Fundamentals in Oncologic Ultrasound

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Sonographic Imaging and Intervention in the Cancer Patient

Foreword by David Cosgrove

Springer

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Foreword

It is a remarkable observation that human creativity can be fostered by spectacular scenery, itself usually the result of tectonic activity which raises mountains of beauty but carries the sting of earthquakes and eruptions. Think of Silicon Valley in California or of the Tokyo-Kyoto corridor in Eastern Japan. Another is the glorious Amalfi coast around Naples, where the authors of this new textbook work in the shadow of Mount Vesuvius. Is it the beauty that inspires or the tension of knowing that one's life may be shattered at any moment if a volcanic or tectonic disaster strikes? Whatever the explanation, these authors' passion for their subject shines through and their work carries not only their enthusiasm but also a rare beauty in its construction/format, for it is a joy to hold and behold with its beautiful all-colour printing and abundant illustrations of excellent quality, mainly, of course, ultrasound images but also corresponding CT scans and numerous elegant diagrams.

But, is there a need for a textbook on ultrasound in oncology? Doesn't everyone accept that CT or PET/CT (and sometimes MR) have nailed the problem of oncologic imaging? Well, while CT is undoubtedly the core imaging technique for the detection, staging, treatment planning and follow-up of tumours, there remain many applications for modern ultrasound, as readers of this textbook will be persuaded. It has the advantages of availability and ready repeatability and, in some situations, the lack of ionizing radiation is an advantage, even in oncology. Furthermore, it provides functional information, especially about blood flow, that may be critical in some oncology problems (choriocarcinoma is an example). It is also the best imaging modality for guiding interventional procedures.

The content of *Fundamentals in Oncologic Ultrasound* goes far beyond a narrow interpretation of the title, in that a wide range of non-tumour conditions is included and illustrated – in fact, wherever a non-tumour mass should be considered as part of the differential diagnosis, it is covered in detail here. This means that it will be indispensable to all clinics using ultrasound in general imaging. A wide-ranging introductory section covers the basics of ultrasound interpretation, including grey scale and Doppler, as well as microbubble contrast agents. In addition, unusually, there is a detailed discussion of the pros and cons of ultrasound compared with other imaging techniques, and a discussion of the benefits and dangers of screening, a topic that is often short-changed. There is also an important discussion of the use of imaging in evaluating response to treatment. As well as sections on the abdomen and superficial structures such as the head and neck, and the breast, there are sections on the genitourinary tract and one on the use of ultrasound to guide interventional procedures, including ablation techniques.

The authors are justifiably renowned for their careful, detailed and precise work in general ultrasound over many years. Their passion for the subject is evident in the detailed descriptions of the wide range of pathologies it includes, both adult and paediatric.

I congratulate Drs. Catalano, Nunziata and Siani on their labour of love and commend this excellent textbook to you.

London, February 2009

David Cosgrove
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Preface

Unlike other volumes of oncologic imaging, ours is not encyclopedic. It does not aim to analyze organ by organ every tumor which may be found there, with a systematic description regarding the etiopathogenetic, epidemiologic, clinical, diagnostic and therapeutic features of the disease. It does not begin, therefore, with a predetermined diagnosis but rather from the clinical problems that may lead there, because this is the reality of daily clinical practice. The volume is therefore structured in seven broad chapters.

Chapter 1. An analysis is made of the general relations between diagnostic imaging modalities, with particular reference to ultrasound, and the principal fields of oncology. An initial presentation is made of the advantages and limitations of US, the knowledge of which is essential for any clinical application of the technique, and therefore also for the study of cancer. The focus then shifts to the different phases in which US and the oncologic disease interact: secondary prevention, intrinsic characteristics of the cancer (with particular reference to neoangiogenesis), cancer staging, the evaluation of response to different types of anticancer treatments, short- and long-term monitoring, and the identification of disease recurrence. Only with an adequate understanding of these features of malignant disease can diagnostic imaging make a truly effective contribution. Chapter 1 also takes into consideration the examination techniques of US, spectral Doppler, color Doppler, power Doppler and contrast-enhanced US (CEUS), with particular reference to the study of neoplastic diseases in their superficial and deep locations. The presentation especially focuses on the current possibility of optimizing the US instrumentation and exploration technique, with the aim of maximizing the detection and morphofunctional analysis of neoplastic lesions. The sections dealing with the examination technique alternate with a presentation of the principal imaging characteristics: although tumors arising in different organs may display different features, the discussion aims to underline the common imaging characteristics so they can be applied from time to time to the various anatomic regions and clinical problems.

Chapters 2–6. The clinical problems connected either directly or indirectly to neoplastic disease of the different body regions are many and varied and can be included in a single volume only in part. Instead of an encyclopedic approach, with systematic discussion of the epidemiologic, clinical, diagnostic and imaging characteristics of the different neoplasms in different body regions, we preferred to begin with the basic clinical problem, which is how the disease is presented to the diagnostic imaging specialist. This approach involves, first of all, an illustration of the general appearance and then the imaging characteristics, first and foremost US, but also CD, spectral Doppler and CEUS.

Chapter 7. The current range of extravascular interventional procedures is extremely broad and constantly on the increase. This chapter describes the main US-guided procedures used in the cancer patient: diagnostic sampling of superficial and

deep lesions (both cytologic – FNAC, and histologic – core biopsy), vacuum-assisted biopsy in breast cancer, placement of presurgical markers, drainage of collections, cysts and liquefactive masses, percutaneous ablation (with special reference to percutaneous ethanol injection and radiofrequency thermal ablation, and especially with regard to focal hepatic lesions). It should, nonetheless, be borne in mind that the number of US-guided interventional procedures is much greater, ranging from biliary drainage to nephrostomy and nerve block for anesthesia or pain management to venous catheterization. US guidance, either alone or in combination with other modalities; this allows all of these procedures to be performed more effectively and with greater safety for the patient than with a "blind" approach". An increasingly widespread diffusion of the technique can therefore be reasonably expected.

In this text the term color Doppler and its abbreviation CD are used, except where specifically stated, in reference to the Doppler techniques in general and therefore including power Doppler. In all cases where the description refers specifically to power Doppler this term will be expressly stated.

The term contrast-enhanced US (CEUS) is always used to refer specifically to gray-scale study with injection of sonographic contrast medium. When the intention is to indicate CD with contrast medium this is always expressly stated and should not be considered associated with the idea of US contrast enhancement.

Throughout the volume the term "US-guided" is a general reference to all procedures performed with US guidance, regardless of the type of transducer used, whether dedicated to the intervention or not. The specific meaning attributed to the terms "freehand", "US-assisted" and "US-guided" is discussed at the beginning of Chapter 7.

Lastly, throughout the text, the term "biopsy" is used as a general indication of diagnostic sampling, both cytologic and microhistologic, where not otherwise specified. The difference between the former (aspirated with a fine needle, with the abbreviation FNAC) and true biopsy (indicated as "core biopsy") is also thoroughly illustrated in Chapter 7. We preferred not to use the well-known abbreviation FNAB at all to avoid confusion in terms.

We thought it useful to provide a compact disc with video material of US examinations performed with various techniques. The choice appears appropriate especially given the difficulty in encapsulating in static images characteristics that can only be fully appreciated in real time, especially with regard to CEUS studies and interventional procedures.

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Abbreviations

3D	three-dimensional
μg	microgram
μm	micrometer
ABBI	advanced breast biopsy instrumentation
ACR	American College of Radiology
ACS	American Cancer Society
ACTH	adrenocorticotropic hormone
AFP	α-fetoprotein
AI	acceleration index
AIDS	acquired immunodeficiency syndrome
BCLC	Barcelona Clinic Liver Cancer
BI-RADS	breast imaging reporting and data system
CA	cancer antigen
CD	color Doppler
CEA	carcinoembryonic antigen
CEUS	contrast-enhanced ultrasound
cm	centimeter
CT	computed tomography
CUP	cancer of unknown primary (tumor)
CVC	central venous catheter
dB	decibel
DPI	Doppler perfusion index
DRE	digital rectal examination
EFOV	extended field of view
EUS	endoscopic ultrasound
FDG	fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
F/M	female/male
FNAB	fine-needle aspiration biopsy
FNAC	fine-needle aspiration cytology
FNH	focal nodular hyperplasia
FOV	field of view
G	gauge
GIST	gastrointestinal stromal tumor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIAA	hydroxy-indoleacetic acid
IOUS	intraoperative ultrasound
IU	international unit

IV	intravenous
Kg	kilogram
kHz	kiloHertz
L	liter
LABC	locally advanced breast cancer
LDH	lactic dehydrogenase
M/F	male/female
MALToma	tumor from mucous-associated lymphoid tissue
MEN	multiple endocrine neoplasm
mg	milligram
MHz	megaHertz
MI	mechanical index
MIBI	methoxyisobutylisonitrile
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mPa	milliPascal
MRCP	magnetic resonance cholangiopancreatography
MR	magnetic resonance
MSCT	multislice computed tomography
MVD	microvessel density
ng	nanogram
NHL	non-Hodgkin's lymphoma
PACS	pictures archiving and communication system
PAT	percutaneous ablation therapy
PC	personal computer
PD	power Doppler
PEI	percutaneous ethanol injection
PET	positron emission tomography
PET-CT	PET and CT fusion
PI	pulsatility index
PIN	prostatic intraepithelial neoplasm
PLAP	placental alkaline phosphatase
PRF	pulse repetition frequency
PSA	prostate specific antigen
PSAD	prostate specific antigen density
PT	prothrombin time
PTT	partial thromboplastin time
QUART	quadrantectomy, axillectomy, radiation therapy
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RF	radiofrequency
RFTA	radiofrequency thermal ablation
RI	resistive index
RIS	radiologic information system
ROI	region of interest
ROLL	radio-guided occult lesion localization
s	second
SD	standard deviation
SF_6	sulfur hexafluoride
SPECT	single photon emission computed tomography
SUV	standardized uptake value
TACE	transcatheter arterial chemoembolization
Tc	technetium
Tis	tumor in situ
TNM	tumor – node – metastasis

TRUS	transrectal ultrasound
TSH	thyroid-stimulating hormone
TUR	transurethral resection
TVUS	transvaginal ultrasound
US	ultrasound
VB	vacuum-assisted biopsy
VEGF	vascular endothelial growth factor
V_{max}	maximal velocity
V_{m}	mean velocity
V_{min}	minimal velocity
vs.	versus
WHO	World Health Organization

General Considerations 1

1.1 Advantages of Ultrasound in Oncology

US has a number of characteristics which make it a very useful diagnostic technique both for general application and for oncology in particular. First of all, US is a simple technique. This **simplicity**, which is sometimes confused with ease of use, is related to the way the examination is performed. No preliminary analysis or special preparation is required and it can always be immediately carried out, making it much more accessible in any hospital setting than the "heavy" devices of CT and MR. The **immediacy** of the image is another advantage, whereby the clinical picture may be clarified at the very time the US transducer is placed on the skin in the anatomic area in question. In addition, the **rapidity** of the examination is an important characteristic, particularly in other areas, such as emergency medicine. In oncology, however, a careful and comprehensive study is recommended, which slowly and repeatedly explores all the anatomic areas involved in the examination in question. This is particularly important in the "positive" patient: a pathologic finding indicating malignancy in a particular organ should increase the level of attention of the US operator due to the elevated probability that there are other associated findings. Special attention should therefore be paid to confirmation of diagnostic suspicions once a specific pathologic finding has been identified.

The possibility of studying normal and pathologic masses in **real time** is a prerogative of US, which in this sense is unique among imaging modalities. Echoscopy is able to visualize anatomic structures and their pathologic alterations "in vivo", with the possibility of studying organ function, e.g. intestinal peristalsis, diaphragm motility, contraction of muscular-tendinous structures, cardiac kinesis, etc. Furthermore there are interventional applications, where real-time US guidance in general terms is preferable, wherever possible, to methods such as CT and MR that are usually characterized by discontinuous scan.

The **multiplanar capabilities** of the technique, i.e. the possibility of obtaining any scan plane by simply rotating the transducer, is a characteristic that is only partly shared with other tomographic imaging modalities. With the advent of multislice devices, CT has achieved true multiplanar capabilities, albeit in the form of electronic reconstructions, whereas MR has always been multiplanar in acquisition, but clearly with the need to obtain the images each time according to a specific scan plane.

The **high spatial resolution** achievable with high-frequency transducers is far superior to other imaging modalities. The possibility of identifying and characterizing the morphologic and vascular structure of small lesions to the skin, the subcutaneous layers, the thyroid, the lymph nodes or other superficial structures is undoubtedly much higher than can be obtained with CT or MR. For example, in the preoperative identification and evaluation of superficial satellite metastases from melanoma, US is able to identify a larger number of nodules than other imaging modalities. Whereas CT and MR rely mainly on the criteria of size, with regard to structures such as superficial lymph nodes, US provides a more detailed study, being able to identify metastatic lymph nodes as small as 3–4 mm, or metastatic foci <1 cm within lymph nodes with an otherwise normal appearance.

US is **transportable** and can therefore be performed at the patient's bedside or in the operating room, a feature which significantly facilitates the study of fatigued patients in an advanced tumor stage. This characteristic is also beneficial in the early postoperative period, as well as during US-guided diagnostic and therapeutic procedures performed at the operating table (not to mention IOUS proper).

US is also highly **repeatable**, and is thus particu-

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larly indicated for serial studies such as the monitoring over time of known findings or in follow-up examinations, as well as in screening. The repeatability is also a consequence of the low costs, simplicity and low level of **invasiveness** of the technique, the latter being associated with the use of nonionizing radiation and the technique generally being performed without intravenous contrast media.

The possibility of **doctor–patient interaction** is greater than with other modalities, with an "ongoing" patient history becoming more specific as the findings appear on the US monitor.

US is a very **diffuse** technique, with a widespread distribution both geographically and in the hospital setting, where numerous devices are present in various departments.

The **costs** are lower than those of other imaging modalities, making it the ideal technique for large-scale or serial applications.

Undoubtedly, from a number of points of view, US is underutilized in oncology, where there is a greater tendency towards more sophisticated modalities such as CT, MR, PET and image co-registration. However, many more or less simple clinical queries can be resolved with US or CEUS. For example, US can often be effectively used as a problem solver in cases of a discrepancy between findings of different imaging modalities or between clinical laboratory findings and radiologic or instrumental findings. An initial and accurate US study in patients with a nonoperable advanced-stage tumor can avoid the need for further more invasive and costly examinations. In general, when hypothesizing a diagnostic investigation to clarify a specific clinical problem, it is worth considering whether the problem can be solved with US or whether more complex modalities are required.

1.2 Limitations of Ultrasound in Oncology

The presence of a number of limitations should be borne in mind not only by physicians prescribing US examinations but by US operators themselves, who are naturally led to "overestimate" the capabilities of "their own" technique with which they clearly have the utmost confidence.

The limited **panoramic view** is definitely the major limitation of US. This limitation should be understood in a number of ways. First of all, air and dense anatomic structures such as bone hinder the evaluation of structures lying deep to them, such that the cranial-encephalic, pulmonary-mediastinal and skeletal structures are barely accessible if at all with US, at least in the adult. It is therefore not materially possible to perform a whole-body US scan in the way that is possible with CT or MR. In addition, the technique only "sees" the body region where the transducer is placed. Therefore, a structure such as a lower limb, which in theory can be panoramically explored in all its soft parts with US, is better defined with multislice CT or MR. For example, in a surgical patient with extensive compartmental excision due to a malignancy of the lower limb, a CT or MR study appears more rational, at least in most cases, with the possibility of detailed targeted evaluation with US rather than vice versa. In special cases US can be used to demonstrate malignant lesions in multiple anatomic regions, either individually and on a single image or in highly specialized anatomic sites, which normally would suggest limited or no application of the technique (Figs. 1.1–1.7, Video 1.1). Nonetheless, US is unable to achieve the possibilities of a CT or MR multidistrict study. Lastly, the **field of view** of US is limited and therefore for diagnostic and interventional purposes only partial visualization of the anatomic structures of the area in question is possible in comparison to CT and MR. Particularly voluminous superficial lesions can be difficult to include in the FOV and to measure on a single image, even when high-frequency transducers with a wide field (e.g. 5 cm) are used or when the visualized area is electronically widened with a trapezoidal FOV. As an alternative, spacer pads can be used or an abdominal transducer, although their lower resolution can render visualization of the margins of the mass difficult and therefore hinder its correct measurement from another perspective.

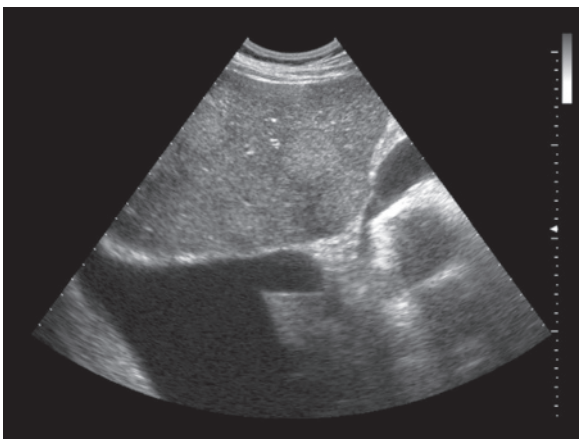
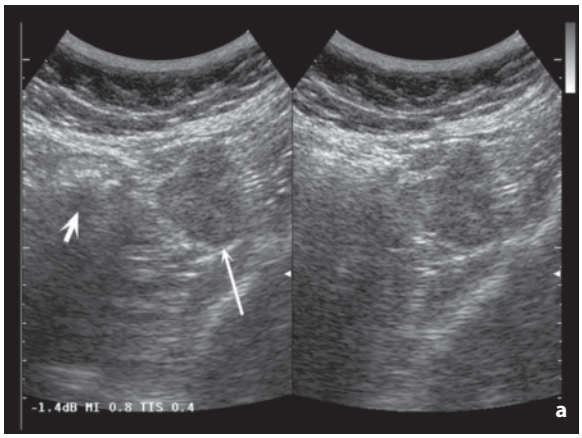
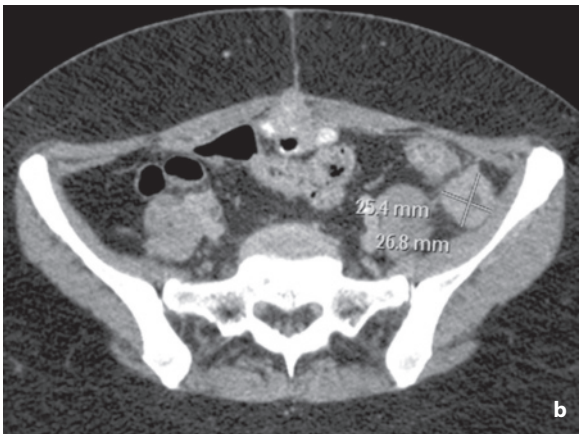


Fig. 1.1 Liver metastases from pulmonary carcinoma associated with pleural and pericardial effusion. Panoramic demonstration in a single US scan of the hepatic lesions, the pericardial fluid layer and the moderate pleural effusion with parenchymal atelectasis. In general, however, US is not a very panoramic technique

The **spatial resolution** is also lower than that of CT and MR with regard to deep structures, which require the use of low-frequency transducers.

US is very accurate in discriminating between solid and fluid-filled structures. In cases where CT is often nonspecific, e.g. demonstrating a near-liquid appearance (visibly or with the measurement of attenuation coefficients), US often is able to demonstrate a solid





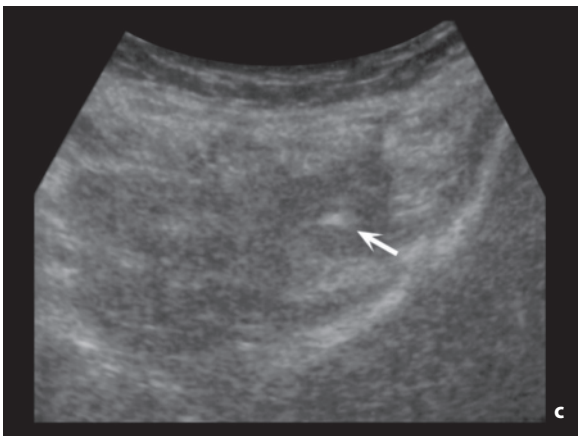


Fig. 1.2a-c Recurrence of cervical cancer. US study (**a**) shows a heterogeneous hypoechoic nodulation in the left iliac fossa (*long arrow*) adjacent to the descending colon (*short arrow*) confirmed by CT (**b**) as well as PET and US-guided biopsy. The finding of this single lesion in an unusual location was possible because of a thorough abdominal-pelvic US study, whereas the finding is immediately recognizable on CT. Confirmation with FNAC (**c**, *arrow*)

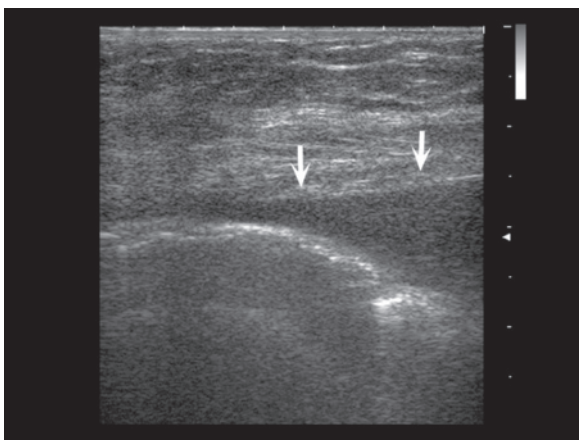


Fig. 1.3 Pleural effusion identified during US study of the thoracic wall. US study of the thoracic wall following radical mastectomy revealed an unexpected underlying pleural effusion (*arrows*)

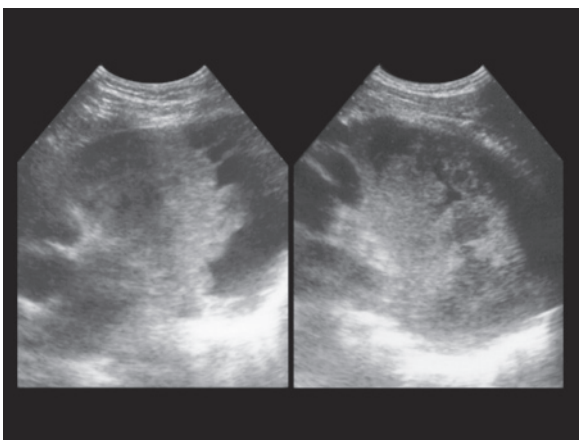


Fig. 1.4 Primary yolk sac tumor of the mediastinum. Heterogeneous echoic mass with hypo-anechoic areas at the level of the anterior mediastinum

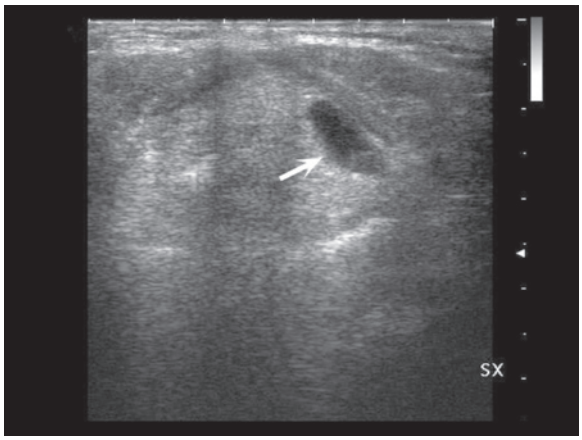


Fig. 1.5 Laryngeal metastasis from melanoma. The targeted US study of the neck in a patient with radiotracer uptake at PET shows a moderately hypoechoic heterogeneous nodulation immediately dorsal to the left thyroid cartilage (*arrow*). The lesion in this site would probably not have been identified without the guidance of the PET finding

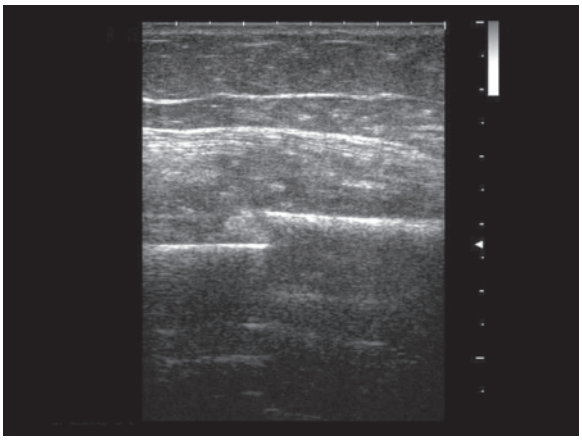


Fig. 1.6 Pathologic fracture of the humerus due to breast cancer metastasis. The examination, performed on indication of a tenderness of the arm, shows the unexpected interruption of the humeral cortex with heterogeneity of the adjacent soft tissue

formation. In addition, fine intralesional alterations can go unrecognized on CT images, especially due to the partial volume effect. Complex cystic formations, for example, can appear homogeneously liquid on CT images, but with fine septations or with internal corpuscular material on US. That being said, it should be underlined that US has low **contrast resolution** and therefore, indirectly, a lower ability to **characterize tissue** than that of CT and MR. Therefore distinguishing between different solid and fluid structures, recognizing necrotic phenomena and identifying fine vasculature are all features which are more difficult, if not impossible, with US.

The US image is not immediately interpretable for clinicians, unless they personally deal with ultrasonography. In general, those who are not involved with diagnostic imaging have greater **confidence** with radiographic images, CT or, to a lesser extent, MR than with US images.

Not unlike other imaging modalities, US requires **adequate information** regarding the clinical setting of the individual patient so that the examination can be correctly focused and the sensitivity maximized. Knowing that CT has identified a suspicious area in a specific hepatic segment, or that PET has demonstrated radiotracer uptake in a particular anatomic area, is completely different from acting without this knowledge. The availability of RIS and PACS, coupled with the possibility of analyzing prior reports, and the images regarding the different examinations performed, only partially overcomes the notorious lack of communication between requesting physicians and those performing diagnostic imaging.

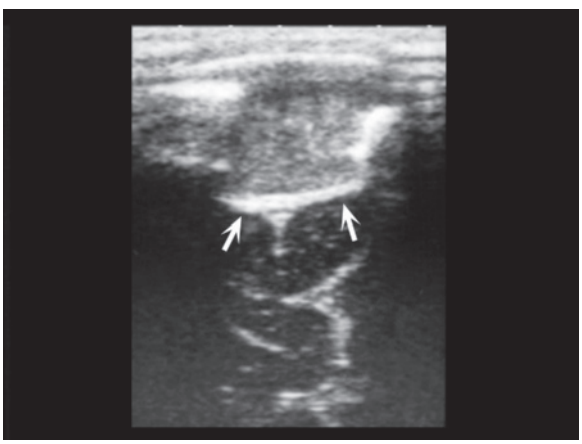


Fig. 1.7 Eosinophilic granuloma of the parietal bone, in a pediatric patient with referred palpable mass of the head. Interruption of the skull due to the presence of an echogenic mass bounded deeply by the meninges (*arrows*)

One of the main risks of diagnostic imaging in oncology, and not only in US, is being influenced by the clinical setting, e.g. considering a finding definitely or probably malignant simply because it is identified in a subject with a prior or current history of cancer. Complicating the problem is the nature of the malignant disease itself, which often exhibits unpredictable behavior, for example in terms of distribution (e.g. unusual site or "skip" of specific lymph node stations or specific parenchymas – as in the case of pulmonary metastases from gastrointestinal tumors in the absence of demonstrable liver metastases) or

timing (e.g. metastasis many years after treatment of the primary tumor). A further complication is the existence of "second" malignancies which develop in patients already treated for malignant disease.

US is a less **objective** technique than other imaging modalities. The imaging findings included in the report, despite being plentiful and detailed with writing and pictures on the images indicating the anatomic area of the findings identified, certainly cannot express what the observation was in real time. When confronted with a small lesion identified with CT, the previous CT examination can be reviewed to understand whether the lesion was already present, whereas this is absolutely impossible with US. Even with the use of video recordings of the examinations performed, the US study remains a not completely objective examination, and this creates problems, especially for trials and off-site evaluations.

However, this should not suggest that US is a subjective technique or, as is commonly stated, **operator dependent**. The findings of any diagnostic examination are in fact dependent on the experience and dedication of the operator. Incorrect timing of the various phases of hepatic contrast in CT or a failure to perform a particular sequence in MR can be dependent on the operator just as much as a failure to identify a US finding. The difference, in terms of reliability, is that a technically suboptimal CT or MR examination can still be recognized after a retrospective evaluation of the images, something which in US can only occur to a much lesser extent. It cannot be demonstrated that US implies a degree of intraobserver or interobserver **reproducibility** of the measurements performed or of the diagnostic results achieved; reproducibility is lower than the other imaging modalities. The problem of variability of measurement in oncology is of undoubted importance in the setting both of clinical trials and diagnostic practice, and to all of the imaging modalities [1].

A more significant problem than the presumed operator dependence, and one which is often underestimated, is **patient dependence**. This is certainly greater in US than in other imaging modalities. Even with the current equipment, patients who are highly obese, with interference from gas (aerated lung, intestinal gas, pneumoperitoneum, subcutaneous emphysema, etc.), with overlying skeletal structures or with particular conformations of the ribcage are a significant limitation for the US study. However, in thin patients visualizing exceptional anatomic detail is possible, e.g. with the use of high-frequency transducers for exploration of the abdomen, the study of internal structures in subjects who are large in build is rather inexact, especially if the structures are deep. Irregularities and hardening of the skin surface associated with prior surgery, radiation therapy, edema (venous or lymphatic) and/or tumor infiltration can create difficulties for the positioning of the transducer – especially with wide transducers – and can therefore hinder optimal US exploration. The prescribing physician, when requesting the examination, and the US operator, when writing the report, should always ask themselves whether that particular patient and that particular problem are effectively accessible with US. Individuals with a considerable body mass should, in general, be investigated with other imaging modalities.

Doppler technique should also be mentioned. The first major problem in this field regards the quality of the equipment, which can significantly influence the sensitivity for low intralesional flows. A nodule may appear avascular with a low-level device and hypervascular with a high-quality device. In addition, the sensitivity depends on the setting of the equipment and the experience of the operator, which becomes an even more important parameter than it already is for grayscale US. With a PRF which is too high or with excessive compression of the transducer against the skin, flow can be totally cancelled even in a highly vascular lesion. An intrinsic limitation of Doppler techniques regards the impossibility of demonstrating slow flows in the parenchymal capillary network and intralesional neoangiogenic vessels, although these limitations can be largely overcome with CEUS.

1.3 Ultrasound and Cancer Screening

Cancer **screening** indicates an array of diagnostic procedures used in the study of more-or-less selected asymptomatic subjects for the early identification of a possible malignancy. This is prompted by the premise that early diagnosis and treatment can positively modify the natural history of the cancer in the individual patient. This is different from the concept of **surveillance**, which is used for asymptomatic individuals at high risk of developing a malignancy and therefore subject to a closer evaluation [2,3].

The aim of secondary prevention in oncology, in terms of both screening and surveillance, is therefore the systematic search of a malignancy in the preclinical phase, i.e. in asymptomatic individuals. The endpoint is the prevention/delay, within reasonable costs and through early treatment, of the advanced stage of the disease itself, thus reducing morbidity and mortality [4–6]. The concept of **natural history** is fundamental. When a subject develops a malignancy during his life, the tumor will first have a preclinical phase, which begins at the time of the biologic development of the disease itself. This is followed by a clinical phase, which begins with the onset of symptoms

and ends with the death of the individual (either due to the disease or from other causes) [7]. The **detectable preclinical phase** is defined as the period between when a diagnostic test is able to recognize the disease and the onset of symptoms. In this period the disease may only be identified with secondary prevention (or as an incidental finding). The **critical point** is the moment in the natural history in which treatment of the disease becomes less effective than before: screening aims to identify the disease before and not after this critical point. For screening to be potentially effective, the critical point should occur during the detectable preclinical phase but the test and diagnosis should occur prior to that point, beyond which treatment becomes relatively ineffective [4,5,7].

The principal factors affecting the **cost effectiveness** of a screening test are cost, diagnostic accuracy, prevalence of disease in the sample and the percentage of "localized" tumors of those identified. [6,8].

A screening program can be planned only if a number of conditions are met or at least not disregarded [4,5,7,8]. With regard to the **test**, it should be ethically and psychologically acceptable so that the maximum number of people may respond to enrolment. It should be simple and accessible to all, especially to the targeted population. The test should also clearly have maximum sensitivity: since the prevalence of most diseases for which screening is proposed is <5%, a sensitivity of at least >95% would be needed (if the specificity is <95%, and vice versa), otherwise the true positives would be less than the false positives. With respect to sensitivity there is, nonetheless, the collateral question of overdiagnosis or pseudodisease. In this case the disease is identified, but the efficacy produced is only apparent because the disease is slow and indolent, and when correlated with age is unlikely to cause the death of the subject. From the probabilistic point of view, screening programs tend to markedly increase the detection of the more indolent and slow-growing tumors, whereas it is relatively unlikely they detect the more aggressive and highly malignant forms. The test should also have maximum specificity: the incidence of false negatives, with the associated consequences (further and possibly more invasive examinations, high costs, psychological effects, etc.), should be as low as possible. The identification of other and often trivial asymptomatic findings such as renal cysts, hepatic cysts, gallstones or kidney stones constitutes a negative effect. The test should be selective in the first instance, with a limited number of subjects – presumably all true positives – who move on to the second level. For this to occur, the number of indeterminate results needs to be minimized. The test should have a low level of invasiveness with the lowest level of mortality and morbidity possible: at the time of the test the subjects examined have a relatively low risk of death or severe symptoms deriving from the disease being investigated, so their safety should be especially protected. In this sense US finds favor over techniques such as CT which use ionizing radiation. The test should be relatively simple to perform and interpret. A test which requires elaborate preparation/implementation or which can only be read by a limited number of super-specialists does not lend itself to wide application. Even the length of the examination and the use of healthcare workers should be kept to a minimum. Lastly, the test should keep economic costs as low as possible. The **disease** should have a known natural history. It should be known when the critical point is reached, since the test can only be effective if this is located in the detectable preclinical phase. In this way the optimal interval for performing the test can also be established. The disease should be severe enough to ethically and economically justify the costs and risks of the screening. The failure to identify the disease should have serious consequences and this is applicable to the category of tumors, although with differences from case to case. The disease should not be overly rare otherwise the pretest and post-test probability would be inevitably low. The disease should not be easily curable during the clinical phase, otherwise there would be little need for preclinical identification, and there should be an effective treatment for the disease if it is identified prior to the critical point, otherwise an early diagnosis simply translates into "falling ill earlier". Lastly, the available treatment should not be overly dangerous or harmful, since some of the selected cases are false positives or pseudo-diagnoses. The **patient** should have an adequate life expectancy and other general characteristics of good health such that in the advent of a positive finding he can be eligible for treatment. The patient should be appropriately motivated, to minimize the number of cases lost at follow-up.

Let us now examine the possible applications of US in the screening of the main forms of cancer.

The early diagnosis of **breast** cancer translates into a reduction in mortality of 25–30% with respect to the cases diagnosed at the time of clinical presentation, with identification of smaller lesions more rarely involving the lymph nodes. One area of debate regards the age to begin and end screening and the appropriate interval. The ACS recommends performing an annual mammography from 40 years onwards to an age to be defined on the basis of the estimation of individual risk. The recommendations for younger women include a clinical evaluation every three years between the ages of 20 and 30 years and an annual evaluation between the ages of 30 and 40 years. Recommenda-

tions for women with an increased risk (family history, personal history of breast cancer or Hodgkin's lymphoma treated with radiation therapy) include an individual definition for an earlier beginning of mammography, US integration and a shorter interval between examinations. Lastly, women with a genetic predisposition (carriers of the genetic mutation *BRCA1* and *BRCA2*) are recommended to undergo surveillance based above all on MR. The association of US with mammography has significantly increased the percentage of breast cancers detected, especially in young women with denser breasts. The combined sensitivity of the two techniques in the various patient populations is 83–91%. The evidence therefore seems to support the additional use of US in the screening of women (age range 30–40 years) with dense or heterogeneous breasts [9].

Palpation is unable to identify most nodules of the **thyroid** with a diameter <15 mm and therefore is generally not considered viable for screening [10]. Moreover, a Japanese study on 88,160 individuals who underwent screening in a period spanning 16 years suggests that the view is sufficient to select suspicious cases to undergo US. Malignant lesions were encountered in 204 individuals (62 males and 144 females) with a percentage of detection in line with the literature [11]. High-resolution US is indisputably able to identify an elevated number of thyroid nodules, and the technique could be proposed for example in conjunction with US screening of the breast, in part because a correlation between the two malignancies has been proposed, although without a clear mechanism [12]. However, there are numerous practical limitations. The incidence of benign nodules in the population is very high (nodules <10 mm are found by US in up to 70% of normal thyroids). Postmortem findings show that the incidence of carcinoma is very low, at least with regard to clinically apparent forms (1.4–6.1/100,000) compared to the significantly higher incidence of apparently silent tumors (5–35% of individuals). There is a similarity in the imaging appearance between benign and malignant nodules, and in theory all identified nodules >8–10 mm should be subject to FNAC (performing FNAC only on suspicious nodules would subtract from screening a quota of carcinomas with a "benign" US appearance). Lastly, 90% of thyroid carcinomas are made up of papillary (especially "microcarcinomas", i.e. nodules <10 mm) and follicular forms which are often indolent, whereas it is rather unlikely that periodic screening would be able to identify the aggressive forms in an early stage, particularly the highly feared anaplastic carcinoma [12–15]. In essence, a program of US thyroid screening risks making a considerably large number of overdiagnoses, with a very high cost–benefit ratio and rather dubious prognostic benefits [15]. The selection of high-risk individuals (subjects with a family history, subjects exposed to radiation therapy of the neck in pediatric age or exposed to environmental radiation, patients with MEN, etc.) could narrow the application field [10].

Prostate cancer is characterized by low mortality, but given its elevated prevalence in the population it is nonetheless the second-leading cause of cancer death [16]. The ACS suggests screening from 50 years of age (45 years of age if first-degree relatives have a history of prostate cancer diagnosed at a relatively young age) with digital rectal examination and PSA assay (protease produced by normal, adenomatous and especially malignant glandular tissue), together with adequate information regarding the benefits and limitations of early diagnosis and treatment. Indeed, while it is true that the PSA assay is able to bring the diagnosis forward by at least 10 years on average, it is also true that this does not demonstrably increase survival. For the most part this is due to silent carcinomas (>30% of cases), which would not effectively progress and are therefore overdiagnosed due to the screening, and as a result overtreated. In addition, PSA is not specific and its widespread use runs the risk of having a large number of patients undergo biopsy who in fact have no malignancy. In Europe many currently advise against the PSA assay in asymptomatic patients and without clinical indications, due not only to the problem of overdiagnosis, but also to the significant percentage of false positives, the undemonstrated effect on the duration of life and the complications of prostatectomy (incontinence, impotence, etc.) [16]. Even the use of TRUS in asymptomatic patients appears to be rather unconvincing, since the technique is characterized by a relatively low positive predictive value (18–52%). This is due to the problem of unrecognizable isoechoic tumors, benign hypoechoic nodules which produce false positives, and the frequent multifocal nature of the disease [16]. Currently screening may be suggested on a voluntary basis, with periodic check-ups and PSA assay and subsequent evaluation with TRUS and/or biopsy in suspicious cases.

General screening for carcinoma of the **ovary** is currently not recommended, although it is indubitably hoped for in the future, should cost-effective systems become available [17]. An early diagnosis can translate into high survival (>80% for stages I and II). However, the relatively low prevalence of the disease, combined with the not very high specificity of the currently available diagnostic options, discourage mass screening [17–19]. There are, nonetheless, categories of increased risk, such as women with a family history, which require surveillance. The annual gyne-

cologic examination with bimanual rectal-vaginal exploration has limited efficacy since it only detects 30% of masses identifiable with TVUS [20]. Screening can instead be based on CA-125 and/or US with a suprapubic approach but preferably with a transvaginal approach: TVUS is currently the imaging modality with the highest sensitivity for small ovarian tumors. It should, however, be borne in mind that while it is true that >80% of women with ovarian cancer have elevated levels of CA-125 (>35 IU/mL), it is also true that this figure falls to around 50% in cases of stage I and stage II disease [19]. Despite an overall elevated specificity, this tumor marker can give rise to false positives. These include healthy women (1%), subjects with cirrhosis, pancreatitis, first trimester pregnancy, pelvic inflammatory disease or endometriosis, and patients with advanced-stage non-ovarian abdominal malignancies (40%) [17,21]. A study of 22,000 women produced discouraging results: 11 tumors were identified (0.05%), of which seven were already in stage III–IV, and seven women with normal levels of CA-125 subsequently developed ovarian cancer [22]. The use of more sensitive biomarkers is desirable, possibly in combination [19]. With regard to TVUS, prospective studies indicate elevated sensitivity (85–95%) but with 2–5% of false positives [18]. The sequential use of an annual CA-125 assay and TVUS in cases with pathologic levels of the marker appears to be the most rational approach, although still not optimal because it is able to reduce the number of false-positive diagnoses and produces a sensitivity of 79–100% [18]. In women with a family history of ovarian cancer a multimodal evaluation combining clinical, US and laboratory findings is indicated to achieve an early diagnosis. There is undeniably the need for monitoring of women with markedly high risk (as high as 40%), i.e. those women with hereditary non-polypoid colorectal cancer, hereditary breast ovarian cancer syndrome or hereditary site-specific ovarian cancer syndrome. Moreover, in these cases prophylactic ovariectomy tends to be advised. In women with a less marked family history, e.g. with a single first-degree relative with a history of ovarian cancer, in whom the estimated risk is around 7%, surgery seems too radical, so periodic screening beginning at 25–30 years is generally the option chosen. In addition, all of these women develop the possible carcinoma of the ovary at a premenopausal age when the CA-125 assay and TVUS more readily produce false positives. Appropriate counseling of the women at risk regarding the current limitations of prevention is therefore advisable.

The rationale behind the screening for carcinoma of the **endometrium** is given by the advanced stage of disease at the onset of symptoms and, in contrast, the favorable prognosis for cases identified early (stage IA) with a 5-year survival rate of 90% [23]. The identification of precancerous lesions (endometrial hyperplasia and polyps) and endometrial carcinoma could benefit from TVUS, also with CD. An endometrial thickness of <5 mm virtually rules out malignancy. A screening program of 1074 asymptomatic women between 57 and 61 years of age, with an endometrial thickness threshold of >4 mm and a PI<1, showed a sensitivity for carcinoma of 94%, but a specificity of only 48% [24]. This suggests that women with an above-average risk should probably be selected for formulating a rational screening program, possibly in combination with the study of ovarian cancer (which has a peak incidence at a slightly younger age) [25]. Currently, however, screening for endometrial cancer is not considered sufficiently beneficial or justifiable, unless it is carried out in high-risk subjects (e.g. women with hereditary non-polypoid colorectal cancer) with the annual measurement of the endometrial thickness at TVUS [17].

With regard to the **testicle**, there are a number of conditions which constitute risk factors for the development of tumors, such as cryptorchidism (present in the history of 3.5–14.5% of patients diagnosed with testicular cancer, particularly with seminoma) and microlithiasis. US is clearly the technique of choice for surveillance (more so than for the screening) of these individuals, with the premise however that cryptorchidism is a clinical diagnosis whereas microlithiasis – defined as the presence of at least five calcified foci in the testicle – can only constitute an incidental US finding [26]. Since orchiopexy prevents infertility but not the risk of cancer (4–10 times higher than in individuals with normally descended testicles), periodic US monitoring is indicated in patients operated for cryptorchidism [27]. As an alternative, a testicular biopsy can be performed at the age of 18–20 years: if this is positive for a germ-cell intratubular tumor (carcinoma in situ), there is a 50% probability of developing an invasive carcinoma, whereas if the biopsy is negative the patient has a risk of cancer similar to that of others of his age and does not require monitoring [28]. With regard to microlithiasis, which is caused by the deposit of calcium in the seminiferous tubules and has a prevalence of 0.05–0.6% (in focal or diffuse form, either uni- or bilateral), its real weight as a risk factor is debatable. An association with testicular tumors has been hypothesized, in particular with germ-cell tumors, but this has not been confirmed by all studies (Fig. 1.8). Currently it does appear prudent to suggest to patients with an incidental finding of microlithiasis (and probably also with non-microlithiasis testicular calcifications) to undergo an annual US examination as well as performing self-palpation, or at least to discuss the existence of the problem.

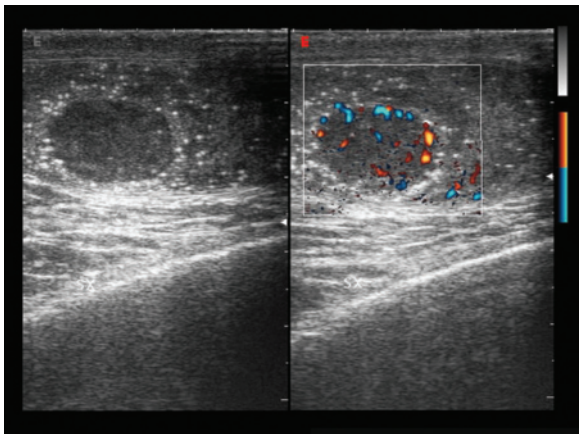


Fig. 1.8 Testicular seminoma associated with microlithiasis. US and PD study shows a relatively homogeneous and well-defined hypoechoic nodule with moderate vasculature within the testicle. Numerous fine calcifications around the lesion and throughout the testicle can also be visualized

The routine use of tumor markers, CT examinations or testicular biopsy in these patients does not appear reasonable [26,29,30]. Beyond these circumstances, the rather low incidence of testicular cancer discourages mass screening, unless reserved for a strict age range (20–30 years).

Hepatocellular carcinoma (HCC) can unquestionably be managed more effectively if it is identified early, in part because the improvements obtained in recent years in the treatment of cirrhosis and HCC itself have enabled an improvement in survival to be achieved in these patients with tumor identified with screening [31–34]. Nonetheless, greater understanding of the natural history of this disease is needed, which has a highly variable doubling time, variable growth rates and variable progression in subjects of different race and with different etiologic factors of hepatitis [32]. Screening is viable in countries with an elevated incidence and, at the same time, adequate healthcare facilities. High-risk subjects need to be selected, especially those with HBV infection (males >40 years, females >50 years, family history of HCC, subjects with cirrhosis), HCV infection (if >40 years), alcohol-induced cirrhosis, genetic hemochromatosis or primary biliary cirrhosis [31,35]. Serum alpha-fetoprotein (AFP) and/or US may be used, although the use of CT or MR has been proposed in the United States [36,37]. Despite these latter modalities being undeniably more accurate, they involve higher costs and greater invasiveness and are relatively unsuitable for the periodic screening needs of countries with a high incidence. In a study simulated on patients aged 50 years with hepatitis C cirrhosis [36], screening for HCC with AFP assay and US produced, in relation to the non-screening option, an increase in the cost-effectiveness ratio of USD 26,689/year, quality of life corrected, an increase of USD 25,232 for screening with AFP assay and CT, and an increase of USD 118,000 for screening with AFP assay and MR. Moreover, no randomized controlled trial has demonstrated a reduction in disease-specific mortality associated with screening for HCC, nor have they clearly defined which is the most cost-effective test, which patients should be included and which interval should be adopted [38]. With regard to the latter, a dynamic CT study is indicated [38] at least every 12 months, with shorter intervals in high-risk subjects, even though CT studies on the growth rate of small HCCs [39] have indicated the need for three-monthly examinations. Annual US screening has identified single lesions in 60% of cases and multiple lesions in 40%. However, only in 30% of cases is the single lesion <3 cm, and only in 23% of cases is it <2 cm and therefore ideal for surgical resection. This suggests the need for more frequent US examinations (2, 3 or even 4 times/year) since the doubling time of HCC is thought to be 2–4 months. Moreover, there are no randomized controlled trials which demonstrate the superiority of the six-month interval over the annual one [31,40]. The mean size of nodules identified with six-monthly screening is smaller than those of HCC identified with longer intervals [35]. In Italy, as in many Asian countries where HCC is particularly widespread, screening is based mainly on three- or six-monthly US, possibly associated with AFP assay. AFP, whose value is not correlated with the size of the lesion but which nonetheless is an important prognostic index, has been found to be absolutely normal (<20 ng/mL) in 31% of cases of HCC identified at US screening, and markedly increased (>400 ng/mL) in only 22–29% of these. The sensitivity is 60% with a threshold of 20 ng/mL but it falls to 22% with a threshold of 200 ng/mL, thus indicating that this marker cannot be used as a single screening test [31,35]. The AFP assay can reduce the number of US false negatives by producing pathologic values in some of these subjects, while at the same time being able to produce a certain increase in false positives [41]. It is not uncommon for the re-evaluation of subjects with negative US and increased AFP to identify small iso-hypoechoic lesion, particularly when deep or superficial, which went unrecognized during an initial US study. US screening has shown extremely variable sensitivity, from 33% to 96%, in different studies in relation to different factors [31,42]. Several prospective and retrospective studies comparing pretransplant US with findings from the explanted liver have shown a rather low sensitivity of 30–50% per patient and 20–45% per lesion, calling into serious question the possible application of US

screening [42–44]. Accordingly, the sensitivity appears not to depend on the degree of heterogeneity of the parenchyma, the hepatic volume or the site of the nodule but strictly on the size of the nodule. The conclusions which can be drawn are that the combination US + AFP with six-monthly intervals, while not being especially sensitive and increasing costs with respect to the two tests taken individually, does have a rationale in the monitoring of at-risk patients, considering the relatively low aggressiveness of HCC in most patients. Protocols which instead alternate AFP and US do not have an adequate rationale [31,45]. Since lesions <10 mm are rarely the expression of a HCC, such US findings tend not to require work-up unless they are associated with an increase in AFP, and are simply monitored. Nodules >10 mm have a good probability of being malignant and therefore undergo the work-up of HCC [31,45]. The individual lesions <3 cm identified by screening are hypoechoic in 60% of cases, isoechoic in 24% of cases and hyperechoic in 16% of cases. In addition, 48% show a mosaic appearance and 36% have a peripheral hypoechoic halo [41]. With regard to the site, defined per patient with individual lesions <5 cm, 50% of lesions are located in a posterior segment, 34% in an anterior segment, 11% in a lateral segment and 4.5% in a medial segment [41].

Renal cell carcinoma (RCC) is relatively too uncommon and relatively too little aggressive to justify any form of screening. In particular, small RCCs – those that would probably be identified during screening – on the one hand tend to have a lower grade and extension than symptomatic lesions, and on the other create greater problems for differential diagnosis. Renal malignancies ≤35 mm identified incidentally are in fact slow growing (on average 3.6 mm/year), especially if well defined. Also bearing in mind that during the follow-up of these lesions the identification of metastases is rare, an approach of "wait and see" has been suggested in elderly, run-down or high-surgery-risk subjects, rather than an approach of aggressive surgery (even though it would be rather difficult to convince an elderly subject with a new diagnosis of a small renal tumor to not undergo surgery!) [46]. On the other hand, several studies have reported sensitivity and specificity for US that is far from optimal in the identification of small RCCs [47]. However, a Japanese study reported the findings of US screening performed on 200,000 subjects over a 13-year period. RCC was identified in 0.09% of cases, with T1 lesions accounting for 38% of cases and a constant absence of lymph node involvement and distant metastases in all identified cases, and with effective resection in 98% of cases (cumulative survival at 10 years of 98%) [48,49]. To increase the cost–benefit ratio, the authors of this study underline the importance of exploring not only the kidneys but the entire abdomen. Hypothetically, US screening for RCC could be combined with screening for aneurysms of the abdominal aorta, which is increasingly encouraged now that endoprostheses are available and could be performed in a similar age range, possibly with the selection of male subjects.

To conclude, one must ask whether a US abdominal examination in asymptomatic subjects can have a rationale for the purposes of general oncologic screening and the search for "disease" in the broad sense. With increasing frequency, individuals are encountered who "self-prescribe" periodic examinations (usually annual) with US of the abdomen, pelvis and often the thyroid, on the basis of an often general "family history". There are no scientific arguments in support of this practice so it therefore does not appear to be sustainable. In Japan, where it should be recalled the average build of the individuals is smaller than that of Europeans and still smaller than that of Americans, the results of a general abdominal US screening program have been reported. In an eight-year study performed on over 200,000 subjects, generally resectable malignancies were identified in 0.31% of cases. These included 201 HCCs, 81 gallbladder carcinomas, 57 pancreatic carcinomas and 169 RCCs, with a 5-year cumulative survival rate of 79.5% [48]. In reality, a US examination performed on non-selected asymptomatic individuals has a much higher probability of identifying relatively irrelevant findings (hepatic cysts, renal cysts, gallstones, kidney stones, etc.) than identifying malignancies in an early stage. Most tumors identifiable with transabdominal US, with the exception of HCC (which nonetheless generally has onset in specific categories of individuals), RCC and bladder cancers, are in fact identified in a relatively advanced stage, often beyond the critical point: gallbladder, pancreas, gastrointestinal tract, female reproductive system and prostate. The false negatives relative to tumors present but not yet identifiable with US are added to the false positives, a source of further costs and often additional unnecessary diagnostic or therapeutic procedures. These are the same considerations that have been made with regard to CT screening [2,3,8], which is encumbered by greater costs and a higher level of invasiveness, but which at least has the extenuating characteristic of greater panoramic views and, when performed with intravenous contrast media, greater diagnostic accuracy.

1.4 Ultrasound and Neoangiogenesis

The **acquired properties of cancer** include: self-sufficiency in growth signals (and insensitivity to anti-growth signals), cellular immortalization (apoptosis),

proliferation (unlimited potential for replication), invasion, metastasization and neoangiogenesis (sustained formation of vessels) [50]. Neoangiogenesis is the requirement for both tumor growth, which is angiogenesis dependent, and metastasization [51]. Tumor growth beyond 1–3 mm in fact requires a functioning network of blood vessels to support its anabolic and catabolic activity [51–53].

Neoangiogenesis is characterized by an increased number of small vessels – the microcirculation – which develop within the tumor from the activity of host endothelial cells activated and stimulated by tumor growth factors [50,54] (Fig. 1.9). The vasculature of the tumor is typically characterized by an irregular and chaotic architecture without a precise "hierarchy" between the different vascular structures, a prevalence of tortuous and dilated capillaries with few complete arteries and veins, variable vessel branching with the possibility of blind collateral branches, an absence of vasomotor control, immature vessels which are fragile and permeable to macromolecules, arteriovenous fistulas and intermittent or unstable flow with acute vessel collapse and hemorrhage [50,53]. The low flow resistance, due to the absence of vasomotor control and arteriovenous fistulas, is counterbalanced by high interstitial pressure, caused by the increased vessel permeability and consequent diffusion of osmotic substances. The result is areas of different flow resistance [55]. The vascular distribution is heterogeneous, with areas of coexisting low and high vessel density, the latter being particularly present in the peripheral regions of the tumor. In part the network is inefficient in terms of oxygen supply, which explains the tendency for necrosis, especially in the central region [56]. The microvessel density (MVD) is inversely proportional to the tumor volume [57].

The **study of tumor vascularity** is important for a number of reasons. It may confirm the effective presence of a lesion, by negatively or positively increasing the contrast with the surrounding tissue. Since the degree of vascular density is correlated with the probability of a malignant nature of a lesion (although with notable exceptions, e.g. the intensely vascular hepatic FNH), it is also correlated with the degree of activity and the propensity to metastasize of the lesion and therefore correlated with prognosis (although at the same time it may indicate greater responsiveness to systemic treatment). The study can also define the anatomic relations of a lesion with the adjacent structures and especially with the vessels (staging, operability, etc.).

The **degree of microvessel density** can be analyzed with direct or indirect systems. Estimation of the intratumoral microvascular density is the main direct method for evaluating angiogenesis and is performed with immunohistochemical staining using antibodies against various endothelial cell-related antigens [54,56]. The degree of MVD is a prognostic variable independent of the malignancies and it correlates with the probability of metastasization and survival, even

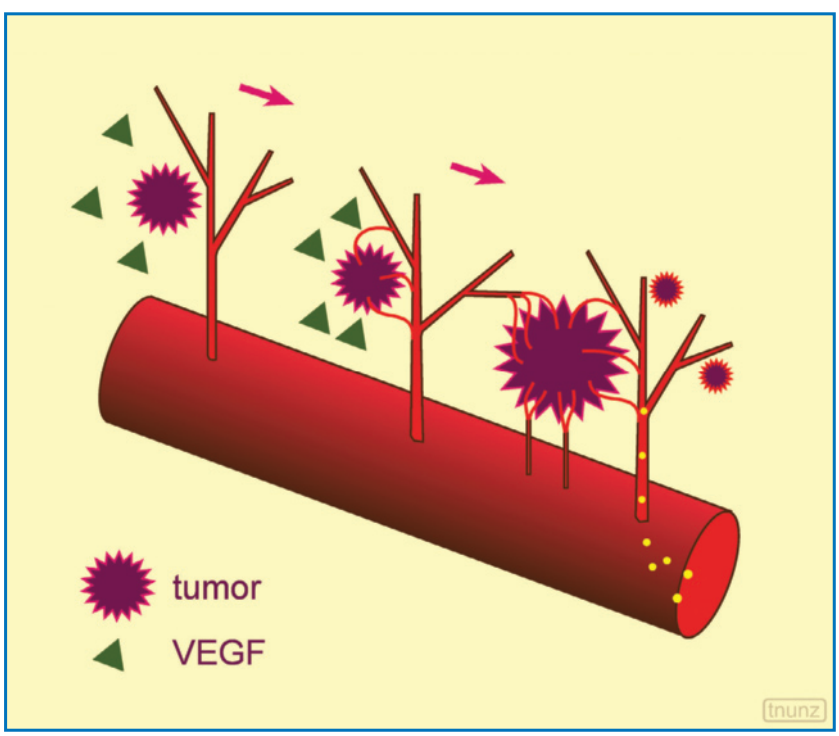


Fig. 1.9 Mechanism underlying angiogenesis. The still small malignancy produces vascular endothelial growth factor (VEGF) which causes the development of new arterioles, which in turn are responsible for further tumor growth

though it is not necessarily related to the rate of tumor growth: a reduction has in fact been measured in animals treated with antiangiogenetic drugs [51]. The vessels of the microcirculation have a very small diameter (2–5 μm) and are only accessible with microscopy: confocal microscopy (resolution ~100 nm), multiphoton microscopy (~100 nm) and electron microscopy (several nm) [53]. These techniques are optimal for the high-resolution evaluation of neovascularization in that they enable calculation of the MVD. However, they do require tumor tissue and therefore a biopsy. In addition they only indicate the MVD at a given location and therefore, in the context of a tumor, numerous central and peripheral samples would be required to reliably define the state of the microcirculation. The estimate of MVD is also a morphologic parameter and does not enable a dynamic functional analysis [50].

The tests for indirectly determining the state of the microcirculation can be divided into two groups: (1) blood angiogenetic factors assay; (2) blood volume and tumor perfusion evaluation with imaging techniques. The latter – some of which are still in the experimental phase or can only be performed in vitro – can be further subdivided into two broad categories: those that indirectly study angiogenesis (perfusion MR, perfusion CT, PET with O^{15}, SPECT, spectral and color Doppler, CEUS, photoacoustic imaging) and those that enable a direct approach, e.g. with contrast media able to bond to the endothelial cells (US with specific microbubbles, MR with specific paramagnetic nanoparticles, PET with tracers bonded to antibodies directed against factors associated with the neocirculation, micro-CT, optical imaging with bioluminescence or fluorescence) [29,58].

The commonly used imaging modalities, however, have a spatial resolution that is inferior to the above-mentioned microscopic techniques: CT 100–500 μm, MR 100–500 μm, CEUS 50–100 μm, PET ~4 mm (up to 1.5 mm in the future), US several mm [29,52,59]. CD is able to identify vessels up to a diameter of 40 μm, especially when they are located superficially and the power mode is used. Imaging modalities are therefore unable to resolve the microcirculation, but they do provide important morphofunctional information in vivo. The techniques are based on the equivalence tumor perfusion and blood volume = MVD (the perfusion is the total blood flow to a tissue, including the capillary flow).

Each of the different imaging modalities used for the study of tumor vascularity – CT, MR (dynamic or with other techniques of functional acquisition), PET (with different radiotracers), Doppler and CEUS – has advantages and limitations, the discussion of which goes beyond the possibilities of this text. Which of these will in the future be the technique or techniques for the evaluation of tumor perfusion cannot be safely stated at present. However, the US techniques are in no way inferior in this sense to CT, MR or nuclear medicine [60,61].

Color Doppler is able to obtain a color signal corresponding to small intraparenchymal or intralesional vessels which are not visible in B-mode. Either in baseline or with contrast media, the Doppler techniques in fact provide a good architectural representation of the tumor macrovasculature, at least with regard to the superficial structures and, above all, with high-frequency transducers [59,62]. Power Doppler, which is more sensitive to slow flow and to morphologic detail than color Doppler, is more susceptible to artifacts and does not bring substantial improvements to the study of tumor vascularity [56,59]. The flow in the small vessels (<200 μm) is similar to the movement through the tissues (<1 cm/s) and therefore cannot be identified with Doppler techniques [59]. In order to be detected by Doppler, a vascular signal needs to have a sufficient intensity and velocity: the first can be increased with the use of contrast media (with the disadvantage of increasing artifacts), but the second cannot be altered. The state of large- and medium-diameter vessels identified with Doppler tends to be (but is not necessarily!) correlated with the state of the microcirculation [62,63]. Correlation between color signal density and histologic grade of the tumor vasculature has been experimentally demonstrated [64,65]. The parameters which have been proposed include pulsatility index, resistance index, acceleration index, peak systolic velocity, color density (quantification of the number of colored pixels with respect to the total number of pixels of the lesion) and other indices calculated on the basis of the color maps. Often, but not always, these parameters correlate with the degree of tumor vascularity measured invasively, such as MVD [56,63,64,66]. From the point of view of MVD, the heterogeneity of the tumor mass also explains the frequent coexistence of different Doppler spectra in terms of profile, systolic velocity and, above all, RI in the same tumor or in different tumors but of the same histotype and grade [56]. This is the source of the heterogeneous data present in the literature. Intraobserver and interobserver reproducibility are also limited and there is the problem of deep attenuation.

CEUS is more sensitive than the Doppler techniques, in that it is able to identify the distribution of contrast medium even in conditions of ultraslow flow, and it is less susceptible to motion artifacts [62,67]. US contrast media are to a certain extent ideal for this type of analysis, since they are intravascular and enable the perfusion study to be performed with maximum temporal resolution, i.e. in real time. The resolution is

also greater than that of Doppler techniques, with the possibility of direct demonstration of vessels 20–40 μm in diameter (corresponding to the precapillary level) [62,63]. CEUS offers a reproducible estimate of the perfusion, and the signal intensity (echogenicity) is proportional to the concentration of microbubbles in the area of interest. The perfusion curve obtained after injection of the bolus of contrast medium is characterized by an initial rapid and intense increase in signal intensity, a brief maximum and a more-or-less rapid decrease over time [60] (Fig. 1.10). The most widely used technique for quantifying the absolute perfusion parameters or the parameters proportional to the blood flow in that particular area is the destruction–reperfusion technique. When all of the microbubbles in a particular section are destroyed by pulses with an elevated MI, the subsequent filling depends on the new microbubbles which enter the section from the adjacent tissues and can be detected in a nondestructive manner (low MI). While keeping the transducer in a fixed location for the entire time, a sequence of predefined ultrasound pulses is transmitted, with a high-power initial pulse and other less intense pulses aimed at the harmonic stimulation of the new microbubbles entering the section [60,62,68]. The percentage of filling, with administration of contrast medium by both infusion and bolus injection (but in the latter case an initial injection is needed for calibration), follows a curve whose initial increase depends on the mean flow velocity in the ROI and whose maximum peak indicates the vascular volume fraction: the product of these measurements is a proportional measure of the real tissue perfusion [57,60,62,68]. Many US devices are equipped with internal software for automatic quantification of the enhancement as an objective estimate of perfusion. As an alternative, the images can be sent to off-line systems. There are numerous perfusion parameters which can be calculated from the intensity/time curves: peak signal intensity, time to maximum enhancement (time to peak), time to enhancement, area under the curve, positive gradient and duration of enhancement [53,62,69,70]. The enhancement detected with the scansion in real time can even be automatically summed into a single vascular map [71]. For quantitative studies, however, the settings of the device should be standard and should not be modified over time, and the same goes for the injection protocol and acoustic window. In addition, the transmission parameters should be correlated with the concentration of the contrast media in the tissue [60]. CEUS findings correlate experimentally with data obtained with immunohistochemical markers of angiogenesis and also with those obtained with dynamic MR. In a recent series, CEUS patterns and parameters were found to correlate more closely with MVD than VEGF expression [72].

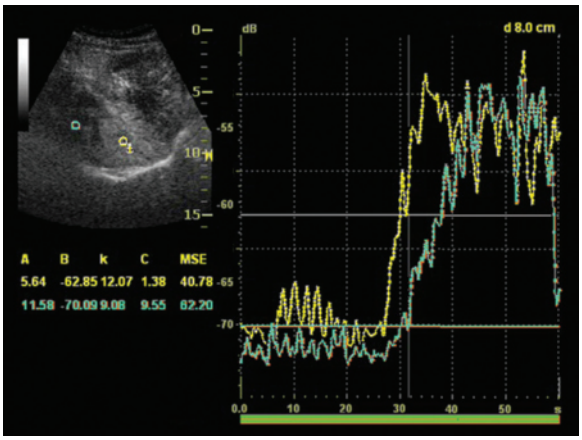


Fig. 1.10 Signal intensity–time curve. Perfusion curves obtained by positioning a yellow ROI on a hypervascular hepatic lesion and a blue ROI on the adjacent normal hepatic parenchyma

In a study on murine neuroblastoma, CEUS, in contrast to PD, was able to distinguish experimental tumors and control tumors based on the different characteristics of the signal intensity at the moment of arrival of the contrast medium [73]. Animal studies have also shown changes in the destruction–reperfusion curves after antiangiogenesis therapy with a reduction in the duration and intensity of the enhancement and an increase in the time required for reperfusion. The regression of functional vascular parameters precedes the reduction in size of the tumor [74]. In addition, an experimental study showed a partial lack in the correlation between CEUS and MR, with the risk of the former underestimating the vascularity of tumors with small and collapsed vessels, due to the greater resistance offered to the microbubbles than to the MR contrast medium [75]. The main limitations of the study of angiogenesis with CEUS are related to the acquisition in a singe layer, recirculation of contrast medium, attenuation in the deep tissues, and dependence on patient build. At the level of the abdomen the patient needs to be able to maintain breath-hold for the entire time required, and the acquisition parameters need to be kept constant. A future outlook is provided by targeted imaging, with microbubbles specifically tailored for the tumors (e.g. with tumor-specific peptides on the surface of the microbubbles) or their vessels (e.g. with antiendothelial monoclonal antibodies on the surface of the microbubbles) [61,76].

1.5 Cancer Staging

In addition to screening, which is a topic in itself, various phases need to be considered when imaging, and in our case US, is used in the diagnosis of the

patient with a malignancy. This includes diagnosis or "first" diagnosis (**identification** of the lesion and therefore its topographical position, **characterization** or differential diagnosis of the lesion, in the sense of non-tumor vs. tumor, benign vs. malignant and primary vs. metastatic), **staging** (evaluation of the spread of the disease, not only for the purposes of completing the diagnosis, but also for treatment and prognosis), **treatment planning** (including an evaluation of operability), the **evaluation of response** during and after treatment (both in the short term for the judgment of radicality, the identification of residual tumor and the exclusion of complications, and in the long term for follow-up) and the identification of **recurrence**.

Staging is fundamental because it influences the treatment and especially the prognosis which, in general, worsens in terms of 5-year survival with increasing stage. Accurate staging is crucial in the patient who is a candidate for surgery. In most cases, the treatment of choice for tumors in the initial stages is in fact **resective surgery with radical or curative intent**. According to the protocols, this can be practiced with a more radical or more conservative intent with respect to the anatomic parts surrounding the tumor. In some cases, radical surgery can even be performed in the event of local recurrence, lymph node involvement or the excision of metastases. A crucial factor in all cases is that the anatomic-pathologic evaluation reveals an adequate margin of healthy tissue around the excised mass. In other cases, with locally advanced tumors, **palliative surgery** and/or **cytoreductive surgery** may be performed. Tumor debulking, i.e. the removal of more-or-less large parts of the tumor mass, makes possible an improvement in the effects of systemic or radiation therapy. Included among the tumors that are generally considered inoperable are tumors with an excessive local extension which would not allow en bloc resection except at the price of persistent functional damage, tumors with a local-regional extension so great as to suggest an elevated probability of still occult distant metastases, and tumors associated with distant metastases, with the exception of those that are highly chemosensitive such as testicular cancers. One method for improving the possibility of performing and the effectiveness of "curative" surgery is the use of chemotherapeutic and/or radiotherapeutic treatment either preoperatively (**neoadjuvant**) or postoperatively (**adjuvant**). In this way curative surgery may be able to obtain a result similar to that of radical surgery but without adjuvant treatment, or it may be possible to eradicate (potential) micrometastases after surgical resection, or to re-evaluate a lesion not initially considered for radical surgery (debulking). In fact neoadjuvant treatment aims at obtaining a downstaging of the tumor, i.e. reducing the stage of the disease with the possibility, in the event of a positive response, of then intervening surgically. Lastly, mention should be made of chemotherapy as an initial palliative choice in cases of advanced disease, in the first diagnosis phase or in the presence of recurrence. Most patients in the metastatic phase of disease are treated with chemotherapy to reduce symptoms and prolong life. Defining the stage of disease is important even in the patient who is not a candidate for radical surgery, at least in the first instance, since the evaluation of treatment response will mainly be based on the comparison between the extent of disease before and after treatment [33,77].

Tumor spread occurs in a number of patterns: continuous spread, in relation to the growth of the tumor itself; contiguous spread, along ligaments, vessels, nerves or other structures adjacent to the mass; lymphatic spread, with involvement of the lymphatic vessels and the lymph nodes draining the anatomic region of the mass; hematogenous spread, from the embolization of tumor cells in distant organs; cavitary spread, with the transmission of tumor cells in the fluids of serous cavities; and iatrogenic spread, as a consequence of seeding of tumor cells during medical procedures.

The TNM staging system of solid tumors is a standardized modality for objectively and concisely defining the anatomic extension of a tumor in a given time so as to make possible the evaluation of changes over time. The system combines information regarding the size and/or depth of the primary tumor (T parameter – **local**) with information concerning spread to the lymph nodes (N parameter – **regional**) and metastases (M parameter – **distant**) in a series of categories or stages. The addition of numbers to the T and N components indicates ascending degrees of tumor extension (T0 – no evidence of primary tumor – T1, T2, T3, T4 – worsening local extension; N0 – no evidence of lymph node involvement – N1, N2, N3 – worsening lymph node involvement), whereas for the M parameter there is only the alternative absence (M0) or presence (M1, with possible distinction between different sites). The definition of the T parameter is generally based on the size of the primary tumor and/or its location and/or deep extension (wall of hollow organs) or invasion of adjacent structures. The N parameter is usually defined on the basis of the site of the lymph nodes involved with respect to the tumor, as well as their number, size and/or mobility. It should be noted that the N parameter includes only the lymph node stations considered to be "regional" with respect to the tumor in question, whereas metastases to "extraregional" lymph nodes are a part of distant spread. Lastly, the M parameter considers the organs and structures involved secondarily by distant metastasization, with the possible

distinction of different sites [78]. In general, stage 0 corresponds to the earliest form with the most favorable prognosis (i.e. carcinoma in situ), stage I to localized carcinoma, stage II to local and/or limited regional spread, stage III to local-regionally advanced spread and stage IV, with the poorest prognosis, to generalized metastasization [78].

The TNM system is used to formulate treatment decisions, to define prognosis, to stratify patients in clinical studies and to compare the populations and results of different centers. TNM is applied to most solid tumors. Exceptions include melanomas (Clark levels for the "T" parameter), gynecologic tumors (FIGO staging) and lymphomas (Cotswold classification of Hodgkin's lymphoma also extended to non-Hodgkin's lymphomas) [77]. Clearly, each level of staging, both clinical-radiologic and surgical-pathologic, can over- or understage disease spread by assigning a stage respectively higher or lower than the real one. In surgery candidates, therefore, a broad range of information needs to be obtained: type of malignancy, size, histologic grade, presence of lymphatic or vascular permeation, presence of associated carcinoma in situ, extent of local invasion, completeness of the excision and state of regional lymph nodes [77]. It should in fact be borne in mind that the anatomic extension of the disease as defined by the TNM staging system or similar systems is not the only parameter for therapeutic management and prognosis, because other factors, such as the degree of tumor cell differentiation (i.e. the grade) and the presence or absence of certain biomarkers (within the tumor tissue and/or in circulation) are also important. Tumor markers have a more-or-less important and specific role to play in the diagnosis, staging, treatment evaluation and prognosis of many malignancies. The main serum markers are AFP (hepatoblastoma, HCC and nonseminomatous germ cell tumors of the testicle, as well as seminomas and ovarian germ cell tumors), beta-HCG (nonseminomatous germ cell tumors of the testicle, ovarian choriocarcinoma), PSA (prostate cancer), PLAP (seminoma), LDH (melanoma, Hodgkin's lymphoma, germ-cell testicular tumors), CEA (gastrointestinal cancers as well as mucinous ovarian adenocarcinomas), CA15-3 (breast cancer), CA-125 (ovarian cancer, peritoneal mesothelioma, advanced abdominal tumors), CA19-9 (gastrointestinal cancers, especially of the pancreas), calcitonin (medullary carcinoma of the thyroid), thyroglobulin (differentiated thyroid carcinomas) and immunoglobulins or their fragments (myeloma, solitary plasmocytoma). The most important urinary markers are 5-HIAA (carcinoid), vanillylmandelic acid (pheochromocytoma), catecholamine (neuroblastoma) and kappa and lambda chains (myeloma) [77].

1.6 Ultrasound and Response to Treatment

The evaluation of the response to treatment refers to the diagnostic procedures used for the study of patients undergoing treatment for a malignant lesion, with the specific aim of verifying the effectiveness or otherwise of the treatment and the possible side-effects. The demonstration of the type of response to local, regional or systemic therapy is a crucial feature of oncologic imaging. Being able to personalize the treatment protocol is in fact fundamental, as it avoids both hypotreatment, with persistence or worsening of the disease, and hypertreatment, with unnecessary pharmacologic or radiation-induced toxicity. Response to treatment determines the subsequent therapeutic choices: as a general rule, in the event of a complete response treatment is consolidated and then suspended, with partial or stationary response the same therapeutic choice is continued, and in the case of disease progression the patient is offered a second-line treatment.

The different types of treatment (conventional multichemotherapy, hormone therapy, antiangiogenetic agents, radiation therapy) produce effects which, in their diversity, are nonetheless the consequence on the one hand of destructive phenomena and on the other of induced reparative phenomena. From many points of view all of this can be detected with imaging modalities, including US.

In general, hypoechoic lesions tend to become hyperechoic following treatment, particularly due to fibrosis, a phenomenon which is particularly present in cases of lymphoma and sarcoma. Lesions that are already hyperechoic tend to become heterogeneous, with the appearance of hypo-anechoic areas due to liquefactive necrosis. The reduction in vascularity is indubitably one of the most important effects, particularly in light of the description above of neoangiogenesis, and this feature will be covered in more detail later. A typical reparative phenomenon is calcification. Tissue necrosis in fact produces a reduction in pH and releases phospholipids and glycoproteins, thus creating favorable conditions for the precipitation of insoluble calcium salts. This is particularly characteristic of mucoid and papillary tumors: typical examples include the calcification of the peritoneal metastases of papillary serous ovarian carcinomas in cases that are responsive to chemotherapy and the calcification of Hodgkin's disease lesions after radiation therapy. In these cases, the residual mass can be quite large and persistent due to the fibrosis, even when the tumor component is completely inactive. The necrosis can be liquefactive or coagulative and can occur rapidly or progressively according to the treatment modality

used. In any case, the US changes are partial and nonspecific: for example, detecting a lymph node treated with radiation therapy or a hepatic nodule treated with PEI on the basis of the echotexture can be challenging. In some malignancies, e.g. soft tissue sarcomas, a positive response to neoadjuvant treatment may be expressed with the formation of a peripheral fibrous pseudocapsule, which better circumscribes the lesion and also facilitates surgical excision. A phenomenon which occasionally occurs in treated lesions is differentiation, as in the case of germ-cell tumors. The differentiation of the tumor tissue produces a series of changes, including a reduction in size, increased margination, an increase in the cystic, adipose and/or calcified components and a decrease in vascularity [79–82]. Even indirect signs, such as the disappearance of retention of the bile ducts or urinary tract, can indicate a response to treatment of a lesion which has reduced its obstructive action on proximal anatomic structures.

Size criteria are in reality the only truly consolidated criteria and certainly the most reliable in clinical practice. The first standard evaluation criteria of response to treatment to be widely adopted were developed by WHO [83]. In this system the measurement of the lesion is bidimensional and is based on the product between the longest diameter and the largest diameter perpendicular to it. The **WHO criteria** include the following categories: (1) complete response: disappearance of all known lesions, confirmed at 4 weeks or more; (2) partial response: reduction of ⩾50% of the sum of the products of all known measurable lesions, in the absence of new lesions, confirmed at 4 weeks or more; (3) disease in progress: increase ⩾25% of the sum of the products of all known measurable lesions, or onset of new lesions; (4) stable disease: size changes not classifiable in the other categories (i.e. reduction <50% or increase <25%), in the absence of new lesions. There are also lesions defined as "non-measurable" by the WHO system, i.e. lesions which can be identified but whose exact size cannot be determined.

A simplified unidimensional estimate was developed in the 1990s by a Canadian-American committee and received immediate and widespread application both in clinical trials and in practice [84,85]. The system involves the measurement of only the longest diameter of the measurable lesions and up to a total of 5 lesions per organ and 10 lesions among the different organs. These lesions, defined as target lesions, are then used as the basis for the classification of response, whereas all the other lesions, defined as non-target lesions, are only evaluated for their presence or absence. This **RECIST system** includes categories which are slightly different from the WHO criteria: (1) complete response: disappearance of all known lesions, target and non-target, and normalization of serum levels of tumor markers, confirmed at 4 weeks or more; (2) partial response: reduction of ⩾30% of the sum of the largest diameters of the target lesions and/or persistence of elevated serum levels of tumor markers, confirmed at 4 weeks or more; (3) disease in progress: increase ⩾20% of the sum of the largest diameters of all target lesions and/or unequivocal progression of known non-target lesions and/or appearance of new lesions; (4) stable disease: size changes not classifiable in other categories (i.e. reduction <30% or increase <20%), in the absence of new lesions.

As can be seen, these are rather complex definitions which should be the domain of the oncologist and not formulated by the US operator, for example at the time of writing the report. Except in special cases, the US operator should only report the measurement of the lesions identified and then indicate a possible "worsening" in terms of the previous presentation, whereas drawing from this a definition of "progression" could prove incorrect (e.g. because afterwards no effective increase ⩾20% of the sum of the diameters of the target lesions occurs).

The definition of a non-target lesion is particularly important. These may be defined as such because they are measurable but small (<20 mm if evaluated with conventional radiologic procedures or <10 mm if evaluated with spiral CT or MR) or because they are non-measurable (bone or cystic lesions, malignant pleural, pericardial or peritoneal effusion, carcinomatous mastitis, pulmonary or cutaneous carcinomatous lymphangitis, leptomeningeal diffusion) [84].

Although the unidimensional measurement of the RECIST system is today the most utilized by oncologists, the US operator should nonetheless continue to indicate the two largest diameters in the report. In addition, in cases of multiple metastases it is crucial that the operator measures at least the five largest lesions in each organ and does not simply provide a generic description of "multiplicity'. The US operator may not be informed regarding which lesions have been defined target lesions and which non-target lesions, so the operator is better off providing an excess of measurements rather than a lack thereof. Current imaging is characterized by multiplanar views, which are intrinsic to US and MR and also adopted by multislice CT. It is therefore possible to accurately define the three largest diameters of the lesions on three orthogonal planes or even calculate the volume of the lesion with 3D acquisitions. In part this involves an abstraction, since the volume can be defined only in lesions with a regular shape or at least well-defined sharp margins. In addition, factors such as the focal

zone depth of the ultrasound beam can influence the measurement (the depth of the focal zone would therefore need to be kept constant in serial examinations of a tumor!) [86]. Nonetheless it is rather peculiar, and perhaps debatable, that in the light of the possibility of such sophisticated measurements the WHO criteria are based on a bidimensional evaluation and the RECIST criteria on a unidimensional evaluation.

It should also be noted that the RECIST criteria, which are primarily aimed at making phase II studies on antitumor treatment comparable, and only secondarily at the application in clinical practice, have an extremely radical position with respect to US. In fact, they state that if the primary aim is the objective evaluation of treatment efficacy, US should not be used except in cases of particularly superficial lesions (i.e. lymph nodes, subcutaneous lesions and thyroid nodules) and therefore open to clinical confirmation [84]. This is an extreme position, related to the poor diffusion of US diagnostic imaging in North America and the attitude of preconceived diffidence of many oncologists ascribable to the lower objectivity of US, defined as "necessarily subjective" [84]. In reality, the applicability of US to the cancer patient should be defined case by case, and when the circumstances enable a sufficiently informative US study to be carried out, there is no reason for utilizing more complex modalities. In fact, even though the final evaluation of antitumor treatment in cancer patients is eminently entrusted to the "heavy machines" of PET, CT and MR, US is often used, especially in the evaluation between the various treatment rounds.

There are two fundamental rules for the **response to treatment evaluation**: (1) a "baseline" examination should be available, i.e. reference imaging performed at the beginning of treatment, or for example immediately after surgery for the primary tumor; (2) the same technique or combination of techniques used in the baseline study should also be used in the subsequent phases of evaluation between treatment rounds and restaging until the end of treatment. It would also be desirable that the baseline and follow-up examinations were always performed with the same scanner, the same examination technique (including the scanner settings) and the same operator, although this is clearly difficult to obtain in clinical practice. In surgery patients, the baseline examination for monitoring is clearly the first postoperative examination, since the examination of initial staging can no longer be used. At the beginning the oncologist, ideally in consensus with the radiologist, should define a precise monitoring plan – open to modifications with changes in the findings – which takes into consideration the techniques used, the body volume to include, the target and non-target lesions and the interval between examinations. The timing depends on a number of factors, such as the "time to progression" [87]; at least for phase II studies an evaluation is recommended after each round, i.e. every 6–8 weeks [84]. In subjects treated with chemotherapy the evaluation takes place immediately after the treatment, whereas in patients who undergo radiation therapy or surgery a period of 3 months is indicated to allow for stabilization of the local modifications.

The ultimate goal of cancer treatment is to increase patient survival. In the evaluation of treatment response, however, it is not always possible to wait for an increase in survival, thus creating the need for surrogates [87,88]. The traditional surrogate is given by the progressive reduction in size and subsequent disappearance of the tumor. Despite their differences, the different evaluation systems – WHO and RECIST – are based on the objective demonstration of a measurable reduction in tumor mass. Even volumetric measurements, setting aside the intrinsic difficulties in measuring the size of the lesion (accuracy, shape and margins of the tumor, etc.), is a relatively late index which often requires months to be verified and which does not in itself express the presence or otherwise of viable residual tumor tissue [85,89]. This is particularly true for some types of relatively recently introduced cancer treatments: treatment with new generation drugs (antiangiogenetic and antivascular drugs), percutaneous ablation treatments, transcatheter treatments (embolization, radioembolization, chemotherapy and chemoembolization) and radiation therapy (conventional or stereotactic) [52,85,90] (Fig. 1.11). In all these cases, distinguishing between responders and non-responders solely on the basis of size measurements is often problematic. One of the obstacles to the development of antiangiogenetic drugs is in fact the lack of effective systems for verifying the effects. These drugs produce a stabilization of the disease with a possible "cystic" transformation and then much later a reduction in the size of the lesion. Therefore, in order to evaluate the effects and modulate the dosage other types of information are required [91,92]. In the setting of percutaneous ablation a perilesional safety margin needs to be included in the treatment area, such that immediately after treatment the lesion actually appears to be increased in size. Then there are certain malignancies, such as lymphomas, which are not amenable to an evaluation exclusively based on size. Moreover, as stated above, there are many occasions when measuring the lesion is difficult or impossible: lesions with a significant calcified, necrotic or cystic component, malignant effusion, lesions located in the meninges, pleura or peritoneum, carcinomatous mastitis, pulmonary carcinomatous lymphangitis, diffuse skin lesions, bone lesions (especially if diffuse), micro-