (380 mg of iodine per millilitre) in 50 studies and iopromide in 25 studies (300 mg of iodine per millilitre in 20 studies and 350 mg of iodine per millilitre in 5 studies); the iodine load ranged between 30 and 45.6 g with an average value per study of 37 g. Scans were performed during and after uniphasic contrast media intravenous administration at 2 ml/s with hand injection (automatic infusion pump unavailable). Approximately 30–45 s after the bolus was started, images of 10-mm-thick contiguous sections (associated with 5-mm-thick contiguous sections to the hilar area for clini-

cal suspicion of Klatskin tumour) were obtained by using 1.9-s scans, a 7-s intersection delay and a 512 × 512 matrix, without instant reconstruction. Nonenhanced CT studies were performed frequently when previous studies, namely US or CT, were nonexistent or unavailable, or if there was suspicion of hypervascular lesion, e.g. of metastatic aetiology. Similarly delayed scans were realized in 45 studies for acquisition of eventual further information and to compare enhancement patterns. A total of 122 lesions were evaluated in 75 studies of 74 patients comprising 45 men and 29 women (age range 0.3–85 years; average age 60 years), taking into account the following inclusion criteria:

1. Lesion diameter superior to 10 mm (due to lack of sensitivity of conventional CT in the characterization of small lesions)
2. Visualization of five or fewer lesions by patient study (except in 1 patient with proven multiple angiomatosis), to avoid reviewer bias that multiple liver lesions would favour malignancy
3. Confirmatory evidence of a definitive diagnosis by clinical, imaging or laboratory follow-up in 6–12 months (comprising 31 patients with 68 lesions), or by cytology, histology or microbiological corroborative studies (available by imaging procedures in 15 subjects with 23 lesions, or by surgery or autopsy in 28 patients with 31 lesions).

Furthermore, lesions caused by trauma or related to postsurgical complications were not included in this study.

Computed tomography images were analysed prospectively by two radiologists not blinded to the clinical data and the result of previous studies. Lesions were classified according to size, contour, enhancement pattern, density and the existence of gas, calcifications, septa, capsule, central scar and nearby venous thrombosis, dilated bile ducts or parenchymatous perfusion changes in order to assign a confidence level for the diagnosis of malignancy, and the answers were grouped into seven different levels; [level 6: malignancy definitely evident (viewers 100 % certain); level 5: malignancy very probably present (80 % certain); level 4: malignancy most probably present (60 % certain); level 3: unsure (50 % certain); level 2: malignancy most probably absent (40 % certain); level 1: malignancy very probably absent (20 % certain); level 0: malignancy definitely absent (100 % certain for benignity). In cases where knowledge of clinical background of the patient might change the confidence level attributed, lesions were categorized into the level immediately below, if definitive diagnosis was malignant, or immediately above, if the definitive diagnosis was benign.

Points of a receiver-operator-characteristic (ROC) curve [15] were obtained with these data. For confidence level 6 the true-positive fraction (TPF) was calculated as the number of true-positive DICT early-phase responses divided by the number of true-positive definitive diagnoses, and the false-positive fraction (FPF) was calculated as the number of false-positive early-phase

DICT diagnoses divided by the number of true-negative definitive diagnoses. The first point of the ROC curve was defined plotting TPF on the ordinate and FPF on the abscissa; the next points, from the second to the seventh, were calculated by combining successive-level responses and again calculating the TPF and FPF.

Sensitivity and specificity were generated considering that: true-positive results confirmed the diagnosis of malignancy for levels 6 to 4; false-negative results missed the diagnosis of malignancy corresponding to levels 3 to 0; false-positive results did not confirm the negative results of malignancy for levels 6 to 3; and true-negative results confirmed the negative diagnosis of malignancy for levels 2 to 0.

Results

DICT diagnosis of malignant lesions

Fifty focal liver lesions were diagnosed as malignant by follow-up or trough corroborative studies and the aetiologies were (Table 1) metastasis of carcinoma (31 lesions), hepatocellular carcinoma (8 lesions), cholangiocarcinoma (6 lesions), angiosarcoma (2 lesions), 1 neoplasm of unspecified origin (hepatocarcinoma or cholangiocarcinoma), 1 hepatoblastoma and 1 peritoneal metastasis simulating liver metastasis.

The results obtained with early-phase DICT are shown in Table 2. The diagnosis of malignancy was considered definitive in 40 lesions. In the other 10 lesions the diagnosis of malignancy was considered very probably present in 4, most probably present in 2 and most probably absent in 4 lesions; these last 4 lesions represented four false-negative diagnoses of malignancy through use of early-phase DICT (confirmed by laparoscopic biopsy) seen in 1 subject with 5 lesions, 4 of them hypodense and with ring enhancement simulating abscesses and categorized into confidence level 2; the fifth lesion of the same patient did not have ring enhancement and was considered malignant with confidence level 4; the second malignant lesion, classified according to confidence level 4, was also metastatic and presented a haemangioma-like appearance.

DICT diagnosis of benign lesions

A total of 72 focal liver lesions were considered nonmalignant and the definitive diagnoses were (Table 1) 34 haemangiomas, 22 pyogenic abscesses, 6 simple cysts, 6 hydatic cysts, 1 benign neoplasm of unspecified origin (haemangioma or focal nodular hyperplasia), 1 focal nodular hyperplasia (FNH), 1 nodule and 1 cystic portal neurinoma simulating benign cystic lesion of the liver.
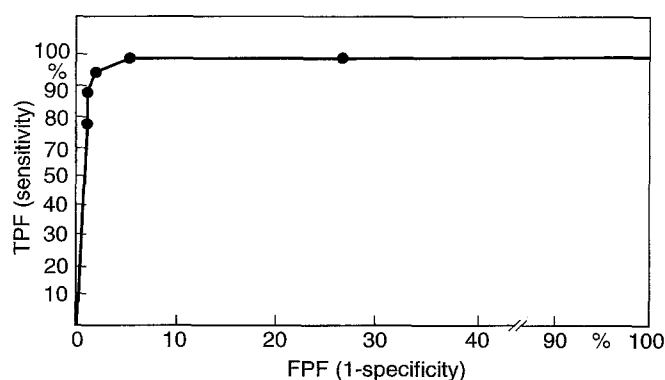
Early-phase DICT made an absolute diagnosis of nonmalignant lesion in 52 lesions as seen in Table 2. In the other 20 lesions the CT diagnosis of malignancy was considered very probably absent in 15, most probably absent in 3, most probably present in 1 and definitively present in 1 lesion. Benign lesions categorized

Table 1. Frequency and size of focal liver lesions diagnosed by early-phase dynamic incremental bolus-enhanced conventional CT (DICT) in the present series. FNH focal nodular hyperplasia

Type of lesion	Size of lesion (cm)							Total (n = 122)
	1–2	2–3	3–4	4–5	5–6	6–9	9–13	
Benign lesions								
Haemangioma	7	11	5	4	3	4	0	34
Pyogenic abscess	2	4	6	5	2	1	2	22
Hydatic cyst	0	0	1	1	1	3	0	6
Simple cyst	3	1	0	1	0	1	0	6
Unspecified benign lesion	0	0	0	1	0	0	0	1
FNH	0	0	0	0	1	0	0	1
Regenerative nodule	0	0	0	0	1	0	0	1
Extrahepatic lesion simulating liver lesion	0	0	0	0	0	1	0	1
Malignant lesions								
Metastasis	5	5	8	6	3	3	1	31
Hepatocellular carcinoma	0	1	1	2	2	1	1	8
Cholangiocarcinoma	3	2	1	0	0	0	0	6
Angiosarcoma	0	0	0	0	0	1	1	2
Unspecified malignant lesion	0	0	0	0	0	1	0	1
Hepatoblastoma	0	0	0	0	0	0	1	1
Extrahepatic lesion simulating liver lesion	0	0	0	0	1	0	0	1

Table 2. Correlation between confidence levels of malignancy with early-phase DICT and the definitive diagnosis in 122 liver lesions

Confidence level	Early-phase DICT diagnosis of malignancy		Definitive diagnosis	
	Probability of malignancy (%)	Number of lesions	Malignant	Benign
6	100	41	40	1
5	80	4	4	0
4	60	3	2	1
3	50	0	0	0
2	40	7	4	3
1	20	15	0	15
0	0	52	0	52

Fig. 1. Receiver-operating-characteristic (ROC) curve for diagnosis of focal malignant liver lesions by dynamic incremental bolus-enhanced conventional CT (DICT) early phase. TPF true-positive fraction; FPF false-positive fraction

into confidence level 1 were 10 haemangiomas, 3 abscesses and 2 cysts, and those classified according to confidence level 2 were 2 cysts, confirmed by imaging follow-up and 1 focal nodular hyperplasia diagnosed by laparoscopic biopsy. There were two false-positive diagnoses of malignancy, the first one a bacterial abscess classified according to confidence level 4 (60 % certainty of malignancy), presenting an irregular contour giving the lesion a suspicious appearance of hepatocellular carcinoma; the second false-positive diagnosis of malignancy was an early amoebic abscess considered 100 % malignant (confidence level 6).

Sensitivity, specificity and ROC curve

Distortion bias related to the knowledge of the clinical problem in some patients was not relevant to the evaluation of sensitivity and specificity of the method, because it was not present in any malignant lesion of level 4 or benign lesion of level 3.

With early-phase DICT there were 46 true-positive, 4 false-negative, 2 false-positive and 70 true-negative diagnoses of malignancy giving a sensitivity of 92 % (46 of 50) and a specificity of 97 % (70 of 72). Figure 1 shows the ROC curve analysis obtained with early-phase DICT for focal malignant liver lesions in the group of patients evaluated.

Discussion

The first and basic issue in the characterization of focal lesions of liver is to diagnose or exclude malignancy because of its subsequent prognostic and therapeutic implications [16, 17]. Most articles published in the literature emphasize the differential diagnosis between benign or malignant tumours, or between haemangiomas and metastasis or hepatomas [10, 18]; the authors opted for a broader evaluation of liver masses because small benign simple cysts and focal inflammatory lesions may sometimes represent a challenge in the differential diagnosis [19, 20].
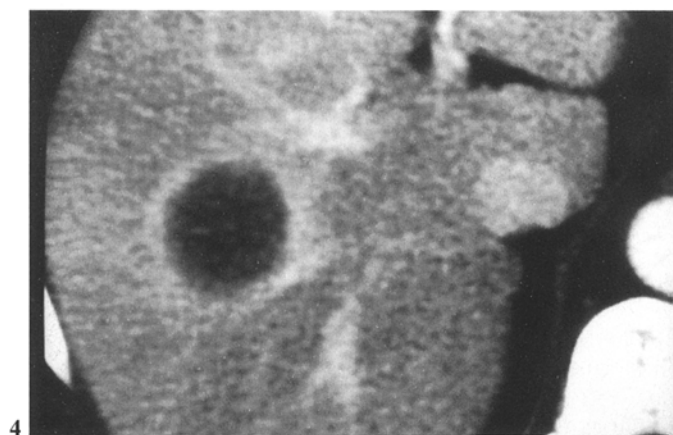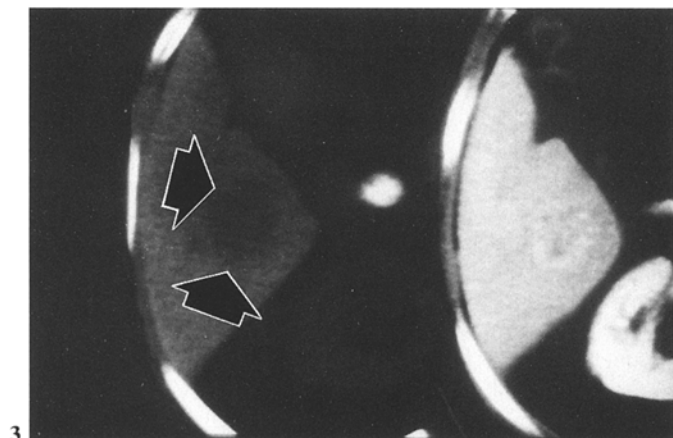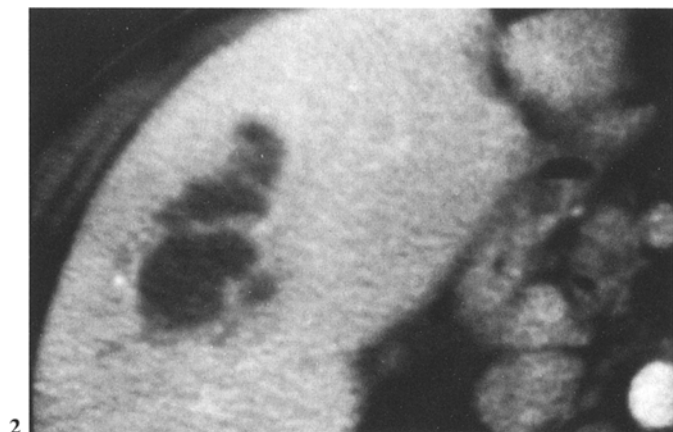
Fig. 2. Example of false-positive diagnosis of malignancy corresponding to a pyogenic abscess with an irregular contour and a hypodense and slightly heterogeneous center

Fig. 3. Noncontrast CT (left) revealing one hypodense lesion (arrows) slightly less conspicuous with early-phase DICT (right), corresponding to an early amoebic abscess wrongly diagnosed as hepatocellular carcinoma

Fig. 4. False-negative diagnosis of malignant lesion (metastasis of carcinoma) revealing a hypervascular contour and central hypodensity that were supposed to be of infectious origin

Fig. 5. Peritoneal metastasis of ovarian carcinoma (confirmed through autopsy) simulating an intrahepatic location. Note acute angle (arrows) between the lesion and normal liver, which might indicate extrahepatic location of the lesion

Fig. 6. Metastatic lesion from colon carcinoma with some central vascularity (arrows), but revealing an iris-like phenomenon simulating hemangioma

Fig. 7. Hilar cholangiocarcinoma diagnosed by early-phase DICT which revealed a small nodular heterogeneous lesion (arrows) causing intrahepatic biliary dilatation

Early-phase DICT allowed a correct diagnosis of benignity in all haemangiomas observed, and the most commonly seen features were globular enhancement (20 haemangioma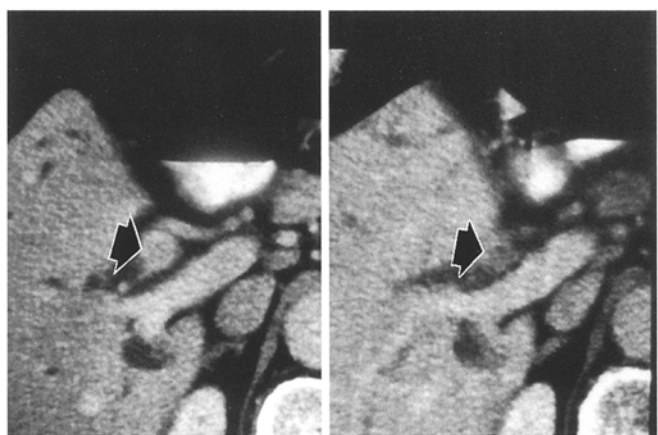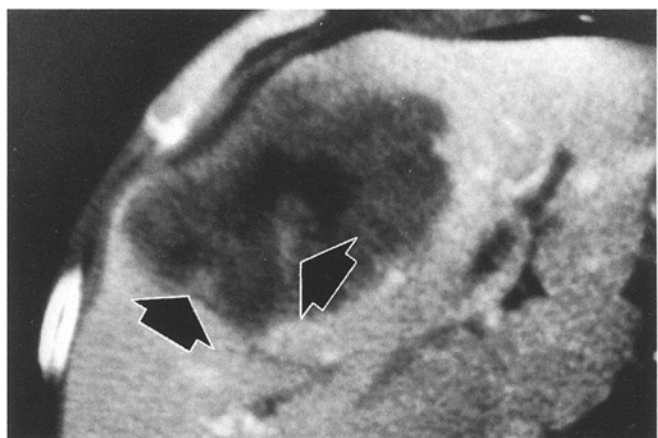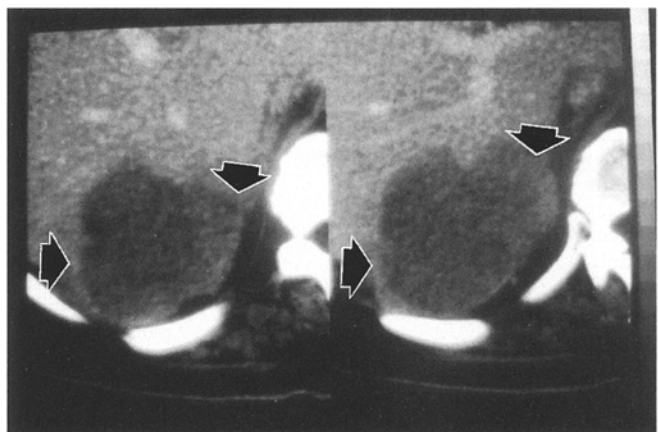s), total hypodensity (7 haemangio-mas) and total hyperdensity (3 haemangiomas). Although there was not a histological confirmation in any lesion, distinctive CT features, stability for 6–12 months and absence of extrahepatic neoplasm was seen in 25 le-

sions of 12 patients, and confirmatory corroborative studies were available in the other 9 lesions. Nevertheless, two haemangiomas (not included in this study) of 14 and 15 mm were seen with US and missed by early-phase DICT, perhaps because they were isodense, due to partial volume effect or to respiratory discrepancy. These results are in concordance with the work of Leslie et al. [21] where a similar technique was proved to be accurate for distinguishing cavernous haemangiomas from metastases, and with the findings of Quinn and Benjamin [22] and Gaa et al. [23] in demonstrating that globular enhancement is a strong indicator of haemangioma. (Only 2 metastatic lesions in our study revealed a pattern similar to globular enhancement.)

Although all infectious focal liver lesions presented with signs described in the literature [20, 24], their differentiation with malignant lesions was less accurate. Two lesions suggestive of hepatocellular carcinoma were misdiagnosed as malignant (Figs. 2 and 3). In addition, 4 metastatic lesions were falsely diagnosed as benign pyogenic abscesses because they revealed a very homogeneous ring enhancement that was interpreted as a sign of infectious aetiology (Fig. 4). These few data are in concordance with the data of Halvorsen et al. [24], which reported high-density foci indistinguishable from metastases and point out that the differentiation between infectious and malignant liver lesions may be difficult sometimes. Because there is insufficient recent data concerning the differential diagnosis between abscesses and malignant liver lesions, further investigation may be needed concerning this issue.

Ten additional lesions correctly diagnosed as benign included 4 small cysts seen in 1 patient with gastric carcinoma, unchanged in two follow-up studies and in accordance with the work of Jones et al. [19] concluding that most small cysts in patients with extrahepatic neoplasms are of benign aetiology. The other 2 lesions that revealed interesting aspects concerned a cystic portal neurinoma simulating a benign cystic liver lesion, although early-phase DICT made a correct diagnosis of benignity and a regeneration nodule revealing moderately well-demarcated contour and slight hyperdensity, a feature rarely seen in this pathology [25]. Besides the four false-negative diagnoses of malignancy already mentioned, all cases of malignant neoplasms were correctly diagnosed. One such lesion corresponded to a peritoneal metastasis of ovarian carcinoma that simulated a hepatic localization (Fig. 5) emphasizing a widespread concept that sometimes multiplanar imaging through US, MRI or spiral CT is superior to conventional CT in depicting a deep mass in the right upper abdomen. Another lesion revealed an apparent iris phenomenon suggesting haemangioma associated with internal heterogeneity which allowed the correct diagnosis of metastasis (Fig. 6). There were 6 cases of cholangiocarcinoma, 5 of them with hilar location, 3 revealing a small heterogeneous and slightly hyperdense hilar lesion (Fig. 7), and 2 revealing a heterogeneous hilar mass with invasion of local vessels and bile ducts. In addition, two additional cases of Klatskin tumours were excluded from the study because DICT did not depict the lesion itself. These re-

sults are similar to those achieved by Yamashita et al. [26], and suggest that early-phase DICT may be complementary or an alternative to delayed CT described by Takayasu et al. [27], or to other imaging techniques, in the diagnosis of Klatskin tumours. In addition, our study was concordant with a somewhat similar study published by Honda et al. [18] where early-phase DICT assisted in the detection of 92 % of 139 hepatomas, haemangiomas or metastases. Although the authors enphasized the role of delayed studies in the detection of 8 % of all tumours, it was also found that some enhancement patterns on first-pass studies were quite suggestive of malignancy or benignity (malignancy of 90, 78 and 86 % in total hyperdensity, mixed density and total hypodensity pattern, respectively; benignity of 63 % in peripheral hyperdensity).

Several limitations are evident in our study and some deserve a special consideration. Firstly, logistical limitations imposed the administration of a uniphasic bolus iodine load averaging nearly 38 g by hand injection, during almost 2 min, which might have influenced the enhancement pattern of lesions evaluated and consequently its characterization. Secondly, the lack of pathological proof available in 42 % of patients (31 of 74) and 56 % of lesions (68 of 122), mainly in lesions with the diagnosis of haemangiomas, might result in overestimation of the number of benign lesions. Thirdly, the lesions were evaluated on a prospective basis by viewers not blinded to clinical data or previous studies, although the compensation factor previously mentioned was added. Fourthly, lesions smaller than 10 mm were excluded from the study because of described limitations in the diagnostic potential of dynamic incremental CT in their evaluation [6, 9, 28], and a comparison with spiral CT or MR was not possible because of unavailability of these techniques in our institution.

We conclude that early-phase DICT is a highly accurate method in characterizing focal liver lesions with a diameter of 10 mm or more, making possible a differential diagnosis between benign and malignant lesions, in as much as technical requirements, attentive analysis of available imaging features and clinical background of patients are taken into account. Concerning this issue, other imaging techniques, more expensive or aggressive, or less available, should be used when early-phase DICT is technically difficult or unfeasible, or when an unquestionable diagnosis has important prognostic or therapeutic implications.

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Book review   European Radiology

Eisenberg R. L.: Gastrointestinal Radiology. Philadelphia, PA: Lippincott-Raven Publishers 1995, $ 195, ISBN 0-397-51480-8, 1216 pages, 1.300 illustrations

This third edition is an enlarged work to reflect the growing importance of cross-sectional imaging in the gastrointestinal tract, and contains nine new patterns related to the gall bladder, liver and spleen.

Its aim lies somewhere between a gamut in radiology and a standard text for gastrointestinal radiology. I find it succeeds admirably in doing so. The title infers a "pattern approach", which is a little misleading. There are 10 chapters, covering the oesophagus, diaphragm, stomach, duodenum, small bowel, ileocaecal valve and caecum, colon, biliary system, cross-sectional imaging of the liver, gallbladder and spleen, and a miscellaneous section. The "patterns" are really predominate pathological signs, such as ulceration, narrowing, diverticula, and fistula in the main parts of the gastrointestinal "tube". Specific changes in various sites, e.g. gastric outlet obstruction, adynamic ileus, coned caecum, and cystic dilatation of the bile ducts are included. The sections are comprehensive, well illustrated and backed up with key references. The text is easy to read and the book has a good layout. It would be impossible for a book of this nature to be complete. However, interest in endoscopic ultrasound is increasing, but there is very little mention of this. I was disappointed not to see any illustration of peritoneography in the section on non-diaphragmatic hernia, but the most significant omission was the pancreas. There is a large section on cholangiography, with limited mention of changes in acute and chronic pancreatitis, but nothing on pancreatography.

This book focuses more on the tube than the solid organs. Its strengths lie in the way it is organised and the ease with which one absorbs information from the text and illustrations. This is much easier than any gamut-style of book. Although some recent textbooks have included gamut-type sections, lists on their own are not enough. Without doing the work of reading up why the lists contain what they do, it is difficult to make sense of any gamut. This book does the work for one. Reading the sections would also be an excellent way of revising, as the information given cuts across so many disease processes that it helps assimilate knowledge. There is also a lot of experience imparted, and perhaps its main use would be to give a broader view of differential diagnosis when reporting. It is a practical book to use and should be part of any departmental library.   C. Bartram, London