Abdominal Radiology (2019) 44:1575–1600
https://doi.org/10.1007/s00261-018-1845-0

REVIEW

Tumor markers: myths and facts unfolded

S. C. Faria[1,3] · T. Sagebiel[1] · M. Patnana[1] · V. Cox[1] · C. Viswanathan[1] · C. Lall[2] · A. Qayyum[1] · P. R. Bhosale[1]

Published online: 29 November 2018

Abstract

Objective The purpose of this article is to review the most commonly used tumor markers in abdominal and pelvic tumors, describe their limitations and explain how to use them in the context of known cancer in order to optimize multidisciplinary care of oncologic patients.

Conclusion Tumor markers are important for the diagnosis, staging, monitoring of treatment and detection of recurrence in many cancers. This knowledge is crucial in the daily interpretation of images of oncologic and non-oncologic patients. However, radiologists should also be aware of the limitations of the most commonly used tumor markers and they should not be used solely, but interpreted in conjunction with diagnostic imaging, clinical history and physical examination that will help optimize the multidisciplinary care and management of oncologic patients.

Keywords Tumor markers · Carcinoembryonic antigen · Prostate-specific antigen · Alpha-fetoprotein · Carbohydrate antigen 19-9 · Carbohydrate antigen 125 · Beta subunit of human chorionic gonadotropin · Lactate dehydrogenase · Chromogranin A

Introduction

Cancer is the second leading cause of death in the United States [1]. Most cancers are found when patients become symptomatic, imaging incidentally or during screening, or by serial follow-up of tumor markers in hereditary or nonhereditary syndromes. Tumor markers are proteins produced by the body in the presence of malignancy. Tumor markers can be found in the blood, urine, stool, or other bodily fluids in patients with cancer. The majority are blood-soluble glycoproteins usually detected by monoclonal antibodies [2].

Tumor markers are playing increasingly important role in cancer detection and management. Tumor markers can be specific for a certain type of cancer or may be present in different types of cancers. Each tumor marker has a variable profile and is useful for screening, determining diagnosis and prognosis, assessing response to therapy, and detecting early recurrent/metastatic disease. Although tumor markers can be elevated in the setting of cancer, some patients may not show marker elevation and, on the other hand, benign conditions can also cause false-positive elevation of these markers [2]. The most commonly used tumor markers in abdominal and pelvic tumors include carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA-19-9), carbohydrate antigen 125 (CA-125), beta subunit of human chorionic gonadotropin (b-hCG), lactate dehydrogenase (LDH), and chromogranin A (CgA) [3] (Table 1).

In this article, we review the common serum tumor markers used in abdominal and pelvic tumors. We will also review the normal values, sensitivity, specificity, and differential diagnosis of these tumor markers in malignant and nonmalignant conditions (Table 2) and discuss the utility and limitations of tumor markers in daily interpretation of imaging studies of oncologic and non-oncologic patients.

✉ S. C. Faria
scfaria@mdanderson.org

[1] Department of Diagnostic Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

[2] University of Florida, Jacksonville, FL, USA

[3] 1400 Pressler St. Unit 1473, Houston, TX 77030, USA

Table 1 Summary of the most common tumor markers associated with abdominal and pelvic tumors

Most common tumor markers	Tumor
CEA (carcinoembryonic antigen)	Colorectal cancer
PSA (prostate-specific antigen)	Prostate cancer
AFP (alpha-fetoprotein)	Hepatocellular carcinoma, germ cell tumor
CA 19-9	Pancreatic cancer
CA 125	Ovarian cancer
B-HCG (beta subunit of human chorionic gonadotropin)	Germ cell tumor
LDH (lactate dehydrogenase)	Germ cell tumor
CgA (chromogranin A)	Neuroendocrine tumors

Table 2 Summary of the normal values and differential diagnosis of the most common tumors markers in tumors of the abdomen and pelvis

Tumor marker	Normal value	Differential diagnosis
CEA (carcinoembryonic antigen)	< 2.5 ng/mL < 5 ng/mL in smokers	Others cancers such as lung, breast, gastric, pancreatic and ovarian. Non-malignant conditions such as cirrhosis, gastritis, and inflammatory bowel
PSA (prostate-specific antigen)	0–4 ng/mL	Benign prostatic hyperplasia, prostatitis
AFP (alpha-fetoprotein)	0–10 ng/mL	Others cancers such as gastric, non-seminomatous germ cell tumors, and lung. Nonmalignant conditions such as cirrhosis, pregnancy, and inflammatory bowel disease
CA 19-9	0–37 U/mL	Other cancers such as bile duct cancers, gastric, gallbladder, ampullary cancer, cholangiocarcinomas, lung, colon, and breast. Non-malignant conditions such as biliary obstruction, pancreatitis, inflammatory bowel disease, and cholangitis
CA 125	0–35 U/mL	Other cancers such as endometrium, lung, pancreas, and breast. Non-malignant conditions such as endometriosis, pelvic inflammatory disease, and pregnancy
b-HCG	< 4.0 mIU/mL	Pregnancy
LDH (lactate dehydrogenase)	140–280 U/L	Pathologies of the muscle, liver and kidneys
CgA (chromogranin A)	≤ 36 ng/mL	Atrophic gastritis

Colorectal cancer

Colorectal cancer (CRC) is the third most common malignancy in the world [4]. The overall 5-year survival is 65%, but varies with the stage of disease. The 5-year survival is almost 90% for stage I cancers but only 5–15% for stage IV disease [5]. Tumor markers play an important role in the management, monitoring of treatment, and surveillance of CRC patients.

Carcinoembryonic antigen (CEA) is the most widely used tumor marker for CRC. The normal CEA concentration in blood is < 2.5 nanograms per milliliter (ng/mL) in nonsmokers and < 5 ng/mL in smokers. CEA is a non-specific marker that can be found in cancers such as breast, gastric, pancreatic, ovarian, and may also be elevated in nonmalignant conditions such as cirrhosis, gastritis, inflammatory bowel disease, diverticulitis, and pancreatitis [6]. Poorly differentiated tumors may not cause elevation of CEA levels, and may produce false-negative results. Thus, CEA is not recommended as a screening test for CRC [7].

The American Society of Clinical Oncology (ASCO) recommends obtaining preoperative CEA levels as it may assist in staging and surgical planning [8]. Increased preoperative CEA levels are associated with adverse outcomes, and this correlates with a worse survival. Wiratkapun et al. showed that the cumulative disease-free survival of patients with CEA within the normal range was significantly better than those whose CEA level was ≥ 5 ng/mL. In addition, the study suggested that the CEA level > 15 ng/mL was an adverse prognostic indicator [9].

Despite potentially curative surgery and the use of adjuvant chemotherapy and/or radiation therapy, more than 40% of patients who present with stage II or III disease will develop recurrent disease. Approximately 85% of patients recur during the first 2.5 years after surgery [10]. In 20–40% of patients with relapse, the liver is the only site of metastases [11]. CEA is indicated in the detection of early recurrence or metastatic disease following curative resection.

Studies have suggested that there is benefit from early detection of isolated metastases as metastectomy improves

patient outcome. In a meta-analysis of eight randomized controlled trials, Scheer et al. showed that intensive follow-up with CEA resulted in a reduction of 20–30% in mortality [12]. ASCO recommends that patients with stage II or II disease have serum CEA testing performed every 3 months for at least 3 years and every 6–12 months in years 4 and 5 [13].

CEA half-life is approximately 5 days. Postoperative CEA monitoring is most useful in patients with elevated preoperative CEA levels that return to normal after surgery. CEA levels that do not normalize after surgery or CEA levels that normalize postoperatively and then rise are indicative of recurrence [14].

The rate of rise of CEA can be used to discriminate between localized recurrence and metastatic spread. It is generally considered that a rapid increase in CEA levels suggests blood-borne metastases, such as liver and lung involvement, the most common sites of systemic recurrence, whereas a slow, gradual rise is more likely to be associated with locoregional recurrence [15]. However, 20–30% of patients with locoregional recurrence have a normal CEA. Conversely, CEA is increased in 80–90% of patients with hepatic recurrences [16] (Fig. 1).

Patients with rising CEA levels are referred for imaging to identify the site and extent of the recurring disease and/or exclude this possibility. The reported per-lesion sensitivity of contrast-enhanced CT imaging in the detection of colorectal liver metastases ranges from 51.8 to 84.6%. The use of hepatocyte-specific gadoxetic acid-enhanced MRI provides higher detectability with a reported per-lesion sensitivity for detection of in colorectal liver metastases ranging from 86.9 to 100% [17, 18]. CT is the imaging modality of choice for the detection of lung metastases [11].

PET/CT is of value in the evaluation of patients with rising tumor markers and a negative or equivocal conventional imaging studies, a well-known management problem in daily clinical practice. Some oncology guidelines recommend PET/CT in the presence of negative CT scan and serial CEA increases [19]. However, in some institutions, PET/CT is performed as the first modality for clinical suspicion of recurrent CRC based on rising or abnormal CEA levels. A recent meta-analysis showed an excellent sensitivity of 94% and acceptable specificity of 77% of PET/CT in the detection for recurrent disease in CRC patients with rising CEA [20]. Some limitations of PET/CT imaging include mucinous adenocarcinoma, subcentimeter lesions, and false-positive diagnosis for inflammatory conditions [21].

CEA is also useful in predicting response to chemotherapy and in monitoring therapy in patients with advanced CRC receiving chemotherapy. CEA should be measured at the start of the treatment for metastatic disease and every 1–3 months during active treatment [22]. Imaging features and tumor markers' levels should be taken into consideration in the evaluation of treatment response even when there is not a significant change in tumor size (Fig. 2).

PET/CT also has an important role in monitoring the treatment response of patients with metastatic CRC [22] (Fig. 3). However, in cases where the presence of metastatic and/or recurrent disease is still not clear, further evaluation with imaging guided intervention, such as ultrasound and CT or MRI-guided biopsy are necessary for histologic confirmation of recurrent or metastatic tumor before treatment recommendations. In addition, image-guided intervention therapy offers the possibility of less-invasive treatments for colorectal metastases in the liver, lung, and bone. Interventional radiology oncologic treatments target tumors by direct percutaneous tumor puncture or by selective intra-arterial methods. Among these less-invasive options, radiofrequency ablation, cryoablation, hepatic arterial infusion chemotherapy, and selective internal radiation therapy with radioactive microspheres are the most commonly used ones [23].

Prostate cancer

Prostate cancer is the most common malignancy in men [24]. Early prostate cancer usually has no clinical symptoms. Digital rectal exam and determination of PSA levels are important diagnostic tools in the assessment for prostate cancer. PSA is a glycoprotein encoded by the KLK3 gene and is almost exclusively produced by the luminal epithelial cells of all types of prostatic glandular tissue, benign and malignant. PSA is normally present in the blood at very low levels. The normal value is $\leq$ 4 ng/mL [25].

Elevated PSA levels are suggestive of prostate cancer; however, benign prostatic hypertrophy (BPH) and prostatitis may also demonstrate high PSA levels. Total PSA (tPSA) is the most commonly used tumor marker, and the majority of the PSA in the blood is bound to serum proteins. The amount of PSA bound to proteins is called (cPSA) [26]. A standard PSA cutoff of 4 ng/mL has a low estimated sensitivity of 21% for the diagnosis of prostate cancer [27]. To increase PSA specificity, the small amount of PSA that is not protein bound, called 'free PSA' (fPSA), can also be used. Determination of the percent of free PSA (%fPSA) is reported to increase cancer detection, especially in men with a PSA between 4 and 10 ng/mL. In men with prostate cancer, the ratio of fPSA to total PSA is decreased. The lower the %fPSA, the higher the probability of prostate cancer [28].

Furthermore, several calculated parameters have been developed including PSA-density (PSAD), PSA-velocity

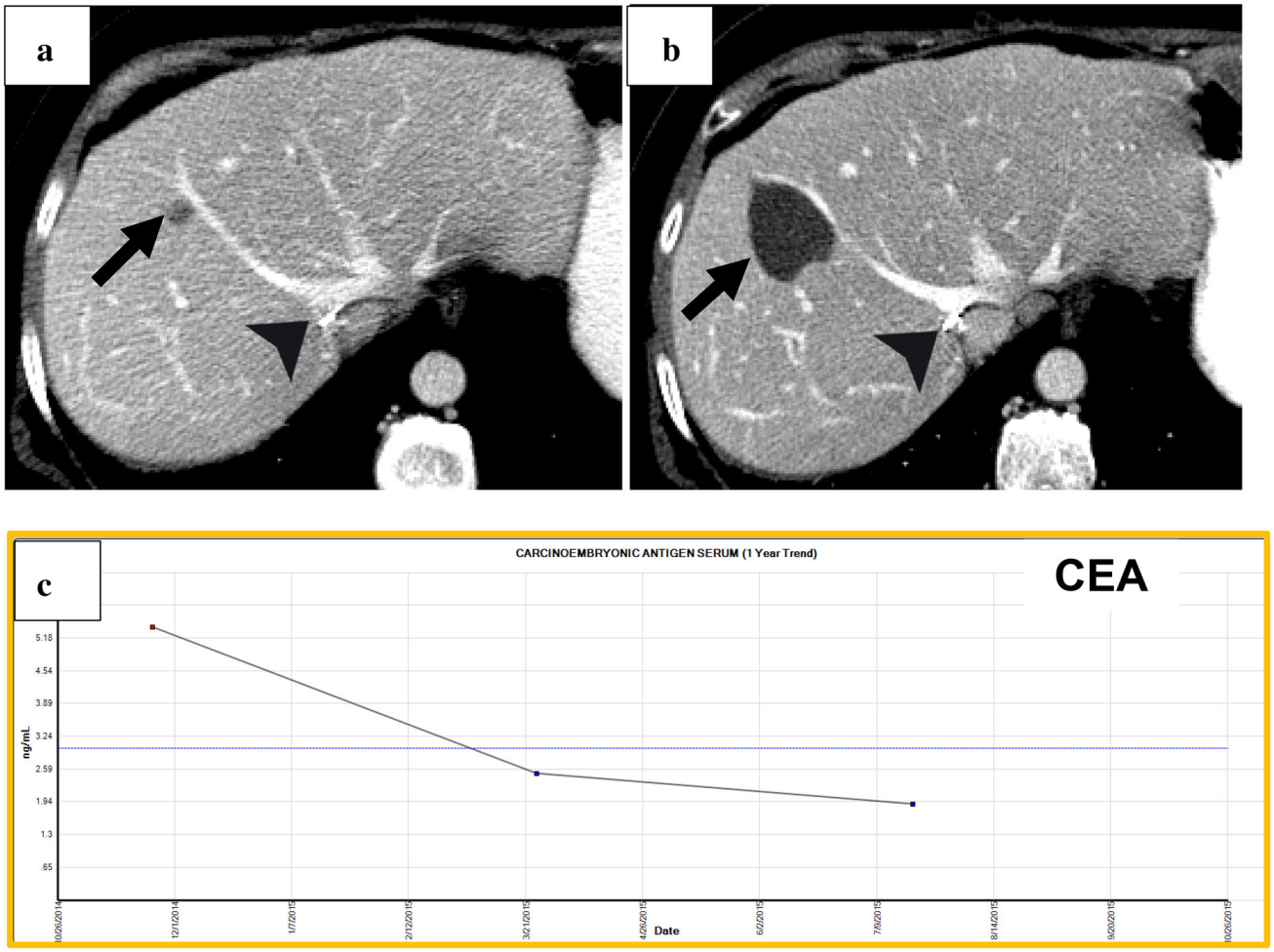


Fig. 1 Second colorectal cancer recurrence in the liver of a 64-year-old female status post transverse colectomy. Carcinoembryonic antigen (CEA) levels were elevated in a surveillance visit 2 years after a partial right hepatectomy for colorectal liver metastases. **a** Axial contrast-enhanced CT image shows a new metastatic lesion in the liver (arrow). Note the surgical clips from prior partial right hepatectomy (arrowhead). Patient underwent radiofrequency ablation of the liver lesion with a follow-up CT scan **b** showing a nonenhancing ablation site (arrow). **c** CEA dropped to normal levels post ablation

(PSAV), and PSA-doubling time (PSADT). PSAD is calculated by dividing the tPSA by the prostate volume and is used to make a distinction between an elevated PSA caused by BPH or prostate cancer [29]. PSAV is the rate of change in PSA over time, and there is little evidence of the utility of PSAV in the diagnosis of prostate cancer. Despite this observation, the National Cancer Center Comprehensive Network recommends PSAV for the use in early prostate cancer detection with recommended biopsy in men with a high PSAV (> 0.35 ng/mL/year) [28].

Despite multiple studies, prostate cancer screening with PSA is still controversial [30]. The use of PSA for the detection of prostate cancer leads to an earlier diagnosis, and probably more curable stages of disease are detected. However, knowledge of the natural history of early lesions suggests that indiscriminate use of PSA will lead to unnecessary biopsies, detection of indolent tumors, and overtreatment in some cases [30]. Furthermore, PSA can be elevated in other prostate disorders than prostate cancer, such as in BPH and prostatitis (Fig. 4).

Since the benefits of PSA-based screening for prostate cancer do not outweigh the harms, the US Preventive Services Task Force (USPSTF), in May 2012, recommended the exclusion of PSA screening from routine primary care for all men [31]. However, in contrast to USPSTF, the American Urological association (AUA) and the American cancer Society (ACS) currently recommend that PSA testing to be offered to asymptomatic men aged 55–69 years (AUA) or men older than 50 years with a minimum 10-year life expectancy (ACS) after patients receive information about the harms and benefits associated with screening [30].

PSA is a valuable tool for determining the prognosis, to risk stratify patients at the time of surgery, and to monitor treatment of patients with prostate cancer. The serum PSA concentration is proportional to the clinical stage of

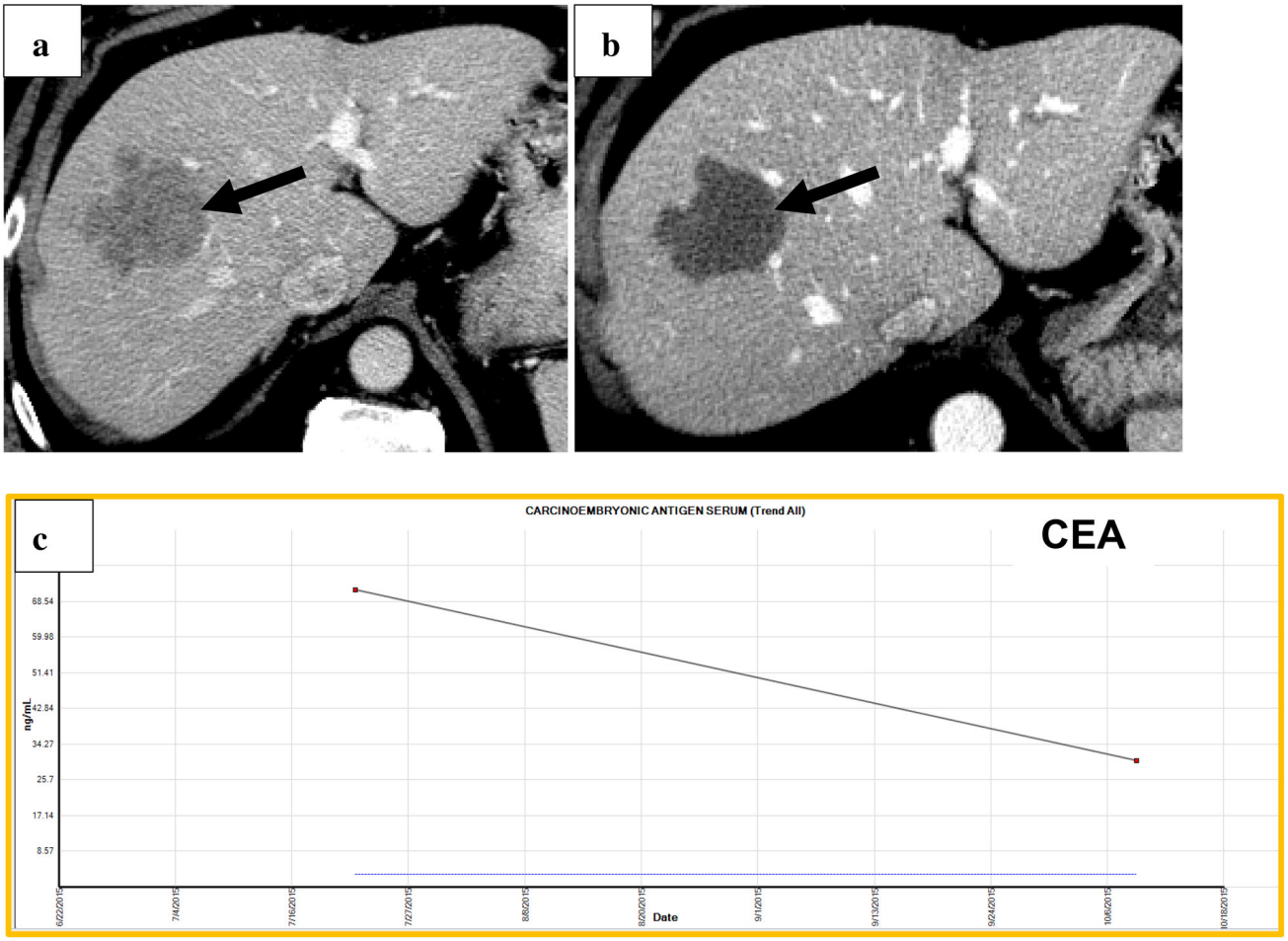


Fig. 2 Monitoring of treatment response of a single colorectal liver metastases in a 63-year-old male with sigmoid colon cancer. **a** Axial contrast-enhanced CT image shows a single hepatic metastasis (arrow). Patient started treatment with FOLFOX plus bevacizumab. **b** Follow-up axial contrast CT image 3 months later shows no change in the size of the metastatic lesion (arrow) but marked decrease in attenuation suggesting treatment response. Response to treatment was supported by a decline in carcinoembryonic antigen (CEA) from 71 to 32 ng/mL (**c**)

prostatic cancer in untreated patient. More important, PSA is also proportional to the volume of cancerous tumor within the prostate. Higher PSA correspond with higher risk of advanced disease and with the aggressiveness of the disease. A PSA level > 20 ng/mL is suggestive of the presence of bone metastases [32].

Clinically localized prostate cancer is treated with surgical resection or radiotherapy, and PSA should become undetectable (< 0.1 ng/mL) after prostatectomy [33]. If the PSA is still detectable even at a very low level after surgery, it does not necessarily mean that cancer is still in the body. It is usually necessary to repeat the PSA levels and follow the PSA levels over time to look for trends. The trend of a rising PSA level is more concerning than a single measurement. On the other hand, monitoring PSA levels in patients treated with radiotherapy or androgen-deprivation therapy, is less reliable. PSA levels may not become undetectable due to the possibility of some remaining prostate cells still produce PSA. In addition, the drop in PSA levels for patients treated with radiotherapy is slower than after prostatectomy and may take many months to reach the lowest level. Transient increase in PSA may occur after radiation therapy [34]. Relapse after local therapy is defined by a rising PSA level > 0.2 ng/mL following radical prostatectomy and > 2 ng/mL above the nadir after radiation therapy [35].

In the setting of a rising postoperative serum PSA, imaging is required to investigate for local or distant recurrence as the treatment may be different. Prostate cancer can recur locally in the prostate bed, or may spread to tissues next to the prostate such as the seminal vesicles, the bladder, the rectum, or the wall of the pelvis. Local recurrence may be amenable to salvage therapy, and a pelvic MRI is indicated for evaluation for local recurrent

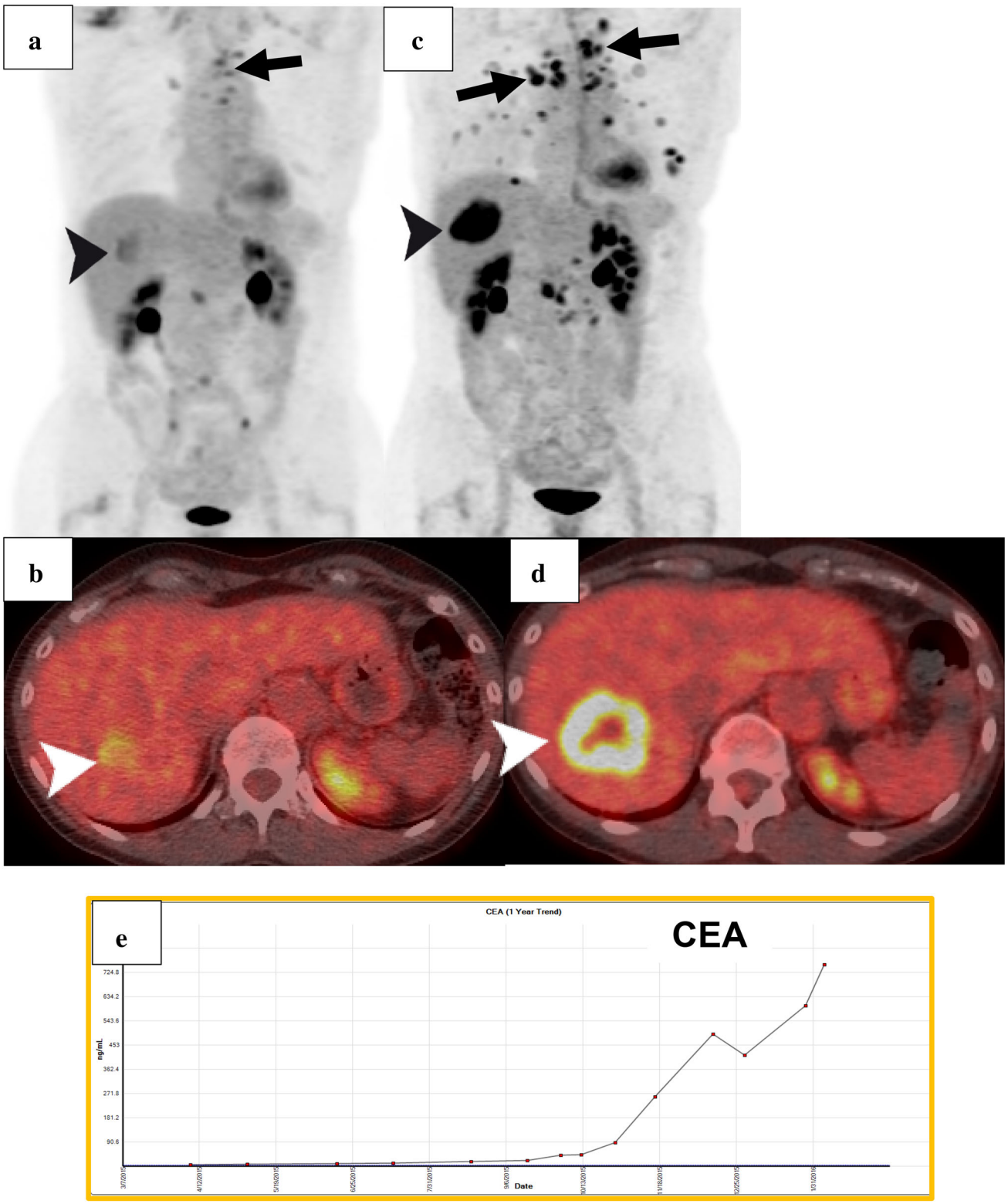


Fig. 3 Metastatic colorectal cancer in a 62-year-old female status post right hemicolectomy. Postoperative surveillance carcinoembryonic antigen (CEA) level was slowly rising. **a**, **b** Initial PET-CT showed small hypermetabolic mediastinal and hilar lymph nodes (arrows) and a suspicious lesion in the liver (arrowheads). Biopsy confirmed metastatic disease. Subsequent PET/CT **c**, **d** showed interval progression of disease with new pulmonary nodules, enlarged mediastinal lymph nodes, and interval increase in size of the metastatic liver lesion concordant with continue increase in CEA levels (**e**)

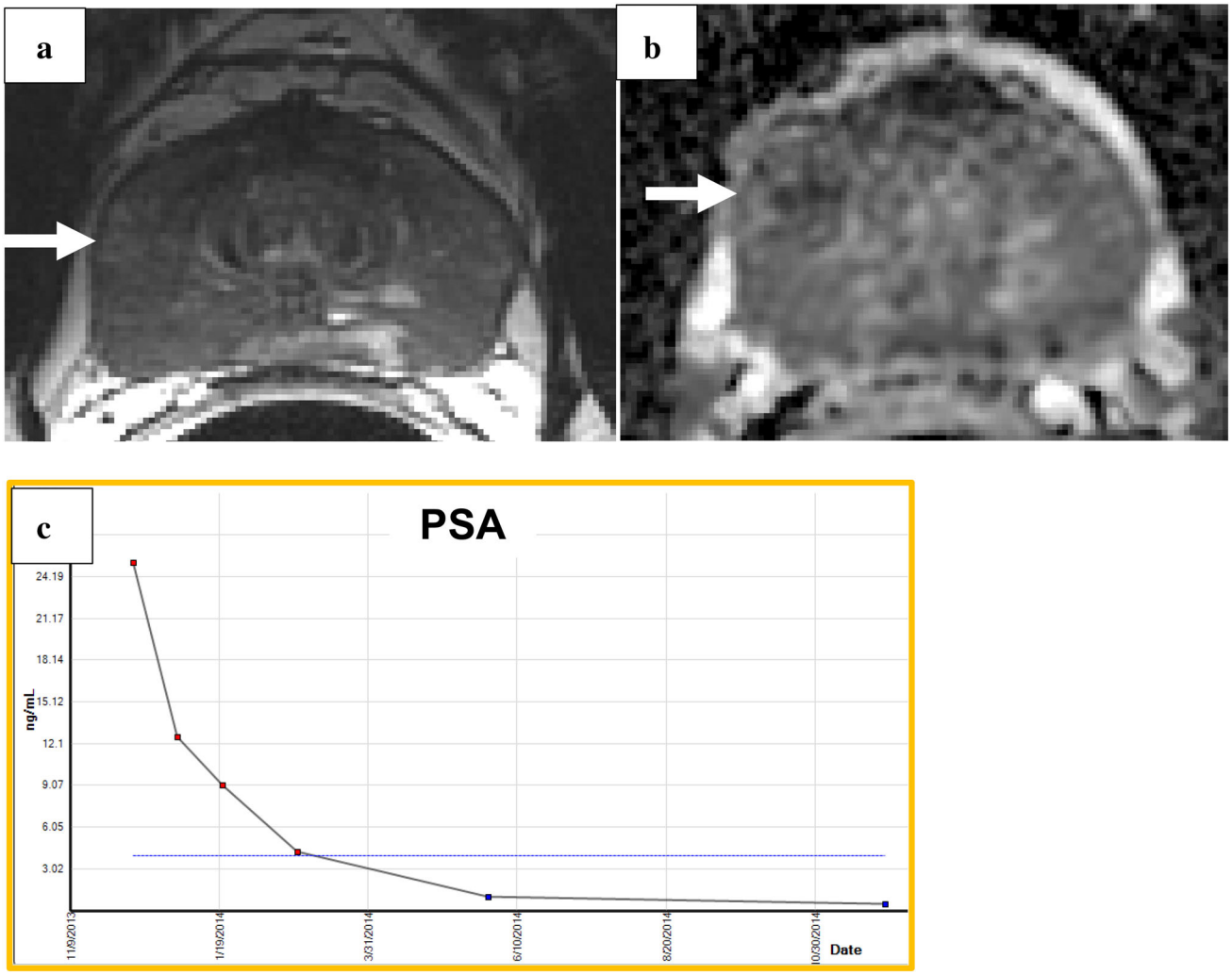


Fig. 4 A 51-year-old male with elevated prostate-specific antigen (PSA). **a** MRI axial T2-weighted FSE images, and ADC map (**b**) of the prostate with endorectal coil showed an enlarged prostate gland with diffusely decreased T2 signal intensity (arrows) without a discrete mass, suggestive of prostatitis. PSA returned to normal after antibiotic therapy (**c**)

disease. The sensitivity and specificity of MRI in the detection of post prostatectomy recurrence are reported as 95% and 100%, respectively [36].

The sensitivity for MRI in the detection of recurrent disease in patients treated with radiotherapy is limited due to decreased contrast between irradiated tissues and recurrent cancer [37]. According to Alonzo et al., the use of dynamic contrast-enhanced (DCE) imaging has an added value in detecting locally recurrent prostate cancer in patients with rising PSA levels after radiotherapy using a 3.0 Teslan MRI [38]. PSA also plays a role in monitoring treatment response in recurrent cases (Fig. 5).

Regarding systemic recurrence, hematogeneous metastases may be present in 35% of patients with prostate cancer [39]. In the setting of elevated PSA, to assess the site of recurrence which may occur in the bone, lung, liver, pleura, and adrenals, a bone scan, and a CT of the chest, abdomen, and pelvis can be helpful in identifying the metastatic site.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the second most common cause of death worldwide. Approximately 500,000 new cases are reported per year [40]. The majority of cases occur in the Asia–Pacific region in patients with chronic hepatitis B virus infection. Most cases in the Western world and Japan, are associated with hepatitis C virus infection, alcoholic cirrhosis, and nonalcoholic steatohepatitis, and the incidence is increasing. Since many patients with early disease are asymptomatic, HCC is frequently diagnosed at

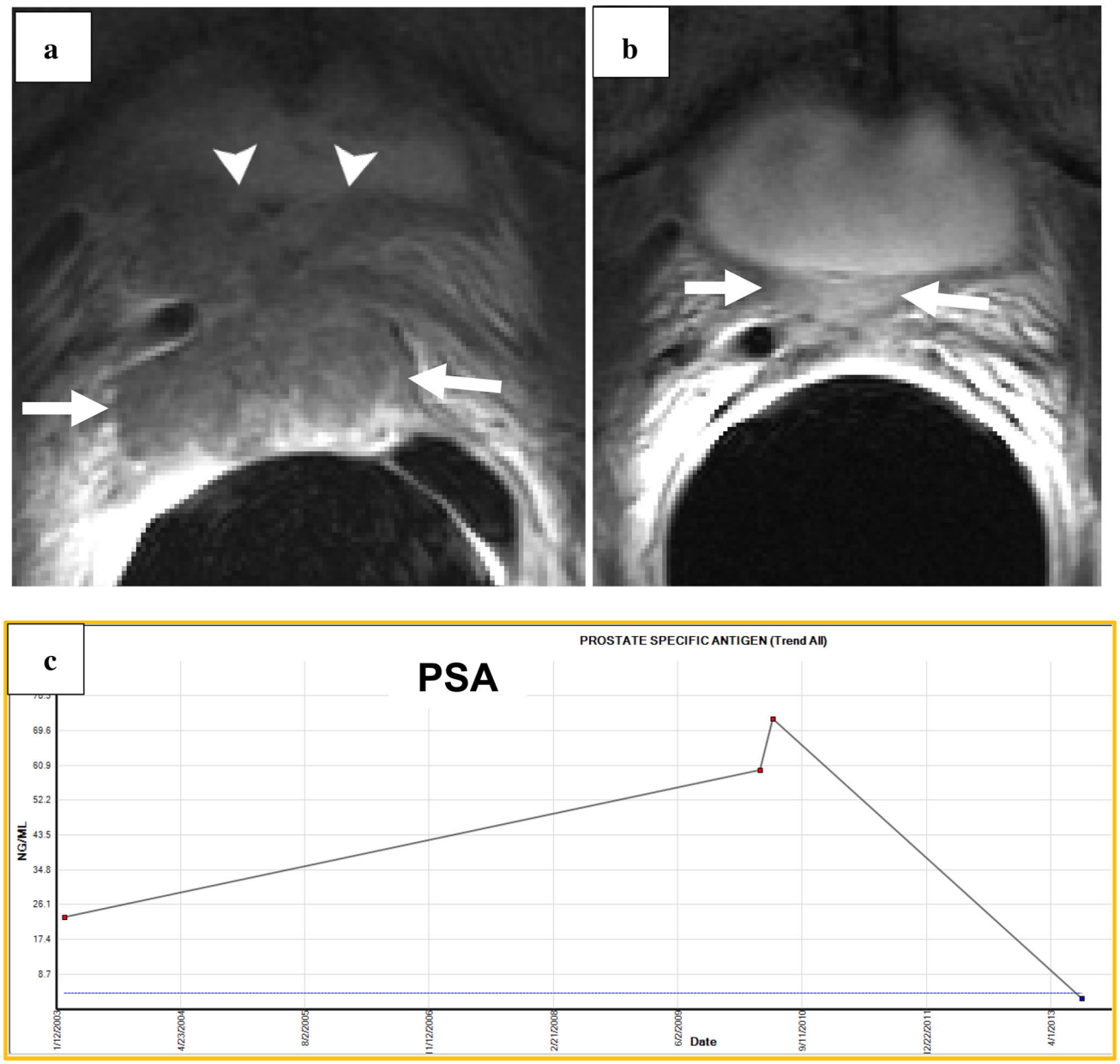


Fig. 5 A 63-year-old male with history of prostate cancer and undetectable PSA after prostatectomy. Two years later, he presented with a PSA of 20 ng/mL. **a** Axial T1-weighted post-contrast endorectal MR images of the prostate bed show a 3.3 × 2.5 cm mass consistent with prostatic bed recurrence (arrows) with invasion of the posterior bladder wall (arrowheads). After treatment with hormone therapy, **b** axial T1-weighted post-contrast endorectal MRI image shows a decrease in size of local recurrence (arrows) and corresponding reduction to PSA levels to 3 ng/mL (**c**)

late stages. Therefore, the prognosis of patients with HCC is generally poor, with a 5-year survival rate of less than 5% [41].

The most commonly used tumor marker for HCC is AFP [42]. AFP is a glycoprotein normally produced in early life by the embryonic liver cells of the viteline sac and fetal intestinal tract. AFP levels decline rapidly after birth, reaching undetectable levels within few months after birth. The normal range of AFP is 10–20 ng/mL [42]. In patients with hepatic cirrhosis, the fluctuating levels of AFP may reflect flare-ups of viral hepatitis, exacerbation of underlying liver disease, or HCC development. Elevated AFP is seen more commonly in Asian countries than in the Western world [43].

AFP sensitivity and specificity for the diagnosis of HCC range from 41 to 65% and 80 to 94%, respectively, for serum AFP levels greater than 20 ng/mL [44]. Due to its low sensitivity, a more appropriate cutoff of this marker

has long been discussed in the literature. In patients with cirrhosis, AFP values > 400 ng/mL generally are considered diagnostic of HCC [45].

Approximately 80% of small HCC show no increase of AFP concentration. The sensitivity of AFP is approximately 25% for HCC < 3 cm and 52% for HCC > 3 cm [46]. Due to its low sensitivity and specificity in the detection of early HCC, screening with AFP is no longer routinely performed.

Although AFP has been removed from the previous American association for the study of liver disease (AASLD) and from the European association for the study of the liver (EASL) noninvasive diagnostic criteria of HCC, AFP correlates with tumor size and volume and may be used as a prognostic factor. High serum AFP level has been associated with increased stage, bilobar involvement, diffuse-type tumors, and portal vein tumor thrombus. According to one study, patients with serum AFP > greater than 1000 ng/ml had a higher incidence of vascular invasion (61%) compared to patients with AFP level ≤ 1000 ng/mL (32%). This may relate to the finding that well-differentiated tumors express lower levels of AFP [47]. AFP doubling time has also been reported to be an important prognostic factor [48].

High AFP levels also correlates with presence of metastatic disease, recurrence rates, and decreased survival following liver transplantation [49]. Schraiber et al. showed that a high AFP level was associated with a 3.32-fold increase in the probability of HCC recurrence following liver transplant [50].

AFP is used to monitor treatment response. AFP levels are usually obtained every 3 months for the first two years and then every 6 months up to 5 years. After treatment of the tumor, AFP concentration typically decreases with a half-life of 3.5–4 days, and complete response is likely if the pretreatment-elevated AFP levels decline to normal levels during subsequent follow-up measurements. In one study, patients with a prolonged decrease in AFP levels following chemotherapy show longer survival when compared to patients with slowly increasing levels [51].

Surgical treatments for early-stage HCC include hepatic resection and liver transplantation. Monitoring of AFP levels is used to detect early recurrent disease after surgical resection or liver transplantation (Fig. 6). Schraiber et al. showed that a high pretreatment AFP level was associated with a 3.32-fold increase in the probability of HCC recurrence following liver transplant [50].

In nonsurgical candidates, locoregional treatments play a key role in the management of HCC. Several locoregional therapies are used in the treatment of HCC including radiofrequency ablation (RFA), transarterial chemoembolisation (TACE) and yttrium-90 (^{90}Y) [52]. Serial AFP measurements may be used to monitor response to TACE and ^{90}Y (Figs. 7, 8).

Nonresectable tumor may be treated with sorafenib, an oral multikinase inhibitor with antiangiogenic and antiproliferative properties, used as systemic therapy and offers a 30% improvement in survival [53]. Treatment with sorafenib will result in a decrease in AFP levels if the tumor is responding.

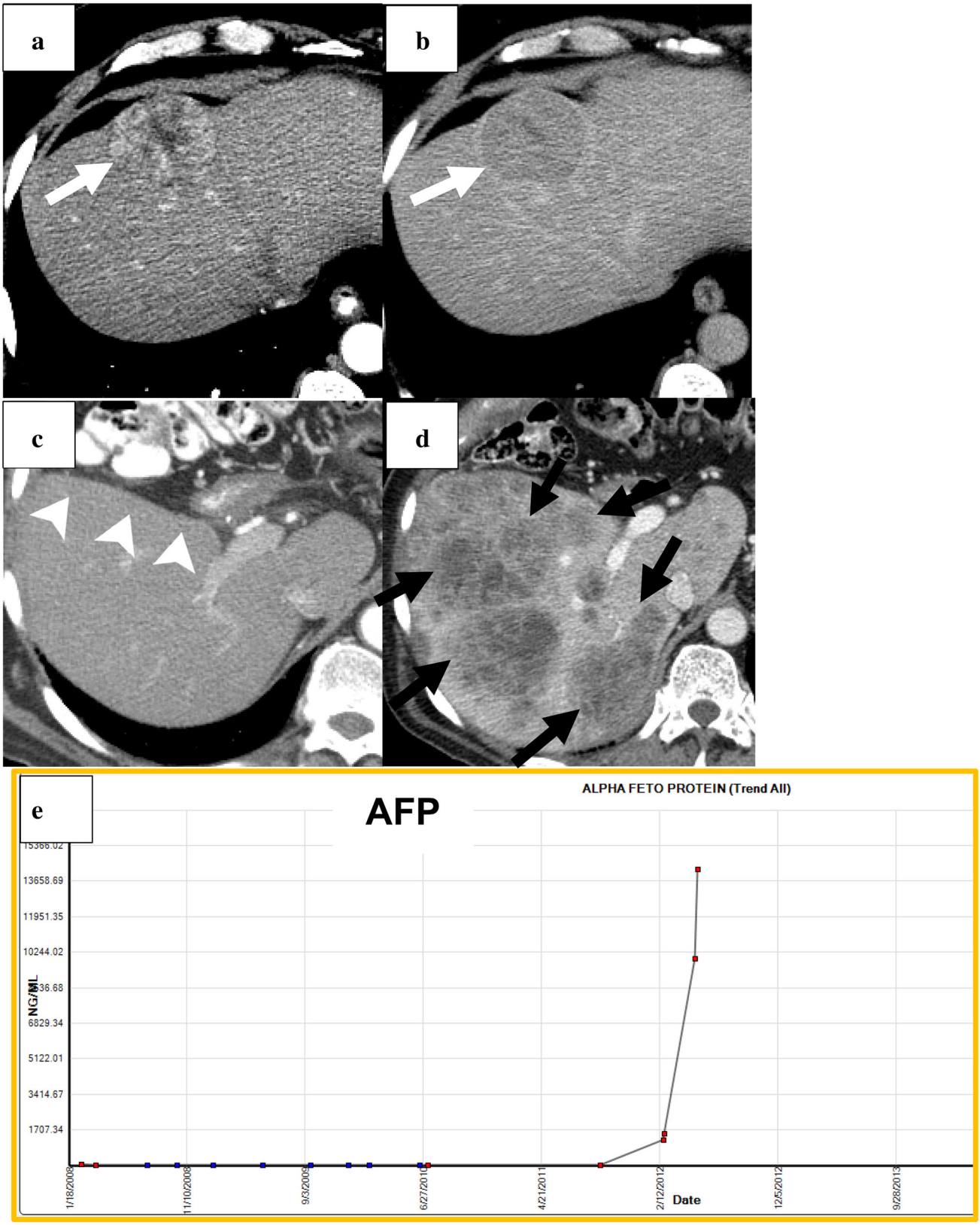
AFP can be elevated in chronic liver disease, acute and chronic hepatitis, pregnancy, in nonhepatic malignancies such as nonseminomatous germ cell tumors of the ovary and testicles, as well as in other malignancies such as gastric, lung, biliary, and pancreatic cancers [52].

Other tumor markers being used in the management of HCC include the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and Des-gamma-Carboxy Prothrombin (DCP), among others. AFP-L3 is the glycosylated subfraction of AFP and is derived only by cancer cells and has been reported to be a more specific marker for HCC [54]. AFP-L3 is an indicator of poor prognosis and considered a marker for the aggressiveness of HCC correlating with early vascular invasion, poor differentiation, intrahepatic metastasis, and advanced HCC [55]. DCP is an abnormal prothrombin induced by vitamin K2 absence/antagonist-II and is increased in the serum of patients with HCC. When used together, the DCP and AFP assays increase the sensitivity for diagnosing HCC to more than 85% of patients [55]. In addition, Johnson et al. reported that the combination of three tumor markers (AFP, AFP-L3, and DCP) offers high sensitivity and specificity, and improves the accuracy for diagnosing and monitoring HCC [56].

Pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the Unites States [57]. No tests are available for early detection, and most patients are diagnosed with advanced disease. At the time of diagnosis, approximately only 20% of patients with pancreatic cancer are considered eligible for surgery. Although surgery cannot guarantee a cure, the 5-year survival is around 10% following resection and increases to 20–30% with adjuvant chemotherapy [58]. The prognosis for patients with locally advanced or metastatic disease is dismal of just a few months. Therefore, early detection is crucial for improving patient prognosis.

CA 19-9 is the most commonly used tumor marker for pancreatic cancer [59]. CA 19-9, also termed sialyl Lewis, is a glycoprotein expressed on the surface of cancer cells and is derived from an aberrant pathway during production of its normal counterpart, diasialyl Lewis. The normal


a
b
c
d
e
AFP
ALPHA FETO PROTEIN (Trend All)
15366.02
13658.69
11951.35
10244.02
8536.68
6829.34
5122.01
3414.67
1707.34
NG/ML
1/18/2009
11/10/2009
9/3/2009
6/27/2010
4/21/2011
2/12/2012
12/5/2012
9/28/2013
Date

◀**Fig. 6** Recurrent hepatocellular carcinoma (HCC) after surgical resection in a 68-year-old male with a history of a single HCC lesion in the background of hepatitis B-related cirrhosis. **a** Axial post-contrast CT image shows a 5.3-cm hypervascular lesion in the liver presenting with intense enhancement on the arterial phase that washes out on the delayed image (**b**). **c** He was treated with left hepatectomy (arrowheads). After surgery, his alpha-fetoprotein (AFP) levels rose rapidly (**e**) corresponding to multiple new metastatic lesions (arrows) in the liver remnant (**d**) characterizing recurrence disease

values for CA 19-9 are less than 37 U/mL. CA 19-9 may be negative in people with Lewis negative phenotype which accounts for approximately 6% of the white population and 22% of the black population in the United States [60]. Serum CA 19-9 has no role in screening asymptomatic populations due to its low positive predictive value but may be used to distinguish benign from malignant pancreatic pathologies. It also has limited value for diagnosis in early stages of disease. Using 37 U/mL as the threshold value, the reported sensitivity and specificity for the diagnosis of pancreatic cancer is 79% and 85%, respectively [61]. The specificity increases to 98% for values greater than 100 U/mL [59].

CA 19-9 is used as a prognostic indicator. A normal (< 37) or low preoperative CA 19-9 (< 100) serum level correlates with early pancreatic cancer stage and independently predicts improved overall survival whereas an elevated CA 19-9 (> 100 U/ml) is associated with a poor prognosis [62]. In patients with nonadvanced disease, CA 19-9 levels correlates with the likelihood of disease resectability and overall survival. Preoperative normal CA 19-9 levels (< 37) have a prolonged median survival (32–36 months) compared with patients with elevated CA 19-9 (12–15 months) [62].

Serial levels of CA 19-9 can assess response to systemic therapy. Halm et al. reported that patients with a decline in CA 19-serum levels of > 20% from baseline after 8 weeks of treatment with gemcitabine chemotherapy had improved median survival compared to patients with a rise or a decrease of < 20% [63]. These patients usually undergo CT of the abdomen before surgical resection. The decrease in CA 19-9 levels usually correlates with a decrease in tumor size by imaging (Fig. 9).

Response assessment of pancreatic adenocarcinoma after neoadjuvant chemotherapy and radiation therapy may demonstrate interval decrease in tumor size and attenuation. However, in some cases, radiation therapy may cause inflammatory changes with peripancreatic fatty stranding without inherent change in tumor size. While interpreting these CT studies, CA19-9 levels should be taken into consideration to differentiate tumor progression from postinflammatory post-radiotherapy treatment-related changes such as stranding surrounding the margins of the tumor or extending to the adjacent vessels and should not be confused with tumor progression.

After surgical resection, postoperative levels of CA 19-9 should normalize. Postoperative normalization or a decrease in CA 19-9 levels is associated with prolonged survival. Ferrone et al. reported that a postoperative serum level of < 37 U/mL was associated with a mean survival of 2.4 years, a level of < 200 U/mL had a mean survival of 2.3 years, whereas a postoperative CA 19-9 serum levels of < 1000 U/mL and > 2000 U/mL had a mean survival of 9 and 5 months, respectively, [64].

CA 19-9 levels are also used for surveillance after potentially curative surgery for pancreatic cancer, and significant or sustained postoperative elevations of a CA 19-9 serum level suggest recurrent or progressive disease [61]. In these cases, CT aids in the identification of the recurrent site. PET/CT may also add value in the diagnosis of recurrent disease (Fig. 10).

Radiologist should be aware of benign conditions which may elevate the CA 19-9 in the absence of a pancreatic cancer such as pancreatitis, obstructive jaundice (Fig. 11), cholangitis, rheumatoid arthritis, diverticulitis, and liver disease [65]. CA 19-9 can also be elevated in other cancers such as in bile duct cancers, gallbladder cancer, cholangiocarcinomas, ampullary cancers, stomach, lung, and colon cancer [65]. Alternative diagnosis should be considered in the presence of a large mass within the pancreas without elevation of CA19-9.

Ovarian cancer

Ovarian cancer is the second most common gynecological malignancy and the fourth most common cause of death from cancer in women [66]. Most of the ovarian cancers are usually detected, unfortunately at a later stage, when patients became symptomatic and the tumor is disseminated throughout the abdomen and pelvis. The 5-year survival ranges from 5 to 50% in women with stage III–IV and increases to 80 to 90% in women with stage I [67]. Therefore early detection is crucial.

CA-125 is a glycoprotein expressed in epithelium lining body cavities and is present in mesothelial cells of the pleura, pericardium, peritoneum and Mullerian epithelium derivatives such as such as tubal, endometrial, and endocervical cells. The normal value is ≤ 35 U/mL [68]. CA 125 is a serum tumor marker for epithelial ovarian malignancy. It can be used to distinguishing malignant from benign pelvic masses, for prognosis, to monitor response to chemotherapy, and to detect disease recurrence in ovarian cancer patients.

In women with epithelial ovarian cancer, approximately 80% will have CA 125 levels > 35 U/mL. CA 125 is

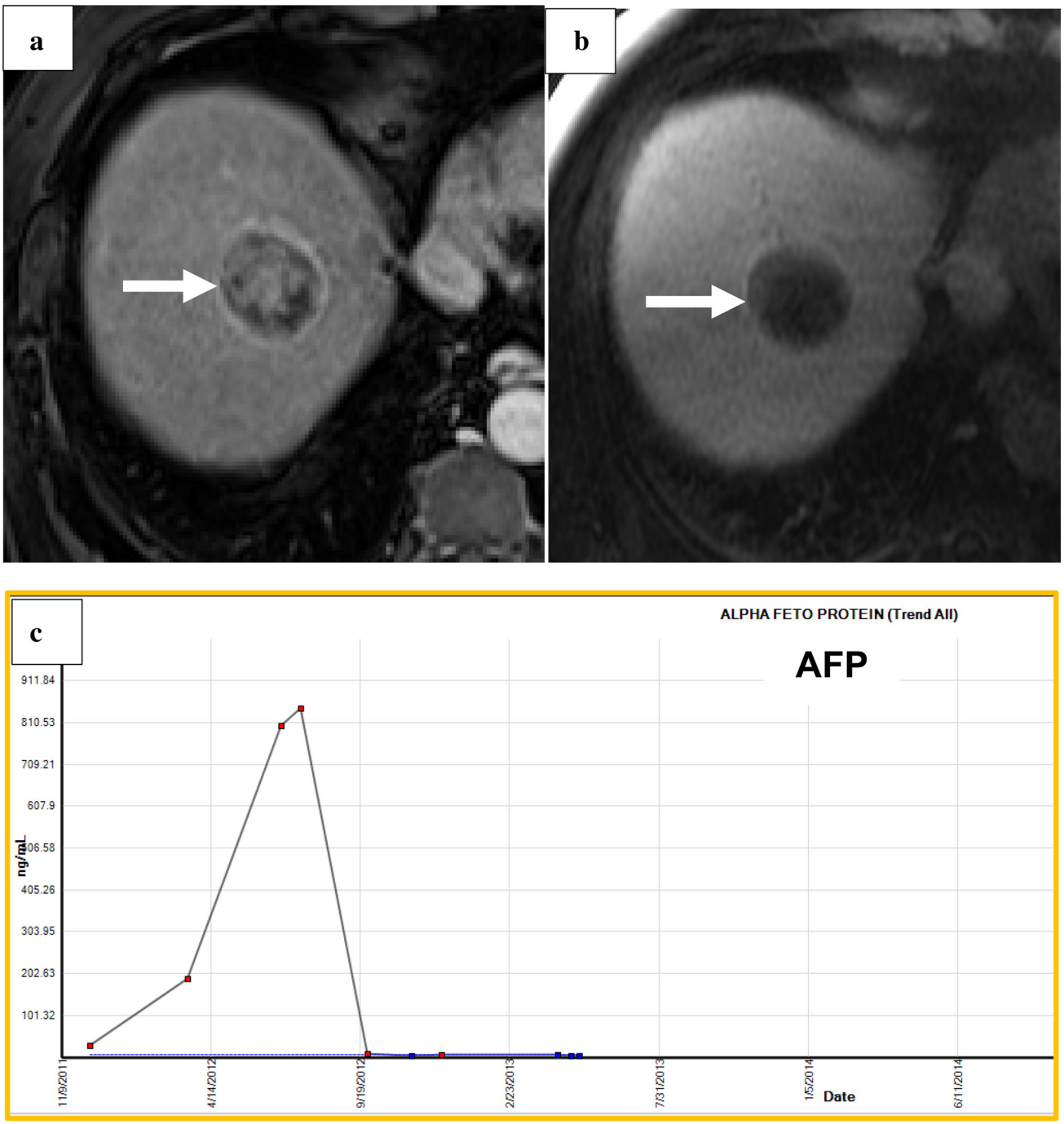


Fig. 7 A 60-year-old male with hepatocellular carcinoma (HCC). **a** Late arterial phase axial contrast-enhanced MRI image performed with gadoxetate disodium showed a 4.4-cm HCC lesion in the liver (arrow). Patient was treated with transarterial chemoembolization (TACE). **b** Post-TACE late arterial phase axial contrast-enhanced MRI image performed with gadoxetate disodium shows the absence of lesion enhancement (arrow). Imaging findings are concordant with the decrease in alpha-fetoprotein levels (**c**)

elevated in 50–60% of patients with stage I ovarian cancer, 80–90% in stage II, and in > 90% in patients with stage III or IV [69]. CA 125 can be elevated in nongynecologic malignancies such as pancreatic and lung cancer. CA 125 may also be elevated in individuals with cirrhosis, hepatitis, and in benign gynecologic disease such as pelvic inflammatory disease, endometriosis (Fig. 12) and pregnancy [70].

CA 125 is not used for screening due to low sensitivity for stage I disease, inability to detect early stage cancers, and negative results for patients with mucinous-type tumors [71]. A randomized controlled clinical trial showed

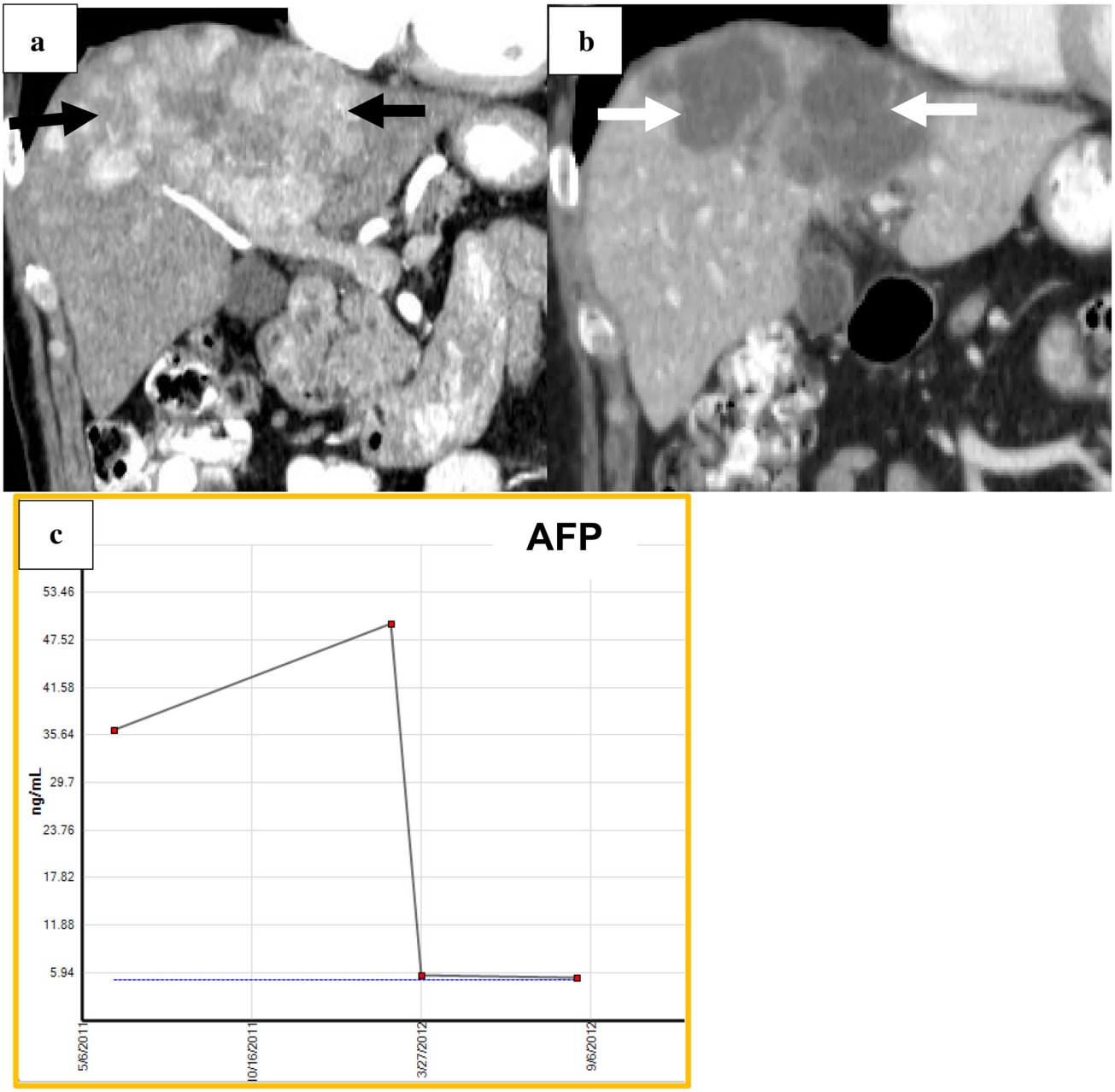


Fig. 8 Multifocal hepatocellular carcinoma (HCC) in a 72-year-old male. **a** Coronal reformatted contrast-enhanced CT image in arterial phase shows multiple hypervascular liver lesions (arrows) compatible with HCC. Patient was deemed unresectable and was treated with yttrium-90. **b** Coronal reformatted contrast-enhanced CT image obtained 3 months after treatment showed response to treatment with marked decrease in tumor attenuation (arrows) concordant with drop of alpha-fetoprotein serum levels (**c**)

that, using both CA 125 and transvaginal ultrasonography in asymptomatic women to screen for ovarian cancer, did not reduce ovarian cancer mortality in the general US population [72]. Therefore, CA 125 is not recommended in screening for ovarian cancer in asymptomatic patients. However, CA 125 is advised annually in women with a hereditary ovarian cancer syndrome, Lynch syndrome and in BRCA-positive patients undergoing screening [73, 74].

In postmenopausal women, CA125 may be used as an adjunct in differentiating between benign and malignant pelvic masses. Values > 95 can discriminate malignant from benign pelvic masses with a positive predictive value of 95% in postmenopauasal women [75].

CA125 has a sensitivity of 84.4% and a specificity of 66.3% in predicting ovarian cancer [76]. To increase the specificity of CA 125 in evaluating the probability of an

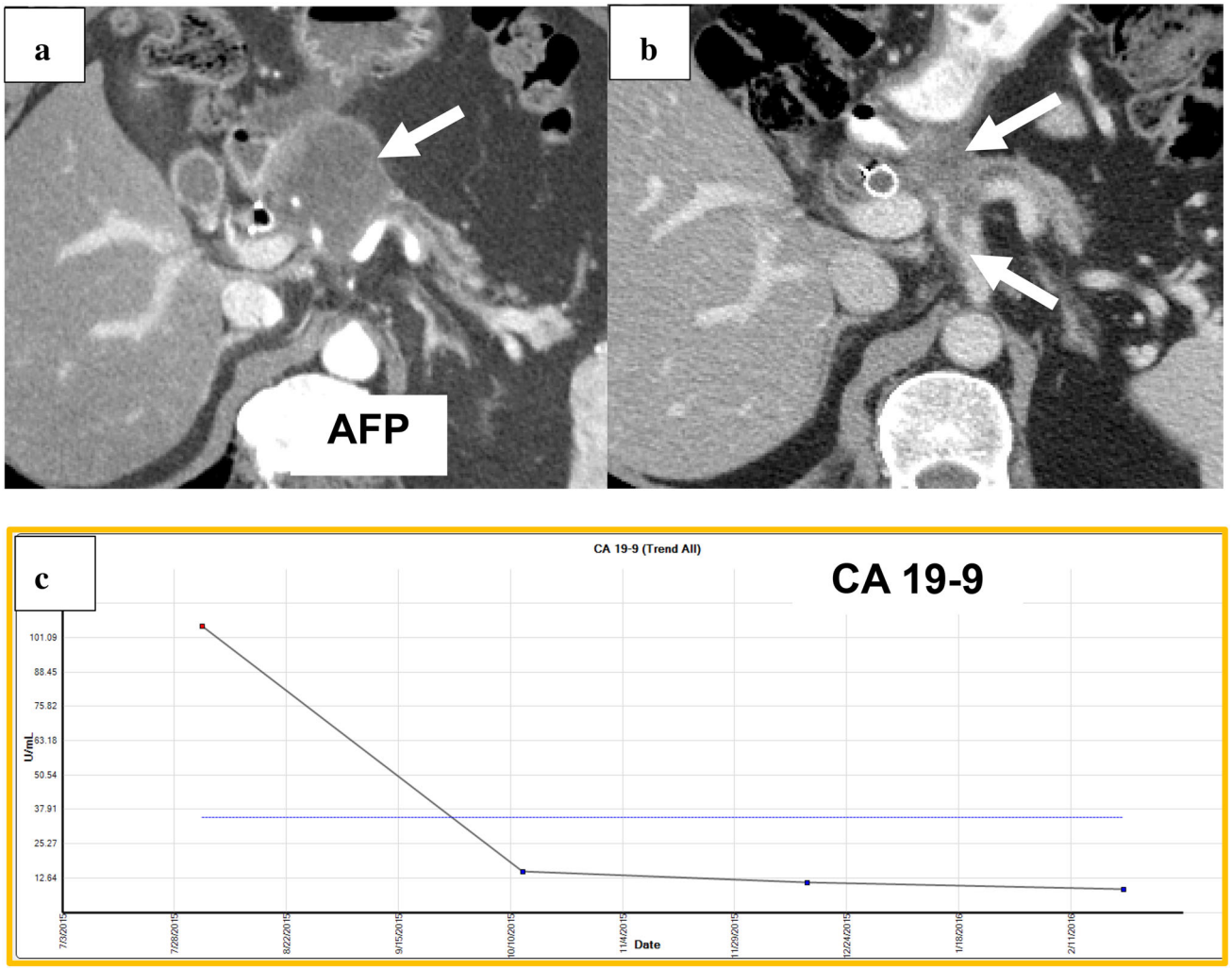


Fig. 9 Monitoring treatment in a 67-year-old male with pancreatic adenocarcinoma. **a** Axial contrast-enhanced CT image shows a large hypodense pancreatic head mass (arrow) that was biopsied with the diagnosis of pancreatic adenocarcinoma. **b** Follow-up contrast-enhanced axial CT image performed 2 months after treatment with chemotherapy revealed good response with a decreasing tumor size and marked decline in CA 19-9 levels (**c**)

ovarian mass being malignant, a risk of malignant index (RMI) has been developed. The RMI is determined based on the menopausal status, ultrasound findings, and serum CA125 levels. The total score > 200 has high specificity in diagnosing malignancy [68]. A single measurement of CA 125 has some limitations in the diagnosis of ovarian cancer because some benign pelvic conditions may have elevated CA 125. Progressively rising CA125 values are more associated with ovarian cancer.

CA125 levels has also been proposed to reflect the relative volume of the ovarian tumor, but this has not been reproducible across studies [77]. High CA 125 preoperative levels (≥ 500 U/mL) is associated with suboptimal debulking cytoreductive surgery [76].

CA 125 can be used for monitoring treatment of ovarian cancer. A rapid fall in CA 125 during chemotherapy predicts a favorable prognosis. A 50% decrease in CA125 after the second cycle of treatment is a reasonably good predictor of achieving a good response [78]. Conversely, a rise in CA 125 will allow the oncologist to consider altering the cytotoxic regimen if imaging shows clear progression. CA 125 is also used in surveillance and detection of recurrent disease (Fig. 13). CA 125 half-life is approximately 2 weeks and it should normalize after surgical resection. Rising CA 125 levels after debulking surgery and chemotherapy indicate recurrent disease with 95% accuracy [79].

The current salvage therapy for ovarian epithelial tumors may not cure the disease in all cases. After cytoreductive surgery, a few small residual nodules cannot be resolved by CT imaging, and serum tumor marker is useful in monitoring such small volume disease. An elevation of CA 125 may precede the clinical detection in approximately 3–5 months [78].

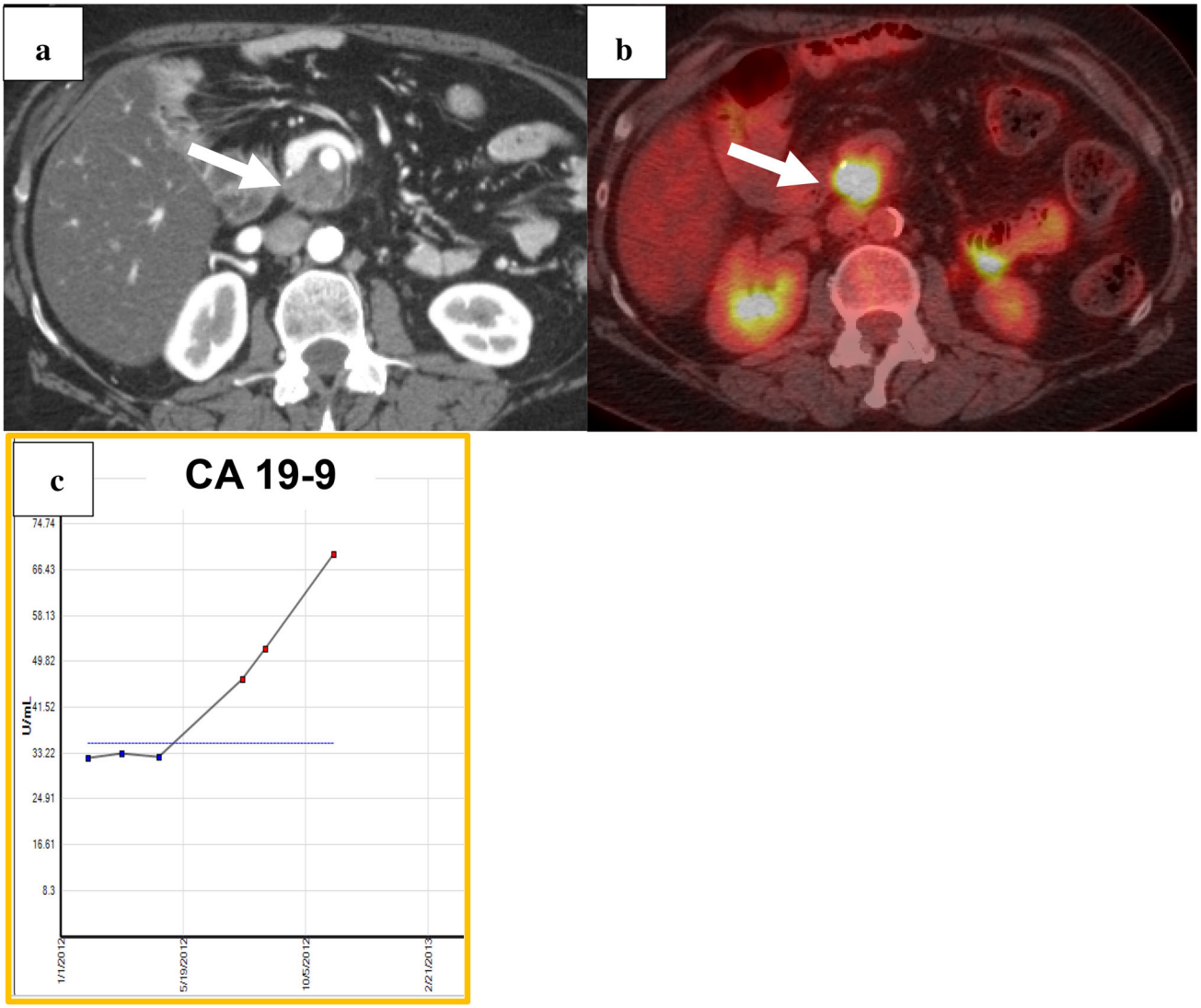


Fig. 10 Recurrent disease in a 65-year-old female with history of prior total pancreatectomy for pancreatic cancer with postoperative normalized levels of CA 19-9. On surveillance clinical visit, CA 19-9 levels have increased. **a** Axial postoperative follow-up contrast-enhanced CT image reveals a soft tissue mass in the pancreatic surgical bed concerning for recurrent tumor (arrow) encasing the superior mesenteric artery and abutting the superior mesenteric vein. **b** FDG PET/CT showed focal hypermetabolism in the same region (arrow). CT-guided biopsy was performed confirming disease recurrence and concordant with rising CA19-9 levels (**c**)

In patients with rising CA 125 levels, imaging is important for the detection of recurrent disease. CT helps in the evaluation of distant visceral metastases and lymphadenopathy and has high sensitivity for the detection of nonresectable recurrent disease such as hydronephrosis and pelvic sidewall invasion [80]. Questionable cases can be further evaluated with a MRI that has a sensitivity and specificity of 84% and 90% in detecting recurrence of ovarian cancer [81].

Most recently, *PET/CT* is *increasingly* being *used* in the management of ovarian cancer patients. PET/CT has sensitivity, specificity, and accuracy of 90.4, 100, and 91.2%, respectively, for the diagnosis of recurrent ovarian cancer [81, 82]. In symptomatic patients with normal CA-125 levels, FDG PET/CT has better sensitivity than contrast-enhanced CT in detecting the ovarian cancer recurrence (Fig. 14) [83].

The absolute value of CA 125 has not been related to a particular pattern of recurrence. Besides the absolute value of CA 125, CA125 doubling time may be used as prognostic factor for survival in patients with ovarian cancer relapsing after first-line chemotherapy. Han et al. reported that the median survival for patients with a CA125 doubling time of 40 days was 10.6 months compared to 22.1 months for those with CA 125 doubling time > 40 days [84].

Other markers and prognostic factors used for ovarian cancer include human epididymis protein 4 (HE4), the risk

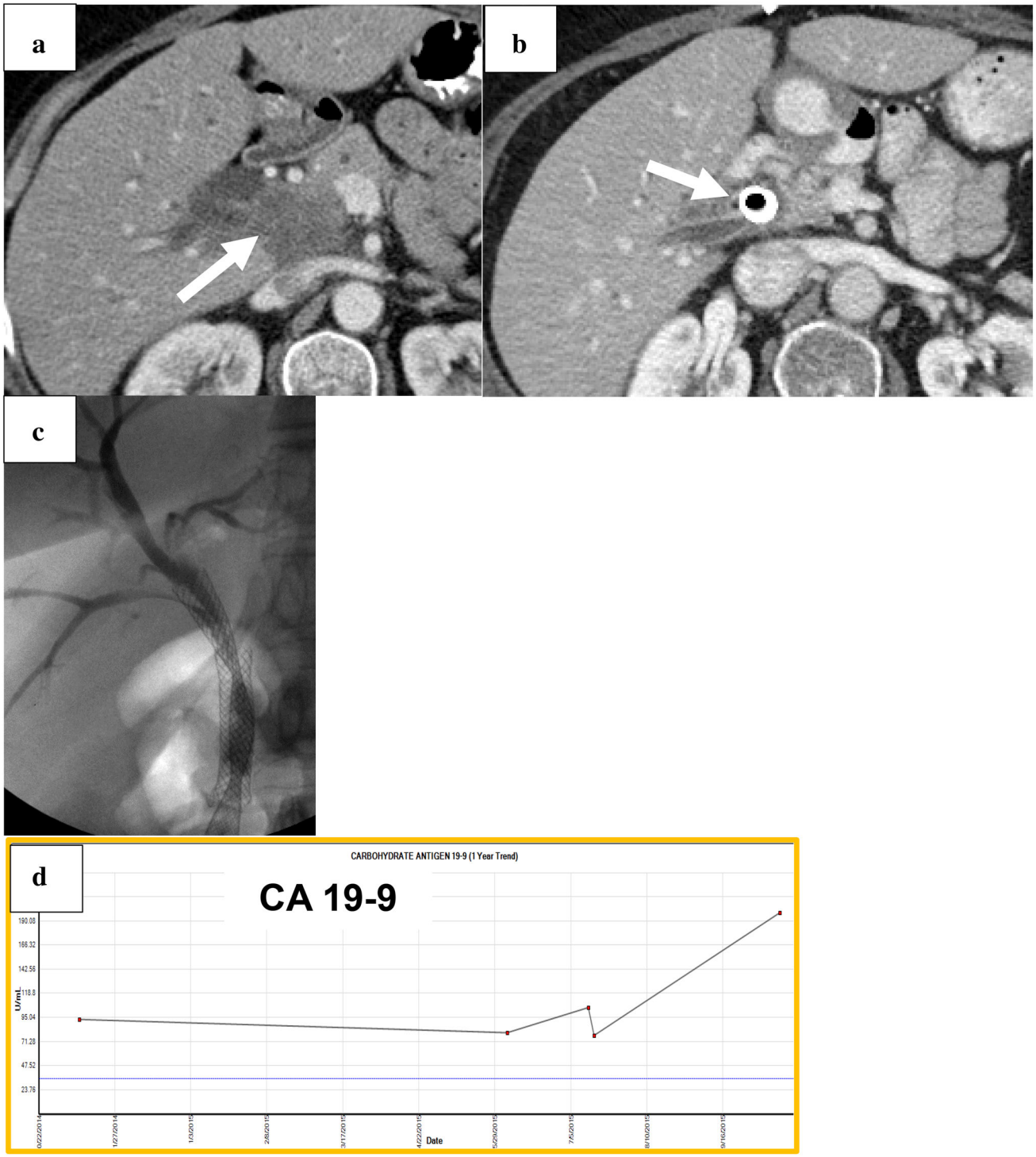


Fig. 11 Bile duct obstruction in a 69-year-old female with history of pancreatic cancer. **a** Axial contrast-enhanced CT image shows a 3.8-cm adenocarcinoma of the pancreatic head (arrow) causing bile duct dilatation. Patient was treated with chemotherapy and chemoradiation. No radiographic recurrence seen over 2 years. Continuous surveillance revealed rising CA 19-9 levels. **b** Axial contrast-enhanced CT imaging performed due to rising CA 19-9 levels showed persistent intrahepatic ductal dilatation with the common bile duct stent in place (arrow). Tumor recurrence not present; CA 19-9 continued rising to 198 U/ml, associated with elevated alkaline phosphatase indicative of biliary stent malfunction. **c** ERCP was performed, and new uncovered wall stent was placed with no evidence of tumor recurrence. Elevated CA 19-9 was attributed to bile duct obstruction (**d**)

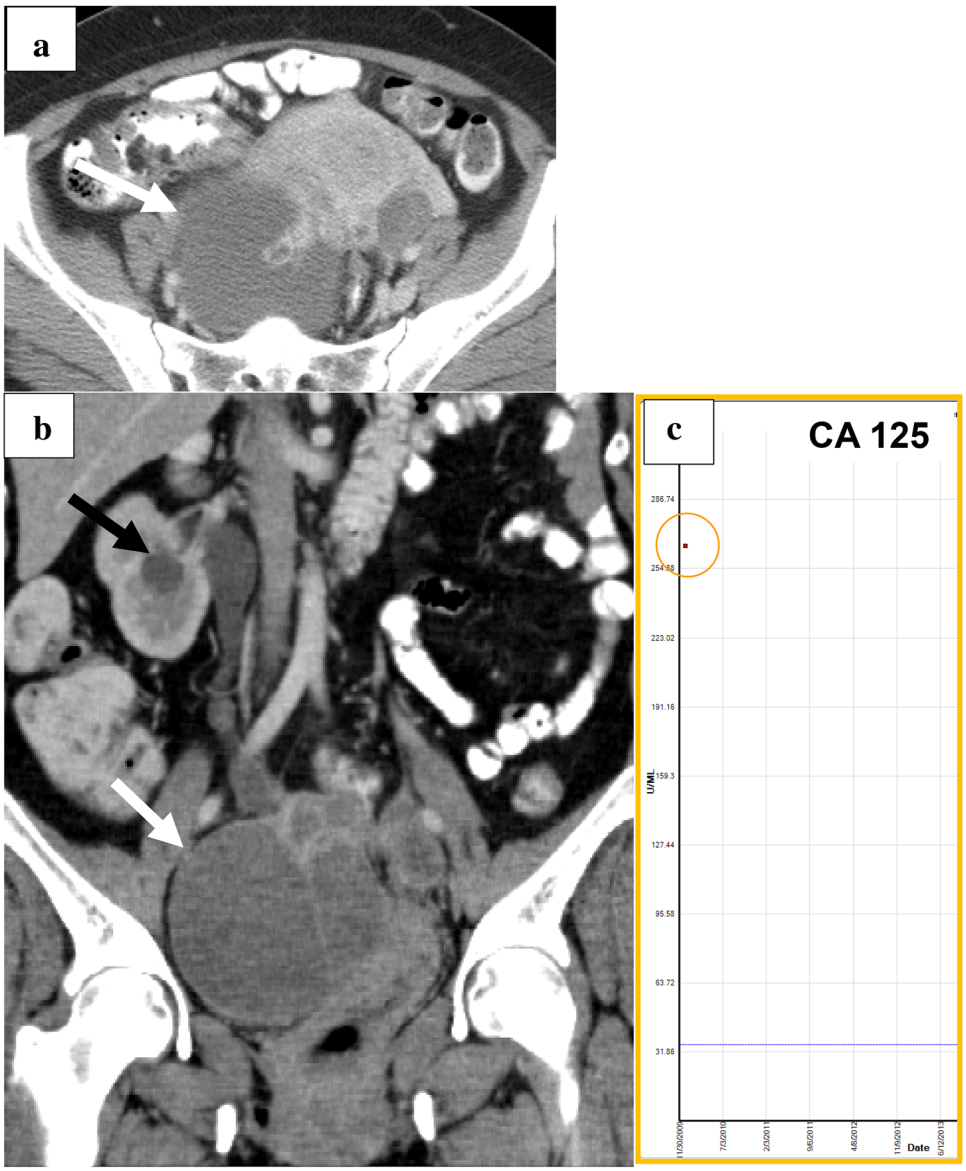


Fig. 12 Endometriosis in 43-year-old female with pelvic pain. **a** Axial and coronal **b** contrast-enhanced CT images of the abdomen and pelvis revealed a large complex right adnexal cystic mass (white arrows), abutting the sigmoid colon, and resulting in right hydronephrosis (black arrow), suspicious for ovarian cancer. CA-125 level was 265 U/mL (**c**). Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed with the final diagnosis of endometriosis demonstrating an example of false-positive CA-125 elevation

of ovarian malignancy algorithm (ROMA) and OVA1. HE4 is a relatively new marker for ovarian cancer, is a glycoprotein encoded by WAP four-disulfide core domain 2 (WFDC2) gene that is overexpressed in epithelial ovarian cancer. HE4 has also been identified in pulmonary, endometrial, breast carcinomas and mesotheliomas [85]. Some authors reported that HE4 has a higher sensitivity than CA 125 in the detection of ovarian cancer while others suggest that a combination of these markers provided slightly improved sensitivity for cancer detection. Studies suggest that HE4 is elevated in more than half of the ovarian cancer patients who do not have elevated CA 125 levels [86, 87].

ROMA was developed to improve the sensitivity in the diagnosis of ovarian malignancy with serum concentrations of both CA125 and HE4 substituted in the mathematical formula. ROMA value $> 13.1\%$ in pre- and $> 27.7\%$ for postmenopausal women, qualified them to a group with a high risk of malignancy of ovarian tumor [87].

OVA 1 is used to assess the risk malignancy in women presenting with an adnexal mass [88]. It evaluates serum concentrations of five markers, two of them are upregulated (CA-125 II, β-microglobulin) and three are downregulated (apolipoprotein A1, prealbumin, transferrin). A multivariate index assay algorithm is created with a software which generates a score between 0 and 10, and then interpreted as high or low probability for malignancy. For premenopausal women, a score ≥ 5.0 is considered high probability; for postmenopausal women, a score ≥ 4.4 is high probability, and they should be referred to an oncological gynecologist [85].The reported sensitivity and specificity of OVA1 are 96% and 28% in postmenopausal and 85% and 40% in

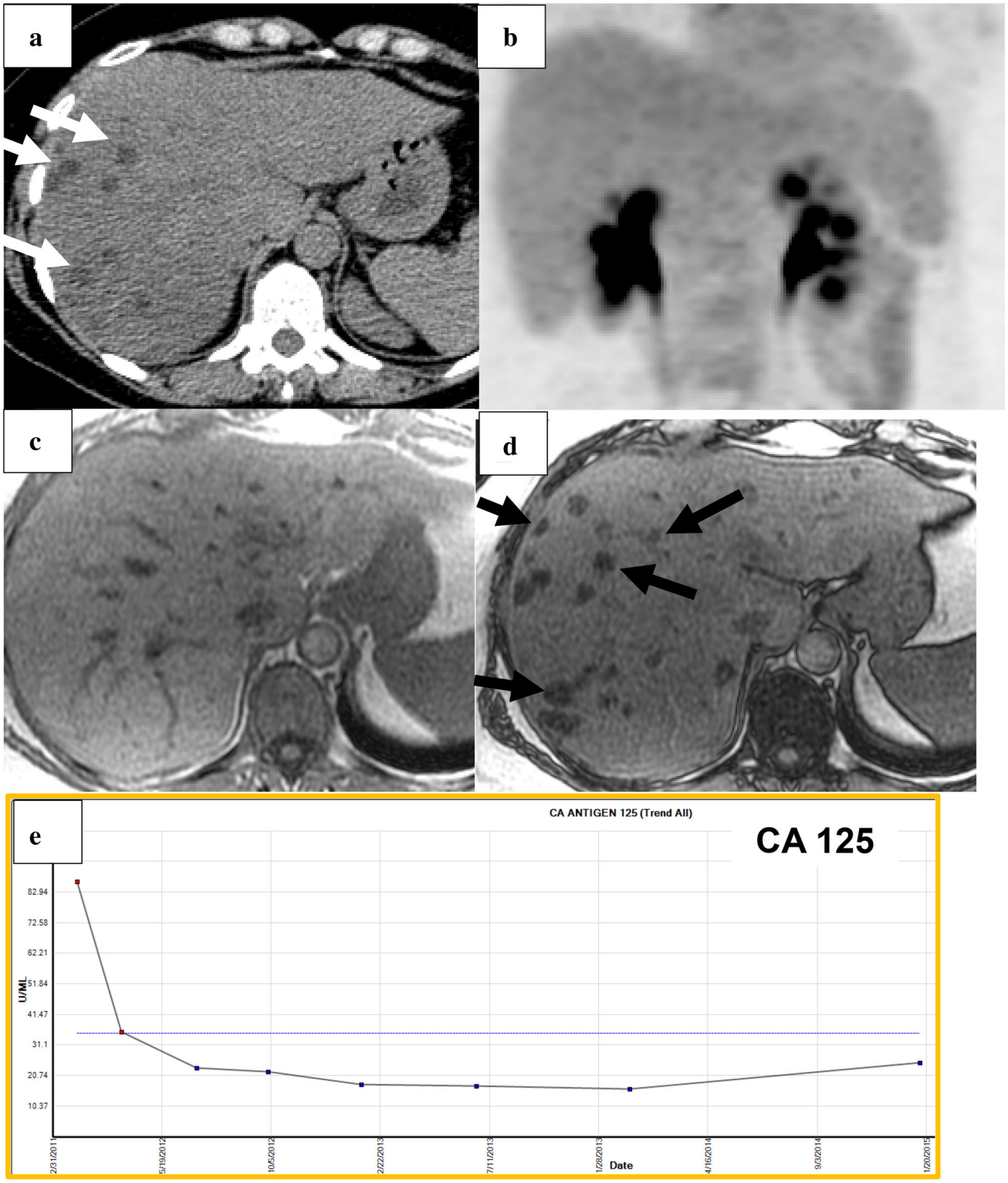


Fig. 13 A 51-year-old female with ovarian cancer status post total abdominal hysterectomy and bilateral salpingo-oophorectomy. CA-125 decreased to normal levels after surgery. **a** Surveillance axial CT images without IV contrast showed new hypoattenuating liver lesions (arrows). CA-125 levels remained within normal range. **b** PET/CT image shows no areas of increased FDG uptake in the liver. **c**, **d** axial in- and out-of-phase MRI images showed several low signal intensity liver lesions only seen on the out-of-phase sequence (arrows), consistent with foci of fat. The stability of the CA-125 levels (**e**) favored lack of recurrent disease

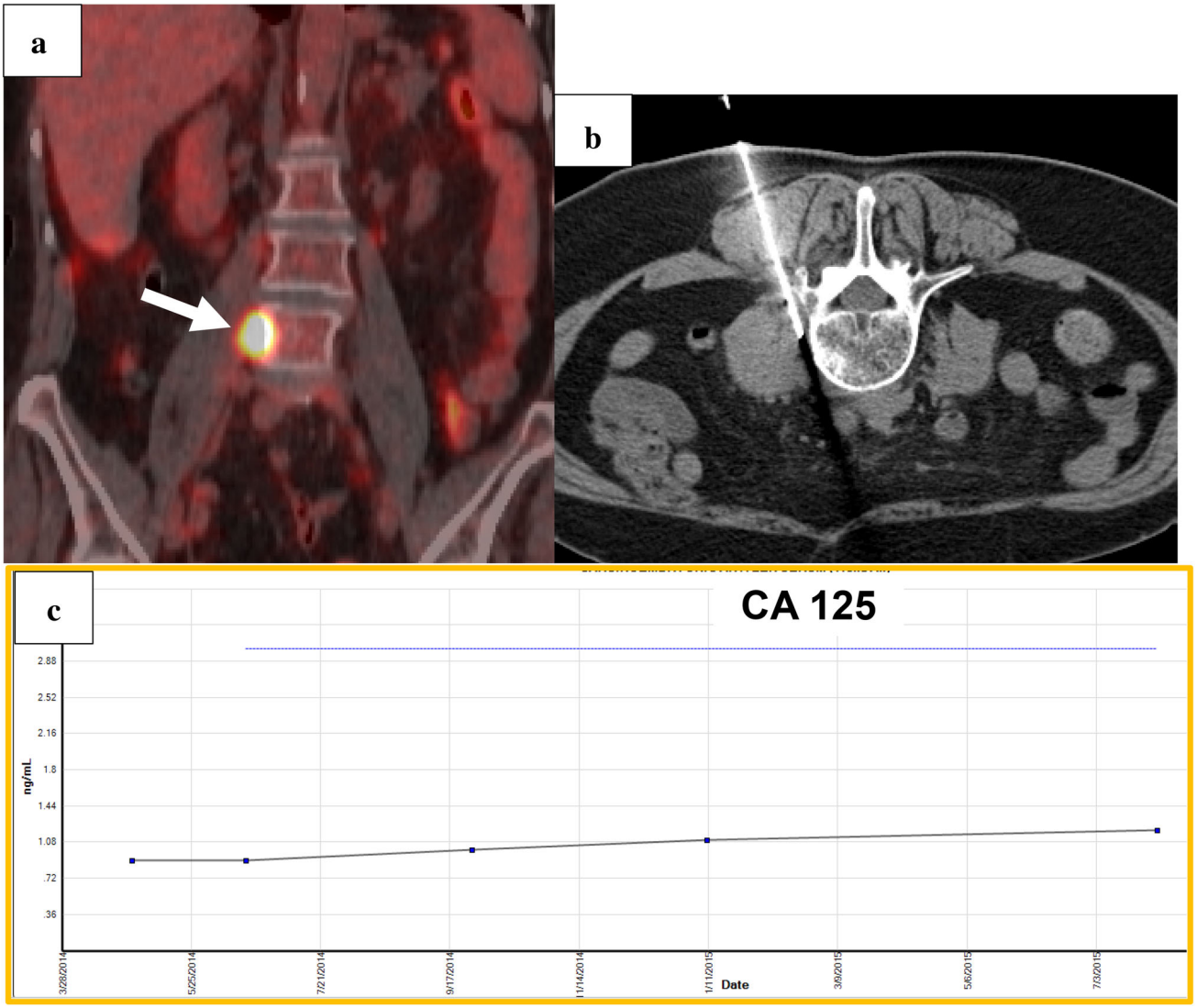


Fig. 14 Recurrent ovarian cancer in a 74-year-old female with ovarian cancer status post total abdominal hysterectomy and bilateral salpingo-oophorectomy. In a surveillance visit, patient presented with new back pain. CA-125 was within normal limits. **a** Coronal PET/CT images showed a small L4 right paravertebral soft tissue area associated with hypermetabolism (arrow) with a maximum SUV of 15. **b** CT-guided biopsy of the small L4 right paravertebral soft tissue area confirmed metastatic disease despite normal CA-125 levels (**c**)

premenopausal women,, respectively. Currently, there are hardly any available studies directly comparing performances of the OVA1 test and ROMA [89].

RMI (risk of malignant index) have been developed by Jacobs et al. and by Tingulstad et al. as RMI 1 and RMI 2, respectively [90, 91]. Both RMI scoring systems are the product of ultrasound score × menopausal score × CA-125 levels. The difference between them is the number of ultrasound findings being considered but their validity is similar.

The International Ovarian Tumor Analysis (IOTA) group published a consensus statement on terms, definitions, and measurements to describe the sonographic features of adnexal masses [92].They also developed predictive models for the evaluation of the risk of malignancy in ovarian masses. The most recent one, called "The Assessment of Different Neoplasias in the adnexa" (ADNEX), contains three clinical and six ultrasound predictors, and discriminates well between benign and malignant tumors and offers excellent discrimination between four subgoups of malignant tumors improving the management of patients with ovarian masses [93].

Germ cell tumors

Germ cell tumors are neoplasms derived from germ cells that normally occur inside the gonads, testicles, and ovaries [94]. GCT may also occur in other areas of the body (extragonadal germ cell tumors), such as within the abdomen,

brain, and chest but they are very rare [94]. We will only discuss GCT of the testicles and ovaries.

Testicular cancer represents only 1% of all cancers diagnosed in men but is the most common solid organ malignancy among men ages 15–35 old [95]. Nearly all testicular tumors are germ cell tumors. They are histologically classified as seminomas (40%), nonseminomatous germ cell tumors (NSGCT) (40%), and "mixed" germ cell tumors (20%) which contain more than one histological type. NSGCT are divided into four subtypes: embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac carcinoma (endodermal sinus tumors) [96].

Different types of testicular cancers exhibit different tumor markers. The most commonly used tumor markers in the management of testicular cancer are AFP, b-hCG and LDH.

AFP is used for diagnosis of testicular cancer. The normal value is $\geq$ 10 nanograms per milliliter (ng/mL). AFP is primarily produced by yolk sac components and to a lesser extent by embryonal carcinomas and teratomas. Pure seminomas do not produce AFP [97]. Patients with elevated AFP levels are assumed to have nonseminomatous components and are treated accordingly. The only type of NSGCT that does not secrete AFP is pure choriocarcinoma. The levels of AFP are directly proportional to the tumor burden; and higher levels are considered as poor prognostic indicators [98].

Human chorionic gonadotropin (hCG) is synthesized by cytotrophoblasts of the placenta and is also produced by germ cell tumors. The normal value for males or non-pregnant females is < 4.0 mIU/mL. Tumors containing choriocarcinomatous elements such choriocarcinomas produces hCG, and it also can be produced by other germ cell tumors such as embryonal carcinoma [98]. Serum concentrations of beta-hCG are elevated in 60–80% percent of men with NSGCTs. It can be markedly elevated in pure choriocarcinomas, and moderately elevated in embryonal carcinoma and mixed GCTs. Elevation of beta-hCG can also be seen in approximately 10–20% of patients with stage I seminoma and up to 30–50% of disseminated seminoma. Patients with seminoma usually have beta-hCG levels less than 500 mIU/mL and levels greater than 1000 mlU/mL are more often seen with NSGCT. Beta-hCG levels may also be elevated in islet cell tumors, tumors of the small and large bowel, hepatomas, lung, and stomach cancers [99].

Lactic dehydrogenase (LDH) is a cellular enzyme with a normal value ranging from 140 to 280 U/L. LDH is less sensitive and less specific tumor marker than either beta-hCG or AFP but may be elevated in 40–60% of men with testicular GCT. LDH may be used as a prognostic indicator because its level is proportional to tumor burden with levels > 200 U/L usually correlating with bulky disease. High LDH levels can also occur in some benign conditions including skeletal muscle disease and myocardial infarction [99].

Serum tumor markers should normalize after curative surgery. Serum markers that do not normalize after orchiectomy indicate residual disease. They can also be used to monitor response to treatment and in detection of recurrent disease (Fig. 15).

Women can also develop ovarian germ cell tumors that are derived from primordial germ cells of the ovary. Many of these are benign, but some are cancerous. These neoplasms account for less than 5% of all malignant ovarian neoplasms [100]. Most ovarian germ cell tumors occur in young women between 10 and 30 years of age, representing 70% of ovarian neoplasms in this age group [100].

The histologic types of ovarian CGT are similar to those developing in the testes, including immature teratomas, dysgerminomas, yolk sac tumors, mixed GCT, embryonal carcinomas, and nongestational choriocarcinomas [101]. Like CGT in the testes, ovarian CGT often produce tumor markers. Some tumor markers are present in some types of ovarian GCT, but not all tumors. AFP can be elevated in yolk sac tumors, embryonal cell carcinomas, mixed germ cell tumors, and some immature teratomas. The hCG may be elevated in embryonal cell carcinomas, ovarian choriocarcinomas, mixed germ cell tumors, and some dysgerminomas. Dysgerminomas also produce LDH. Surgery is the treatment of choice for ovarian GCT, and the tumor markers are vital in the management and surveillance of these tumors [101].

Neuroendocrine cancer

Neuroendocrine tumors (NET) arise from cells of endocrine and nervous system and account for about 2% of all cancers [102]. Tumors of the neuroendocrine system most frequently involve the gastrointestinal tract and pancreas but can also occur within the lung, thymus, and others tissues. Most gastrointestinal NET are usually small at presentation and initially asymptomatic. The classical carcinoid syndrome is relatively uncommon, seen in only 10–15% of cases and usually associated with metastatic disease. The overall 5-year survival rate for patients with gastrointestinal NET is approximately 58% [103].

CgA (chromogranin A) is the most commonly measured tumor marker for the diagnosis and management of NET [104]. CgA is a glycoprotein that belongs to the chromogranin family and is stored in secretory granules of neuroendocrine cells [104]. It is co-secreted with the amines and peptides that are present in the neurosecretory granules. The primary concern regarding the use of serum CgA as a diagnostic test is its low sensitivity. The sensitivity

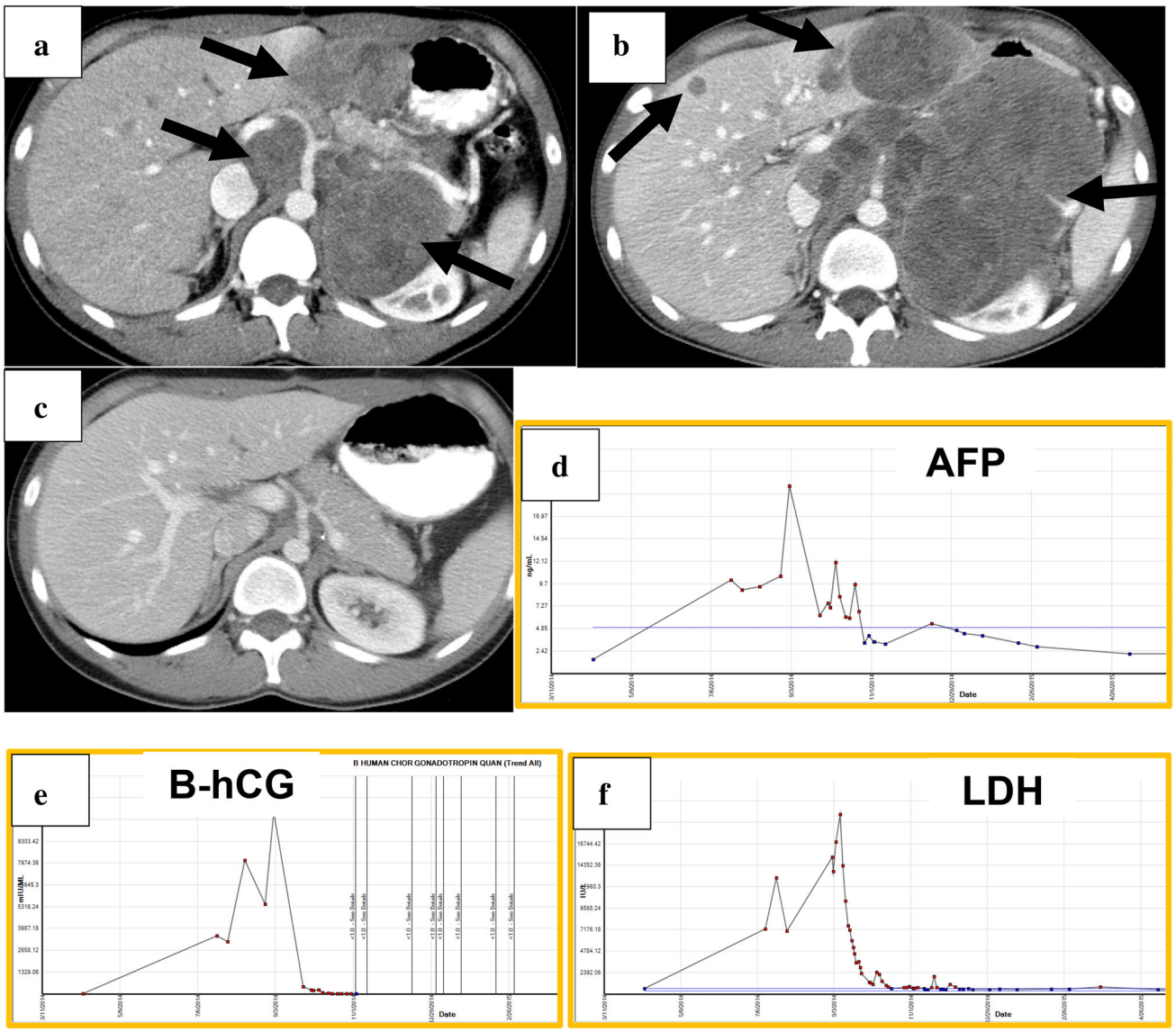


Fig. 15 Monitoring treatment in 21-year-old male with nonseminomatous mixed germ cell tumor treated with chemotherapy and retroperitoneal lymph node dissection. One year later, he presented with elevated beta-hCG, alpha-fetoprotein, and LDH. **a** Axial contrast-enhanced CT image of the abdomen showed recurrent retroperitoneal adenopathy (arrows). The patient was treated with chemotherapy, but the tumor markers continued to increase. Axial CT image (**b**) showed increase in size of the lesions and hepatic metastasis compatible with disease progression. Treatment was changed, and he underwent a retroperitoneal tumor resection and stem cell transplant. **c** Follow-up contrast-enhanced CT image revealed complete response to treatment. His tumor markers (AFP, b-HCG and LDH) decreased and remained within normal limits (**d–f**)

reported in the literature ranges broadly between 27 and 63% according to the stage of disease, grade of differentiation, and the presence of a functional and/or hereditary syndrome [105].

Elevated CgA levels have been demonstrated in serum of patients with hormone-secreting or non-hormone-secreting neuroendocrine tumors. It is elevated in 50–100% of neuroendocrine tumors, and the most used reference ranges for serum CgA normal levels are $\leq$ 36 ng/mL [106].

CgA levels depend on the location of the primary NET. The midgut NETs have a higher CgA than for pancreatic NETs. The CgA levels and sensitivity also depend on the stage of disease, with higher levels usually seen in patients with liver metastases. CgA is not useful as a prognostic indicator in poorly differentiated tumors [107].

Serial measurements can be used as a clinical tool in monitoring therapeutic response to treatment (Fig. 16). CgA levels are also used to evaluate for progression of disease and the tumor recurrence after definitive or palliative therapeutic intervention. Bajetta et al. reported an elevation of CgA in 83% of patients with clinical progression and in 100% of patients with progressive liver metastasis [108].

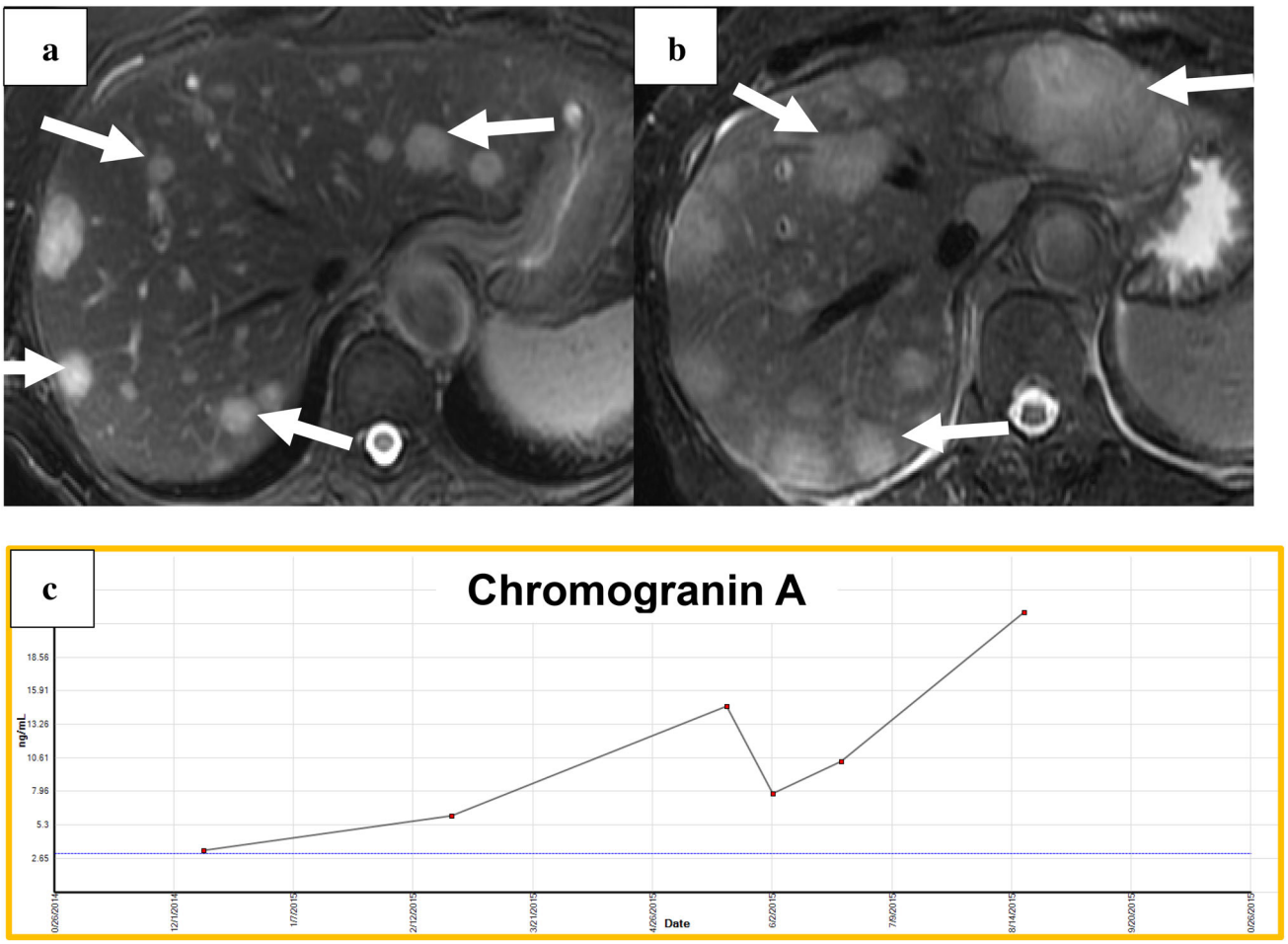


Fig. 16 Monitoring treatment in a 66-year-old female with a history of neuroendocrine tumor. **a** Axial T2-weighted FSE with fat suppression MRI image showed multiple hepatic metastases (arrows). Patient was treated with Sandostatin injections monthly. Chromogranin A continued to rise despite treatment. **b** Follow-up axial T2-weighted FSE with fat suppression MRI image showed interval increase in size and number of hepatic metastases consistent with disease progression (arrows) in concordance with rising Chromogranin A levels (**c**)

CgA can be elevated in patients with other cancers such as HCC, breast cancer, ovarian cancer, colorectal cancer, small cell lung cancer, neuroblastoma, and some prostate carcinomas [109]. CgA may also be elevated in noncancer pathologies such as endocrine diseases, autoimmune and rheumatologic diseases, chronic atrophic gastritis, inflammatory bowel disease, renal or hepatic insufficiency, pulmonary obstructive disease, and in those who use proton pump inhibitors [109].

Conclusion

Tumor markers are important for the diagnosis, staging, monitoring of treatment, and detection of recurrence in many cancers. However, they should not be used solely, but interpreted in conjunction with diagnostic imaging, clinical history, and physical examination.

Decreasing tumor marker levels following initiation of therapy correlate with tumor regression and conversely elevation of tumor markers should lead to a high index of suspicion for progression and/or recurrent tumor. However, although tumor markers can be elevated in the setting of cancer, some patients may not show marker elevation, and, on the other hand, benign conditions can also cause false-positive elevation of these markers. Radiologists should also be aware of the limitations of the most commonly used tumor markers. In addition, applying this knowledge in daily routine interpretation of imaging studies will help optimize the multidisciplinary care and management of oncologic patients.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Statement for informed consent was not applicable to this manuscript.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics. CA Cancer J Clin 68(1):7–30. https://doi.org/10.3322/caac.21442
2. Duffy MJ (2013) Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract 22(1):4–11. https://doi.org/10.1159/000338393
3. Holdenrieder S, Pagliaro L, Morgenstern D, Dayyani F (2016) Clinically meaningful use of blood tumor markers in oncology. Biomed Res Int 2016:9795269. https://doi.org/10.1155/2016/9795269
4. Lech G, Slotwinski R, Slodkowski M, Krasnodebski IW (2016) Colorectal cancer tumour markers and biomarkers: recent therapeutic advances. World J Gastroenterol 22(5):1745–1755. https://doi.org/10.3748/wjg.v22.i5.1745
5. Aslam MI, Kelkar A, Sharpe D, Jameson JS (2010) Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers. Int J Surg 8(4):305–313. https://doi.org/10.1016/j.ijsu.2010.03.005
6. Goldstein MJ, Mitchell EP (2005) Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. Cancer Invest 23(4):338–351
7. Iwanicki-Caron I, Di Fiore F, Roque I, et al. (2008) Usefulness of the serum carcinoembryonic antigen kinetic for chemotherapy monitoring in patients with unresectable metastasis of colorectal cancer. J Clin Oncol 26(22):3681–3686. https://doi.org/10.1200/jco.2007.15.0904
8. Locker GY, Hamilton S, Harris J, et al. (2006) ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 24(33):5313–5327. https://doi.org/10.1200/jco.2006.08.2644
9. Wiratkapun S, Kraemer M, Seow-Choen F, Ho YH, Eu KW (2001) High preoperative serum carcinoembryonic antigen predicts metastatic recurrence in potentially curative colonic cancer: results of a five-year study. Dis Colon Rectum 44(2):231–235
10. Su BB, Shi H, Wan J (2012) Role of serum carcinoembryonic antigen in the detection of colorectal cancer before and after surgical resection. World J Gastroenterol 18(17):2121–2126. https://doi.org/10.3748/wjg.v18.i17.2121
11. Miles K, Burkill G (2007) Colorectal cancer: imaging surveillance following resection of primary tumour. Cancer Imaging 7(Spec No A):S143–S149. https://doi.org/10.1102/1470-7330.2007.9011
12. Scheer MG, Sloots CE, van der Wilt GJ, Ruers TJ (2008) Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases. Ann Oncol 19(11):1829–1835. https://doi.org/10.1093/annonc/mdn398
13. Scheer A, Auer RA (2009) Surveillance after curative resection of colorectal cancer. Clin Colon Rectal Surg 22(4):242–250. https://doi.org/10.1055/s-0029-1242464
14. Duffy MJ, Lamerz R, Haglund C, et al. (2014) Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int J Cancer 134(11):2513–2522. https://doi.org/10.1002/ijc.28384
15. Konishi F (2002) CEA doubling time and CEA half-life in the prediction of recurrences after colorectal cancer surgery. Jpn J Clin Oncol 32(2):41–42
16. Connor S, Hart MG, Redhead DN, et al. (2007) Follow-up and outcomes for resection of colorectal liver metastases in Edinburgh. Eur J Surg Oncol 33(1):55–60. https://doi.org/10.1016/j.ejso.2006.09.017
17. Bipat S, van Leeuwen MS, Comans EF, et al. (2005) Colorectal liver metastases: CT, MR imaging, and PET for diagnosis—meta-analysis. Radiology 237(1):123–131. https://doi.org/10.1148/radiol.2371042060
18. Vreugdenburg TD, Ma N, Duncan JK, et al. (2016) Comparative diagnostic accuracy of hepatocyte-specific gadoxetic acid (Gd-EOB-DTPA) enhanced MR imaging and contrast enhanced CT for the detection of liver metastases: a systematic review and meta-analysis. Int J Colorectal Dis 31(11):1739–1749. https://doi.org/10.1007/s00384-016-2664-9
19. Gade M, Kubik M, Fisker RV, Thorlacius-Ussing O, Petersen LJ (2015) Diagnostic value of (18)F-FDG PET/CT as first choice in the detection of recurrent colorectal cancer due to rising CEA. Cancer Imaging 15:11. https://doi.org/10.1186/s40644-015-0048-y
20. Lu YY, Chen JH, Chien CR, et al. (2013) Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. Int J Colorectal Dis 28(8):1039–1047. https://doi.org/10.1007/s00384-013-1659-z
21. Mittal BR, Senthil R, Kashyap R, et al. (2011) 18F-FDG PET-CT in evaluation of postoperative colorectal cancer patients with rising CEA level. Nucl Med Commun 32(9):789–793. https://doi.org/10.1097/MNM.0b013e3283477dd7
22. Selzner M, Hany TF, Wildbrett P, et al. (2004) Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann Surg 240(6):1027–1034 ((discussion 1035–1026))
23. de Baere T, Tselikas L, Yevich S, et al. (2017) The role of image-guided therapy in the management of colorectal cancer metastatic disease. Eur J Cancer 75:231–242. https://doi.org/10.1016/j.ejca.2017.01.010
24. Attard G, Parker C, Eeles RA, et al. (2016) Prostate cancer. Lancet 387(10013):70–82. https://doi.org/10.1016/s0140-6736(14)61947-4
25. Grubb RL 3rd (2018) Prostate cancer: update on early detection and new biomarkers. Mo Med 115(2):132–134
26. Schmid HP, Riesen W, Prikler L (2004) Update on screening for prostate cancer with prostate-specific antigen. Crit Rev Oncol Hematol 50(1):71–78. https://doi.org/10.1016/j.critrevonc.2003.11.001
27. Adhyam M, Gupta AK (2012) A review on the clinical utility of PSA in cancer prostate. Indian J Surg Oncol 3(2):120–129. https://doi.org/10.1007/s13193-012-0142-6
28. Salman JW, Schoots IG, Carlsson SV, Jenster G, Roobol MJ (2015) Prostate specific antigen as a tumor marker in prostate cancer: biochemical and clinical aspects. Adv Exp Med Biol 867:93–114. https://doi.org/10.1007/978-94-017-7215-0_7
29. Nordstrom T, Akre O, Aly M, Gronberg H, Eklund M (2018) Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis 21(1):57–63. https://doi.org/10.1038/s41391-017-0024-7
30. Drazer MW, Huo D, Eggener SE (2015) National Prostate cancer screening rates after the 2012 US preventive services task force recommendation discouraging prostate-specific antigen-based screening. J Clin Oncol 33(22):2416–2423. https://doi.org/10.1200/jco.2015.61.6532
31. Moyer VA, Force USPST (2012) Screening for prostate cancer: U.S. preventive services task force recommendation statement.

Ann Intern Med 157(2):120–134. https://doi.org/10.7326/0003-4819-157-2-201207170-00459
32. Stamey TA, Yang N, Hay AR, et al. (1987) Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 317(15):909–916. https://doi.org/10.1056/nejm198710083171501
33. de Boo L, Pintilie M, Yip P, et al. (2015) Time from first detectable PSA following radical prostatectomy to biochemical recurrence: a competing risk analysis. Can Urol Assoc J 9(1–2):E14–E21. https://doi.org/10.5489/cuaj.2147
34. Makarewicz R, Lebioda A, Terlikiewicz J, Biedka M, Wisniewski T (2009) PSA bouncing after brachytherapy HDR and external beam radiation therapy: a study of 121 patients with minimum 5-years follow-up. J Contemp Brachyther 1(2):92–96
35. Cornford P, Bellmunt J, Bolla M, et al. (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71(4):630–642. https://doi.org/10.1016/j.eururo.2016.08.002
36. Futterer JJ (2012) Imaging of recurrent prostate cancer. Radiol Clin North Am 50(6):1075–1083. https://doi.org/10.1016/j.rcl.2012.08.005
37. Pucar D, Hricak H, Shukla-Dave A, et al. (2007) Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol Biol Phys 69(1):62–69. https://doi.org/10.1016/j.ijrobp.2007.03.065
38. Alonzo F, Melodelima C, Bratan F, et al. (2016) Detection of locally radio-recurrent prostate cancer at multiparametric MRI: can dynamic contrast-enhanced imaging be omitted? Diagn Interv Imaging 97(4):433–441. https://doi.org/10.1016/j.diii.2016.01.008
39. Schaefer O, Langer M (2007) Detection of recurrent rectal cancer with CT, MRI and PET/CT. Eur Radiol 17(8):2044–2054. https://doi.org/10.1007/s00330-007-0613-2
40. El-Serag HB, Rudolph KL (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 132(7):2557–2576. https://doi.org/10.1053/j.gastro.2007.04.061
41. Mazzanti R, Arena U, Tassi R (2016) Hepatocellular carcinoma: where are we? World J Exp Med 6(1):21–36. https://doi.org/10.5493/wjem.v6.i1.21
42. Zhao YJ, Ju Q, Li GC (2013) Tumor markers for hepatocellular carcinoma. Mol Clin Oncol 1(4):593–598. https://doi.org/10.3892/mco.2013.119
43. Kew M (1974) Alpha-fetoprotein in primary liver cancer and other diseases. Gut 15(10):814–821
44. Gupta S, Bent S, Kohlwes J (2003) Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med 139(1):46–50
45. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. (2001) Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 34(4):570–575
46. Saffroy R, Pham P, Reffas M, et al. (2007) New perspectives and strategy research biomarkers for hepatocellular carcinoma. Clin Chem Lab Med 45(9):1169–1179. https://doi.org/10.1515/cclm.2007.262
47. Sakata J, Shirai Y, Wakai T, et al. (2008) Preoperative predictors of vascular invasion in hepatocellular carcinoma. Eur J Surg Oncol 34(8):900–905. https://doi.org/10.1016/j.ejso.2008.01.031
48. Johnson PJ, Williams R (1980) Serum alpha-fetoprotein estimations and doubling time in hepatocellular carcinoma: influence of therapy and possible value in early detection. J Natl Cancer Inst 64(6):1329–1332
49. Vibert E, Azoulay D, Hoti E, et al. (2010) Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. Am J Transplant 10(1):129–137. https://doi.org/10.1111/j.1600-6143.2009.02750.x
50. Ldos SS, de Mattos AA, Zanotelli ML, et al. (2016) Alpha-fetoprotein level predicts recurrence after transplantation in hepatocellular carcinoma. Medicine (Baltimore) 95(3):e2478. https://doi.org/10.1097/md.0000000000002478
51. McIntire KR, Vogel CL, Primack A, Waldmann TA, Kyalwazi SK (1976) Effect of surgical and chemotherapeutic treatment on alpha-fetoprotein levels in patients with hepatocellular carcinoma. Cancer 37(2):677–683
52. Bruix J, Gores GJ, Mazzaferro V (2014) Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 63(5):844–855. https://doi.org/10.1136/gutjnl-2013-306627
53. Llovet JM, Ricci S, Mazzaferro V, et al. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4):378–390. https://doi.org/10.1056/NEJMoa0708857
54. Oka H, Saito A, Ito K, et al. (2001) Multicenter prospective analysis of newly diagnosed hepatocellular carcinoma with respect to the percentage of Lens culinaris agglutinin-reactive alpha-fetoprotein. J Gastroenterol Hepatol 16(12):1378–1383
55. Bertino G, Ardiri A, Malaguarnera M, et al. (2012) Hepatocellualar carcinoma serum markers. Semin Oncol 39(4):410–433. https://doi.org/10.1053/j.seminoncol.2012.05.001
56. Johnson PJ, Pirrie SJ, Cox TF, et al. (2014) The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomark Prev 23(1):144–153. https://doi.org/10.1158/1055-9965.epi-13-0870
57. Zhang Q, Zeng L, Chen Y, et al. (2016) Pancreatic cancer epidemiology, detection, and management. Gastroenterol Res Pract 2016:8962321. https://doi.org/10.1155/2016/8962321
58. Thomas A, Dajani K, Neoptolemos JP, Ghaneh P (2010) Adjuvant therapy in pancreatic cancer. Dig Dis 28(4–5):684–692. https://doi.org/10.1159/000320099
59. Ballehaninna UK, Chamberlain RS (2011) Serum CA 19-9 as a biomarker for pancreatic cancer-A comprehensive review. Indian J Surg Oncol 2(2):88–100. https://doi.org/10.1007/s13193-011-0042-1
60. Del Villano BC, Brennan S, Brock P, et al. (1983) Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA 19-9. Clin Chem 29(3):549–552
61. Poruk KE, Gay DZ, Brown K, et al. (2013) The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med 13(3):340–351
62. Berger AC, Meszoely IM, Ross EA, Watson JC, Hoffman JP (2004) Undetectable preoperative levels of serum CA 19-9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. Ann Surg Oncol 11(7):644–649. https://doi.org/10.1245/aso.2004.11.025
63. Halm U, Schumann T, Schiefke I, et al. (2000) Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer 82(5):1013–1016. https://doi.org/10.1054/bjoc.1999.1035
64. Ferrone CR, Finkelstein DM, Thayer SP, et al. (2006) Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol 24(18):2897–2902. https://doi.org/10.1200/jco.2005.05.3934
65. Humphris JL, Chang DK, Johns AL, et al. (2012) The prognostic and predictive value of serum CA199 in pancreatic cancer. Ann Oncol 23(7):1713–1722. https://doi.org/10.1093/annonc/mdr561

66. Cramer DW (2012) The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin N Am 26(1):1–12. https://doi.org/10.1016/j.hoc.2011.10.009
67. Mironov S, Akin O, Pandit-Taskar N, Hann LE (2007) Ovarian cancer. Radiol Clin N Am 45(1):149–166. https://doi.org/10.1016/j.rcl.2006.10.012
68. Aggarwal P, Kehoe S (2010) Serum tumour markers in gynaecological cancers. Maturitas 67(1):46–53. https://doi.org/10.1016/j.maturitas.2010.04.017
69. Duffy MJ, Bonfrer JM, Kulpa J, et al. (2005) CA125 in ovarian cancer: European Group on tumor markers guidelines for clinical use. Int J Gynecol Cancer 15(5):679–691. https://doi.org/10.1111/j.1525-1438.2005.00130.x
70. Soletormos G, Duffy MJ, Othman Abu Hassan S, et al. (2016) Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European group on tumor markers. Int J Gynecol Cancer 26(1):43–51. https://doi.org/10.1097/igc.0000000000000586
71. Cohen JG, White M, Cruz A, Farias-Eisner R (2014) In 2014, can we do better than CA125 in the early detection of ovarian cancer? World J Biol Chem 5(3):286–300. https://doi.org/10.4331/wjbc.v5.i3.286
72. Buys SS, Partridge E, Black A, et al. (2011) Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial. JAMA 305(22):2295–2303. https://doi.org/10.1001/jama.2011.766
73. Petrucelli N, Daly MB, Feldman GL (1993) BRCA1 and BRCA2 hereditary breast and ovarian cancer. In: Pagon RA, Adam MP, Ardinger HH, et al. (eds) *GeneReviews(R)*. Seattle: University of Washington, Seattle
74. Lu KH, Daniels M (2013) Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. Fam Cancer 12(2):273–277. https://doi.org/10.1007/s10689-013-9664-5
75. Bast RC Jr, Xu FJ, Yu YH, et al. (1998) CA 125: the past and the future. Int J Biol Mark 13(4):179–187
76. Rein BJ, Gupta S, Dada R, et al. (2011) Potential markers for detection and monitoring of ovarian cancer. J Oncol 2011:475983. https://doi.org/10.1155/2011/475983
77. Skates SJ, Jacobs IJ, Knapp RC (2001) Tumor markers in screening for ovarian cancer. Methods Mol Med 39:61–73. https://doi.org/10.1385/1-59259-071-3:61
78. Bast RC Jr, Badgwell D, Lu Z, et al. (2005) New tumor markers: CA125 and beyond. Int J Gynecol Cancer 15(Suppl 3):274–281. https://doi.org/10.1111/j.1525-1438.2005.00441.x
79. Bottoni P, Scatena R (2015) The role of CA 125 as tumor marker: biochemical and clinical aspects. Adv Exp Med Biol 867:229–244. https://doi.org/10.1007/978-94-017-7215-0_14
80. Funt SA, Hricak H, Abu-Rustum N, et al. (2004) Role of CT in the management of recurrent ovarian cancer. AJR Am J Roentgenol 182(2):393–398. https://doi.org/10.2214/ajr.182.2.1820393
81. Balestreri L, Bison L, Sorio R, et al. (2002) Abdominal recurrence of ovarian cancer: value of abdominal MR in patients with positive CA125 and negative CT. Radiol Med 104(5–6):426–436
82. Gu P, Pan LL, Wu SQ, Sun L, Huang G (2009) CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. Eur J Radiol 71(1):164–174. https://doi.org/10.1016/j.ejrad.2008.02.019
83. Bhosale P, Peungjesada S, Wei W, et al. (2010) Clinical utility of positron emission tomography/computed tomography in the evaluation of suspected recurrent ovarian cancer in the setting of normal CA-125 levels. Int J Gynecol Cancer 20(6):936–944. https://doi.org/10.1111/IGC.0b013e3181e82a7f
84. Han LY, Karavasilis V, Hagen T, et al. (2010) Doubling time of serum CA125 is an independent prognostic factor for survival in patients with ovarian cancer relapsing after first-line chemotherapy. Eur J Cancer 46(8):1359–1364. https://doi.org/10.1016/j.ejca.2010.02.012
85. Nowak M, Janas L, Stachowiak G, Stetkiewicz T, Wilczynski JR (2015) Current clinical application of serum biomarkers to detect ovarian cancer. Prz Menopauzalny 14(4):254–259. https://doi.org/10.5114/pm.2015.55887
86. Anastasi E, Marchei GG, Viggiani V, et al. (2010) HE4: a new potential early biomarker for the recurrence of ovarian cancer. Tumour Biol 31(2):113–119. https://doi.org/10.1007/s13277-009-0015-y
87. Moore RG, McMeekin DS, Brown AK, et al. (2009) A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 112(1):40–46. https://doi.org/10.1016/j.ygyno.2008.08.031
88. Nolen BM, Lokshin AE (2012) Multianalyte assay systems in the differential diagnosis of ovarian cancer. Expert Opin Med Diagn 6(2):131–138. https://doi.org/10.1517/17530059.2012.661711
89. Bast RC Jr, Skates S, Lokshin A, Moore RG (2012) Differential diagnosis of a pelvic mass: improved algorithms and novel biomarkers. Int J Gynecol Cancer 22(Suppl 1):S5–S8. https://doi.org/10.1097/IGC.0b013e318251c97d
90. Jacobs I, Oram D, Fairbanks J, et al. (1990) A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 97(10):922–929
91. Tingulstad S, Hagen B, Skjeldestad FE, et al. (1996) Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Br J Obstet Gynaecol 103(8):826–831
92. Timmerman D, Valentin L, Bourne TH, et al. (2000) Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the international ovarian tumor analysis (IOTA) group. Ultrasound Obstet Gynecol 16(5):500–505. https://doi.org/10.1046/j.1469-0705.2000.00287.x
93. Van Calster B, Van Hoorde K, Valentin L, et al. (2014) Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ 349:g5920. https://doi.org/10.1136/bmj.g5920
94. Ueno T, Tanaka YO, Nagata M, et al. (2004) Spectrum of germ cell tumors: from head to toe. Radiographics 24(2):387–404. https://doi.org/10.1148/rg.242035082
95. Milose JC, Filson CP, Weizer AZ, Hafez KS, Montgomery JS (2011) Role of biochemical markers in testicular cancer: diagnosis, staging, and surveillance. Open Access J Urol 4:1–8. https://doi.org/10.2147/oaju.s15063
96. Bosl GJ, Motzer RJ (1997) Testicular germ-cell cancer. N Engl J Med 337(4):242–253. https://doi.org/10.1056/nejm199707243370406
97. Germa-Lluch JR, del Muro XG, Maroto P, et al. (2002) Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish germ-cell cancer group (GG). Eur Urol 42(6):553–562 ((discussion 562-553))
98. Barlow LJ, Badalato GM, McKiernan JM (2010) Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol 7(11):610–617. https://doi.org/10.1038/nrurol.2010.166

99. Favilla V, Cimino S, Madonia M, Morgia G (2010) New advances in clinical biomarkers in testis cancer. Front Biosci (Elite Ed) 2:456–477
100. Smith HO, Berwick M, Verschraegen CF, et al. (2006) Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 107(5):1075–1085. https://doi.org/10.1097/01.AOG.0000216004.22588.ce
101. Parkinson CA, Hatcher HM, Earl HM, Ajithkumar TV (2011) Multidisciplinary management of malignant ovarian germ cell tumours. Gynecol Oncol 121(3):625–636. https://doi.org/10.1016/j.ygyno.2010.12.351
102. Oronsky B, Ma PC, Morgensztern D, Carter CA (2017) Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 19(12):991–1002. https://doi.org/10.1016/j.neo.2017.09.002
103. Modlin IM, Moss SF, Oberg K, et al. (2010) Gastrointestinal neuroendocrine (carcinoid) tumours: current diagnosis and management. Med J Aust 193(1):46–52
104. Modlin IM, Gustafsson BI, Moss SF, et al. (2010) Chromogranin A—biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol 17(9):2427–2443. https://doi.org/10.1245/s10434-010-1006-3
105. Pulvirenti A, Rao D, McIntyre CA, et al. (2018) Limited role of Chromogranin A as clinical biomarker for pancreatic neuroendocrine tumors. HPB (Oxford). https://doi.org/10.1016/j.hpb.2018.09.016
106. Nolting S, Kuttner A, Lauseker M, et al. (2012) Chromogranin a as serum marker for gastroenteropancreatic neuroendocrine tumors: a single center experience and literature review. Cancers (Basel) 4(1):141–155. https://doi.org/10.3390/cancers4010141
107. Frilling A, Modlin IM, Kidd M, et al. (2014) Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol 15(1):e8–21. https://doi.org/10.1016/s1470-2045(13)70362-0
108. Bajetta E, Ferrari L, Martinetti A, et al. (1999) Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer 86(5):858–865
109. Wang YH, Yang QC, Lin Y, et al. (2014) Chromogranin A as a marker for diagnosis, treatment, and survival in patients with gastroenteropancreatic neuroendocrine neoplasm. Medicine (Baltimore) 93(27):e247. https://doi.org/10.1097/MD.0000000000000247