Diagn Interv Radiol 2012; 18:171–182

REVIEW

Applications of PET-CT in patients with esophageal cancer

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ABSTRACT
Although esophageal cancer is not among the common cancers as prostate, lung, breast, or colon malignancies, it has an exceedingly high mortality rate, with its incidence close to the cancer-specific mortality. Currently, the only potentially curative treatment is surgery. Unfortunately, surgical treatment is extensive and may have significant morbidity and mortality related with it. Given these facts, selection of patients who are amenable to surgical treatment is of utmost importance. Conventional morphology based cross-sectional imaging modalities are extremely helpful for pre-surgical evaluation and follow-up of these patients, however, they have very well-known limitations. Positron emission tomography-computed tomography (PET-CT) is a relatively new, highly promising molecular imaging technique which may overcome some of the fundemental limitations of these conventional cross-sectional modalities in the pre-surgical evaluation and follow-up of these patients. In this review, we evaluated the applications of PET-CT in patients with esophageal cancer.

Key words: • *PET scan* • *cancer* • *esophagus*

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Received 21 February 2011; revision requested 17 March 2011; revision received 13 April 2011; accepted 19 April 2011.

Published online 23 December 2011
DOI 10.4261/1305-3825.DIR.4309-11.1

The esophagus is a muscular tube that begins at the level of the cricopharyngeus muscle in the neck and terminates after joining the cardia of the stomach in the abdomen. Along its relatively long course, it traverses the neck and the whole chest, and passes through the right crus of the diaphragm. In order to simplify its anatomy, it has been divided into three different segments; the cervical, thoracic, and abdominal segments (Fig. 1). The cervical esophagus comprises the uppermost part of the esophagus and is approximately 6 cm in length. The thoracic esophagus is the longest portion (approximately 25 cm in length) and is located in the posterior mediastinum. The abdominal portion is the shortest part of the esophagus and measures approximately 4 cm in length.

Esophageal cancer is not as common as prostate, lung, breast, or colon malignancies but has an exceedingly high mortality rate. In the USA in 2006, esophageal cancer was the 15th most common cancer, with an estimated 14 550 cases, but it had the highest mortality rate, with an estimated 13 770 deaths (1).

Epidemiology and pathology

There is significant variation in the incidence of esophageal cancer as a function of geographical location. There is a ten-fold difference in incidence rates between countries with a low incidence in the USA, and a high incidence in China and Iran (2). This marked variation in incidence rates suggests that environmental factors are significant contributing factors in the etiology of this malignancy. The regions that have the highest incidences in the world are located in southern and eastern Africa, in addition to the central Asian belt that passes from Turkey through countries like Iraq, Iran, and Kazakhstan and that extends into northern China. The incidence in high-risk areas may be up to 100 cases/10 000 people per year in comparison to 5–10 cases/10 000 people per year in developed Western countries (2). The high-risk areas are characterized by high rates of poverty and poverty-related illnesses, and data from the USA also reveal that the incidence of this disease tends to decrease with increasing wealth and accessibility to health care (1–3).

Squamous cell carcinoma (SCC) is the most common form of esophageal cancer, and it is among the top ten most common cancers globally; hence, this disease poses an important public heath care problem. The male:female ratio of people who developed this disease is 3:1, except in high-risk areas wherein the distribution is more equal, which likely represents an equal exposure of both genders to predisposing factors (4). Pathologically, SCC is thought to develop through a multi-step process of basal hyperplasia that derives from chronic esophagitis, and an increasing severity of dysplasia to the point of invasion (5). The risk

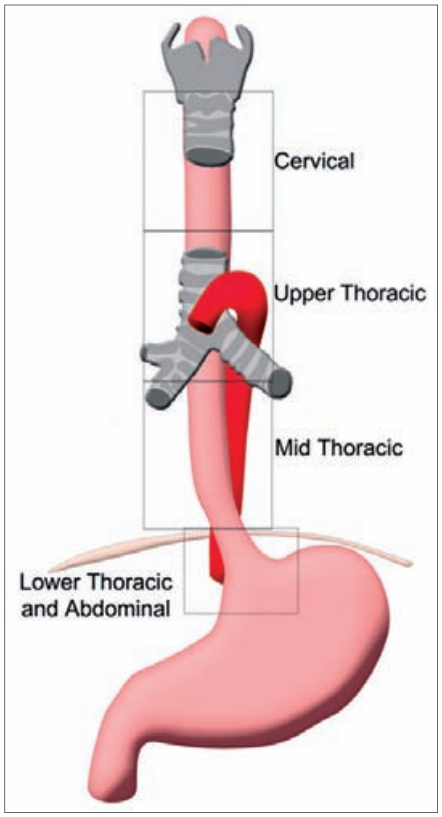


Figure 1. Schematic drawing of the anatomic segments of the esophagus.

of carcinoma increases with the degree of dysplasia. The relative risk for developing cancer has been reported to be 2.9 for mild dysplasia, 9.8 for moderate dysplasia, 28.3 for severe dysplasia, and 34.4 for carcinoma in situ at 13 years follow-up (6). Approximately 50%–60%, 30%, and 10%–20% of SCCs occur in the middle third, lower third, and upper third of the esophagus, respectively.

Adenocarcinoma is the second most common cancer of the esophagus. The most significant risk factor for adenocarcinoma is Barrett's esophagus. Rarely, adenocarcinomas arise from heterotopic gastric tissue or the submucosal glands. Adenocarcinomas that arise from these rare locations and Barrett's-associated adenocarcinomas share similar morphologies (7–10). The last 30 years have seen a dramatic decrease in the incidence of non-cardia gastric cancer and a decline in the incidence of SCC of the esophagus (11). Over the same period of time, the incidence of adenocarcinoma of the lower esophagus, which was once a rare disease with an incidence of <1 case/100 000 people, has risen more rapidly than any other malignancy in the Western world, and in some reports, its incidence has been reported to be exceeded that of SCC (12). The relative risks for developing esophageal adenocarcinoma are 29.8 for Barrett's esophagus, 4.5 for reflux esophagitis, and 3.1 for gastroesophageal reflux without Barrett's esophagus or reflux esophagitis (13). A patient with Barrett's esophagus has a 5% lifetime risk of developing esophageal adenocarcinoma. The dysplasia that develops in the progression to adenocarcinoma is related to the duration of the reflux disease and the presence of a hiatal hernia (14–16).

The role of PET-CT in the diagnosis and staging of esophageal cancer

Technique

Positron emission tomography-computed tomography (PET-CT) is a relatively new imaging modality that can detect functional abnormalities before any structural changes have taken place. Its role in the primary diagnosis and follow-up of oncology patients is continuing to increase because of the emergence of new data, further development of the technique and accumulation of experience in the imaging community. PET-CT is basically an integrated scanner that combines both CT and PET capabilities into two sequential gantries, thereby avoiding the need for patient transfer between the PET and CT machines. Using this co-registration, motion artifacts can also be minimized, and the incidence of misregistration problems and diagnostic confusion can be significantly decreased. The pre-imaging work-up of patients is extremely important before a PET-CT study, and fasting for at least six hours before the PET-CT procedure is recommended. PET images are acquired in the two- or three-dimensional mode while the patient performs shallow breathing in a quiet and non-distracting environment for 3 min per bed position approximately 60–90 min after the intravenous (IV) administration of 300–400 MBq of 18-F-fluoro-2-deoxy-D-Glucose (FDG). FDG is currently the most commonly used radiopharmaceutical in PET imaging and differentiates physiologically active tissues from malignant tumors based on enhanced glucose transport in the tumors. FDG is an analog of glucose, and both FDG and glucose can be taken up by cells via glucose transporters (GLUT) that are located in the cell membranes. Both molecules can be phosphorylated by hexokinase, which is an enzyme in the glycolysis circle. Unlike glucose, FDG does not cross the cell membrane and gets trapped inside of the cell, making it able to be visualized. Not surprisingly, the degree of FDG uptake is directly proportional to the number of GLUT molecules that are in the cell membrane. The tendency of malignant cells to express abundant GLUT-1 is the key to the amount of uptake, and an abundance of these transporters may be a good predictor of the malignant potential of these cells and may correlate with the invasive potentials of tumors and the observed poor survivals in some types of cancer. Hexokinase levels are also increased in some cancers, including esophageal cancers, which result in high FDG uptake levels. Increased blood flow and hypoxia may also increase the level of FDG uptake (17, 18). PET-CT images may be acquired at least one hour after the FDG injection. A delay in the time of imaging may improve the tumor-to-background signal ratio, although the associated increased decay of the radioactive material and subsequent decrease in image quality is the major downside. High blood glucose levels may interfere with imaging due to competition with FDG at the receptor level, that is, imaging in patients who have high blood glucose levels may decrease the tumor-to-background signal ratio. During the time between the injection and image acquisition, the patient should be kept in a quiet and warm environment.

Attenuation correction is performed in order to improve the anatomic localization and quantification of abnormal FDG uptake. The use of oral and IV contrast agents for the CT component of the imaging also increases the diagnostic potential of the examination. With the implementation of oral and IV contrast agents, invaluable morphological information can be extracted that may be extremely helpful in interpreting the information that is acquired from the PET part of the examination. The data that are acquired from the PET images are reconstructed using standard reconstruction algorithms that incorporate ordered subset expectation maximization. The data that are obtained from the PET may be

quantitatively, semi-quantitatively, or qualitatively analyzed. The most commonly used parameter for FDG uptake quantification is the standardized uptake value (SUV). This value is the ratio of injected radioactivity to body weight (the mean measured activity in the volume of interest [millicuries per milliliter]/injected dose of FDG [millicuries] per gram of body weight). Although the SUV is reliable for comparisons in the same patient on the same scanner using standard imaging protocols, the same values might not be applicable in different scanners.

The combination of multidetector CT technology with PET scanning allows the display of overlaid images in multiple different planes, which may greatly help correct the anatomic localization of abnormal FDG uptake foci. PET-CT has a higher diagnostic accuracy in comparison to CT alone and has the potential to decrease unnecessary surgery, which is highly extensive with considerable morbidity and mortality, by detecting metastases that are occult to CT (19, 20).

Staging

The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have staged esophageal cancers using the TNM system, wherein T categorizes the depth of invasion into or through the esophageal wall, N denotes invasion into the regional lymph nodes, and M indicates distant metastases (21).

The accurate staging of esophageal carcinoma is of paramount importance because the prognosis and treatment modalities and the sequence of different treatment modalities are highly variable as a function of the disease stage. Unfortunately, up to 50% of patients presents with advanced disease with multiple areas of nodal involvement and distant metastases. Patients who have limited disease may be treated with surgical methods after the administration of chemoradiotherapy. Patients with distal metastases are not surgical candidates and should be treated with chemoradiotherapy.

T stage

The T indicator is determined according to the extent of invasion into or through the esophageal wall. The T stage has a direct impact on the patient's stage, the likelihood of metastatic nodal disease, and poor outcome (Fig. 2) (22, 23). The location of the primary tumor does not have a direct correlation with the prognosis of the tumor but may influence the management strategies and determination of the location of the locoregional lymph nodes.

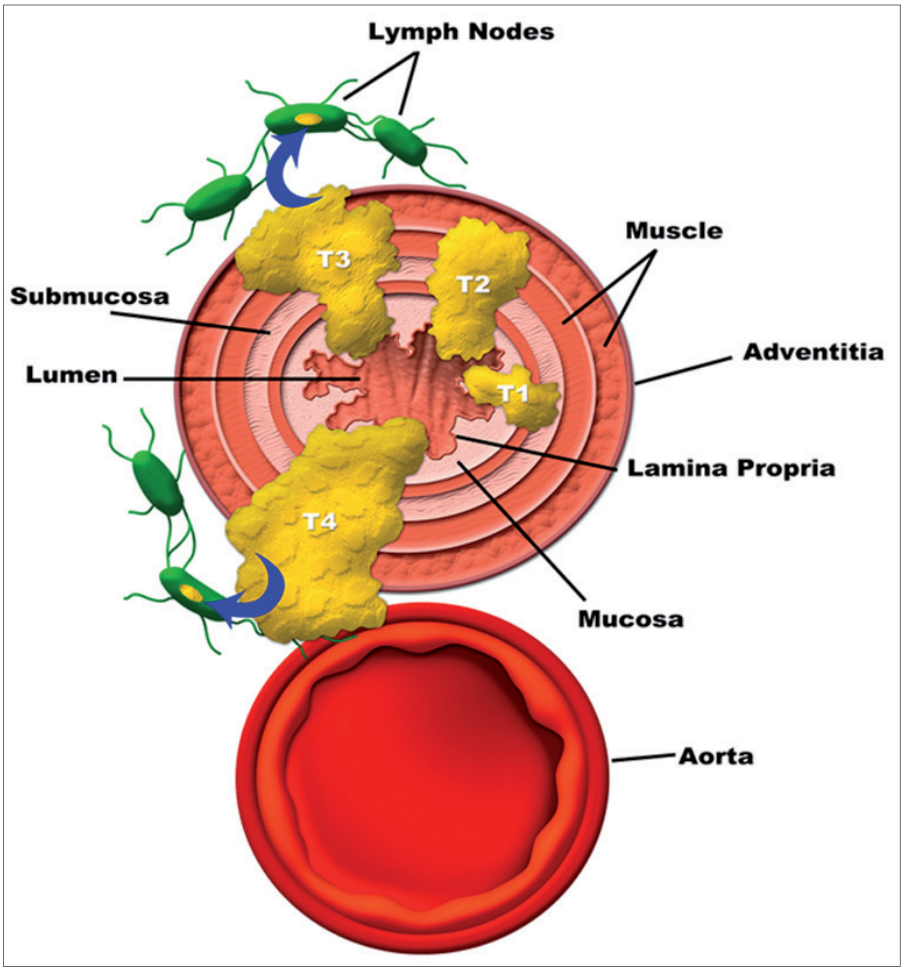
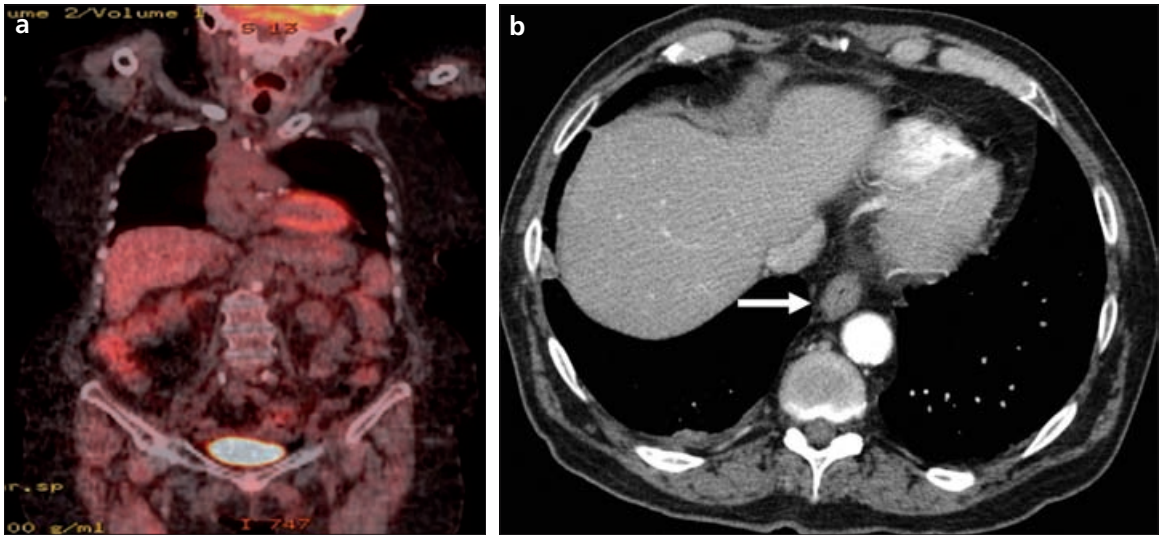


Figure 2. Schematic drawing that depicts the T staging of esophageal tumors.

In the case where the primary tumor is confined to the esophageal wall (T1-T2), surgical resection is possible. A T3 determination denotes tumor extension into the periesophageal adventitia, which may still be potentially resectable, although resection is typically combined with another treatment modality. In the case of the T4 classification, the tumor has already infiltrated adjacent structures, such as the aorta, diaphragm, liver, and pancreas, and is almost always inoperable.

Both adenocarcinomas and SCCs demonstrate high FDG avidities, although SCC is more FDG-avid than adenocarcinomas (Fig. 3) (24–26). False positive uptakes may be caused by esophagitis or post-dilatation of the esophageal strictures (Fig. 4). False negative results may be encountered in small tumors that are below the PET resolution.

PET-CT has limited utility in the T staging of esophageal cancers; however, signs of adjacent organ infiltration can be detected in some patients (27). Endoscopic ultrasonography (EUS) is the imaging modality of choice for the evaluation of T staging because of its superior resolution (27). Diagnostic-quality CT that is done as a part of the PET/CT imaging procedure has the potential to increase the accuracy of the evaluation of the primary tumor and adjacent organ invasion. After the treatment of the primary tumor, the diagnosis of invasion of adjacent anatomical structures may become even more challenging, and confident decisions can be made only with surgery in such patients.



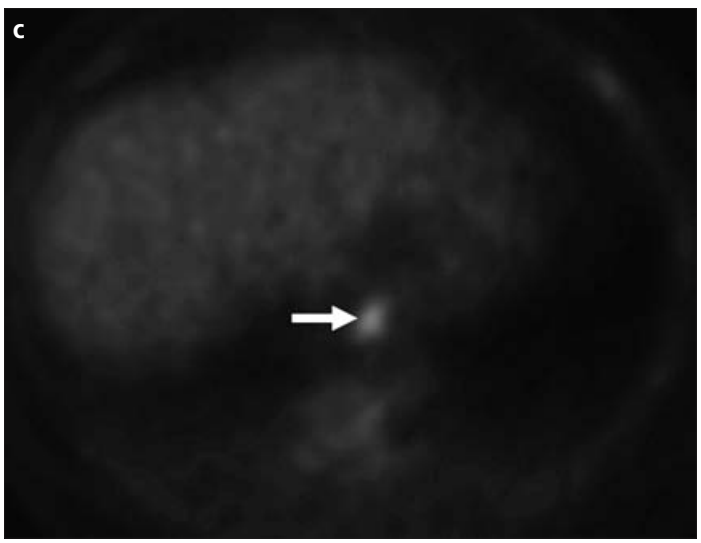


Figure 3. a–c. Biopsy-proven adenocarcinoma of the distal esophagus in a 64-year-old man. There is no abnormal FDG uptake in the fused coronal images **(a)**. There is no significant mass lesion in the distal esophagus on the axial CT scan **(b,** *arrow***)**. The axial PET image of another patient with biopsy-proven adenocarcinoma of the lower esophagus indicates only mild FDG uptake in the tumor location **(c,** *arrow***)**.

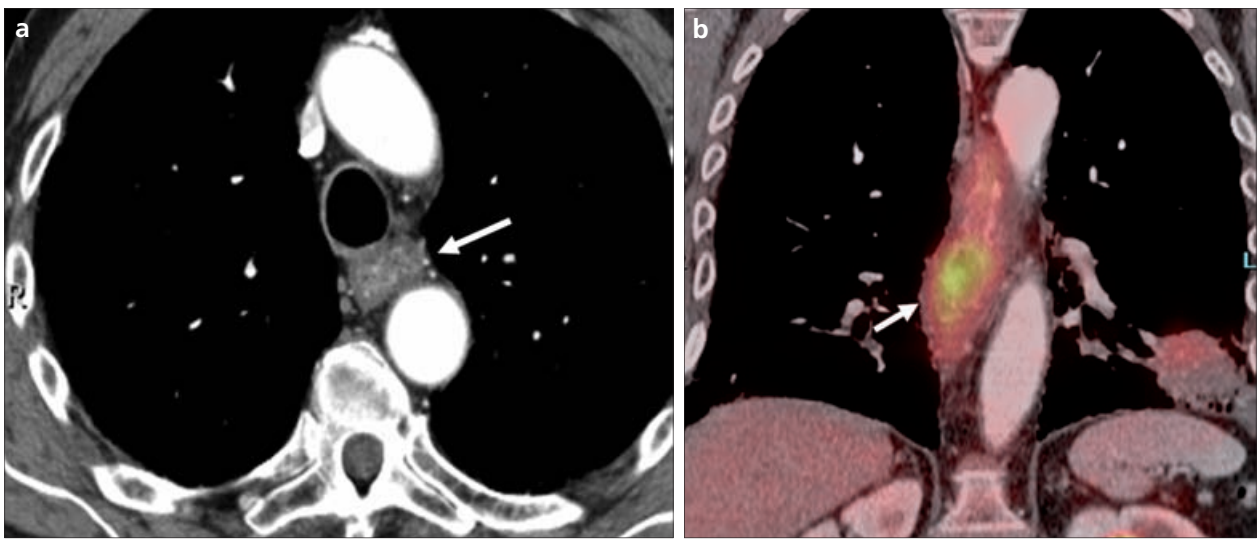


Figure 4. a, b. Biopsy-proven diffuse esophagitis in a 44-year-old man with lymphoma who was treated with irradiation of the chest. On the axial CT scan, the diffuse thickening of the cervical esophagus is noted **(a,** *arrow***)**. Coronal fused PET-CT image of the patient shows diffuse FDG uptake in the esophagus, most markedly in the distal esophagus **(b,** *arrow***)**.

N stage

The lymphatic drainage of the esophagus is rich and highly unpredictable. The location of the primary tumor is not a reliable predictor of which local node stations would be affected during the course of the disease. There may be nodal involvement in the abdomen in 12% of upper esophageal tumors, whereas cervical lymph nodes are affected in 27% of lower esophageal tumors (28).

In the staging of the nodal metastases, N0 denotes no malignant lymph nodes, whereas N1, N2, and N3 denote 1–2, 3–6, and ≥7 positive regional lymph nodes, respectively (21). The locoregional lymph nodes encompass any paraesophageal lymph nodes from the cervical nodes down to the celiac nodes.

For tumors in the cervical esophagus (Fig. 5), scalene, internal jugular, and supraclavicular lymph nodes also encompass the locoregional lymph nodes. For tumors that are located in the thoracic esophagus, they include periesophageal and subcarinal lymph nodes (Fig. 6). For tumors that originate from the gastroesophageal junction (Fig. 7), the locoregional lymph nodes consist of the lower periesophageal and pulmonary ligament lymph nodes, diaphragmatic lymph nodes (on the dome of the diaphragm or in the retrocrural regions), pericardial lymph nodes (immediately adjacent to the gastroesophageal junction), left gastric lymph nodes, and celiac lymph nodes (21).

Any lymph node metastasis that occurs outside of these stations is regarded as a distant metastasis and portends a dismal prognosis.

Nodal staging has a profound effect on the survival rates. The five-year survival of patients with negative lymph node invasion is 42%–72%, compared to 10%–12% in node-positive patients (29). Traditionally, size criteria have been used to differentiate benign lymph nodes from their malignant counterparts. The threshold for subdiaphragmatic lymph nodes was 8 mm, and nodes between 6 and 8 mm in size have been considered to be indeterminate (30); however, these size criteria may be extremely unreliable in the context of esophageal cancer. In a recently published study that consisted of 1196 lymph nodes from 40 patients with esophageal cancer, the average

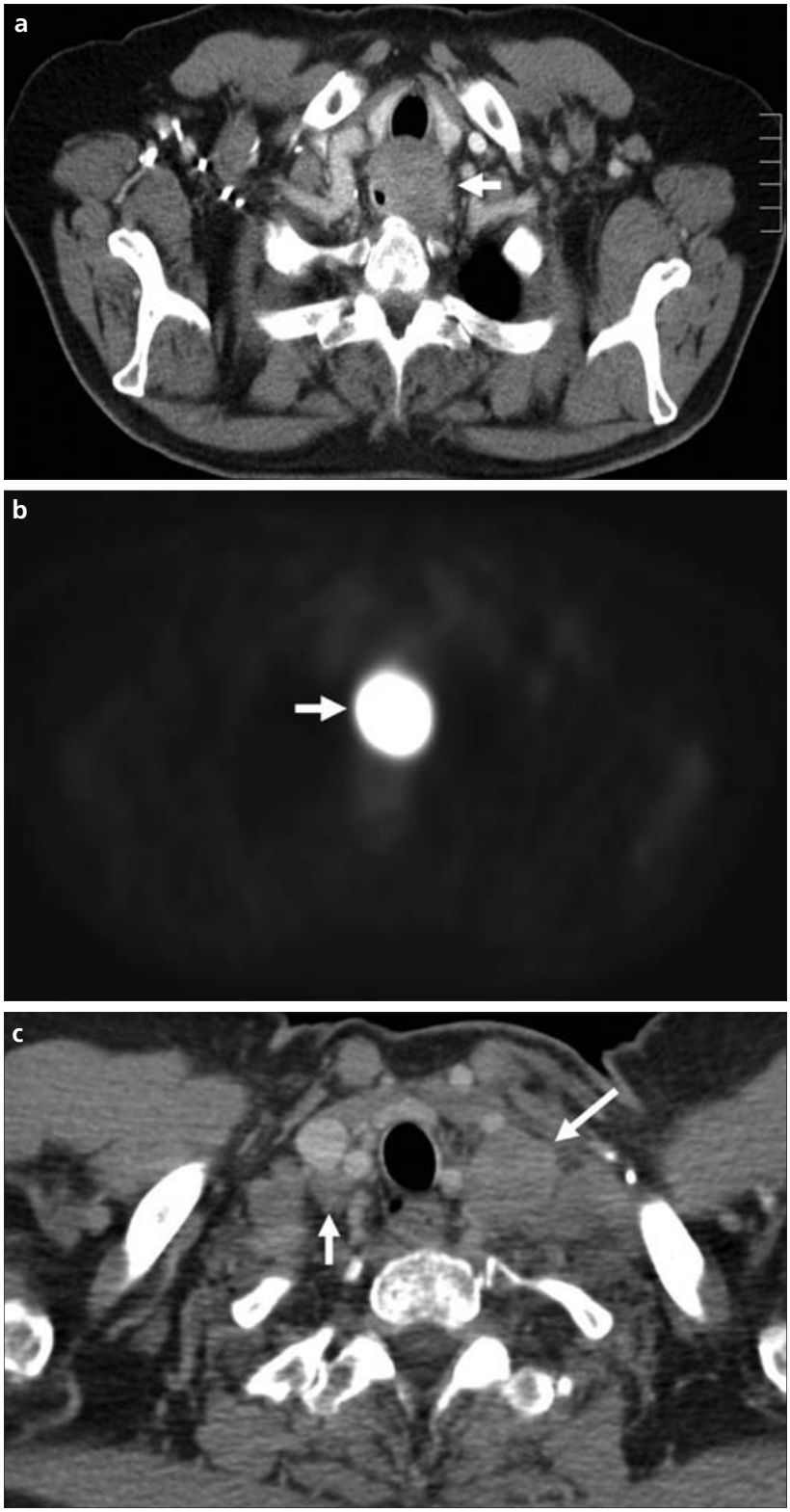


Figure 5. a–c. Biopsy-proven squamous cell cancer of the cervical esophagus. Axial contrast-enhanced CT indicates an asymmetric mass in the cervical esophagus with invasion of the posterior wall of the trachea **(a,** *arrow***)**. Note the corresponding intense FDG uptake on the axial PET image **(b,** *arrow***)**. The multiple cervical metastatic lymph nodes **(c,** *arrows***)** are seen on an axial CT image.

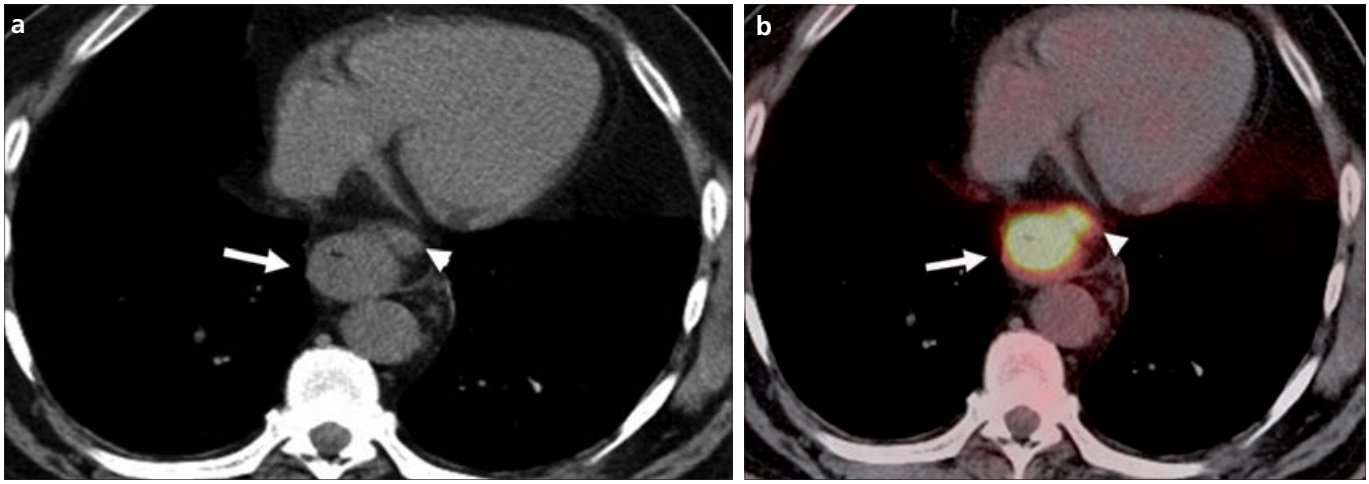


Figure 6. a, b. Biopsy-proven squamous cell carcinoma of the thoracic esophagus in a 67-year-old man. On unenhanced axial CT image, a mass in the thoracic esophagus *(arrow)* and the small periesophageal lymph node *(arrowhead)* are clearly visible **(a)**. Both the mass *(arrow)* and the periesophageal lymph node *(arrowhead)* are intensely FDG-avid, confirming the metastatic nature of the small periesophageal lymph node **(b)**.

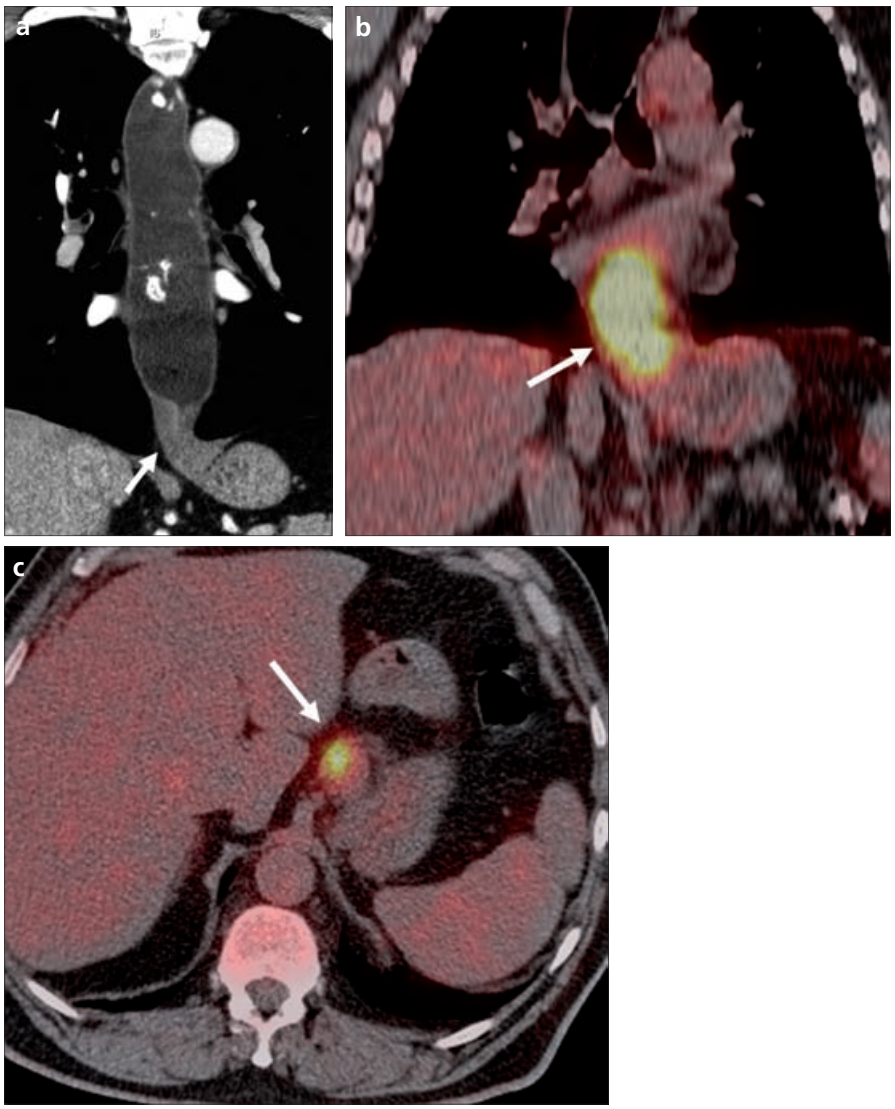


Figure 7. a–c. Biopsy-proven squamous cell carcinoma of the thoracic esophagus in a 62-year-old woman. A coronal reformatted CT image clearly indicates an obstructing mass **(a,** *arrow***)** in the distal esophagus. A fused PET-CT image in the coronal plane indicates intense FDG uptake **(b,** *arrow***)** in the distal esophagus. The small perigastric lymph node in the gastrohepatic ligament also shows intense FDG uptake **(c,** *arrow***)** on a fused PET-CT image in the axial plane.

size of the 129 metastasis-positive lymph nodes was 6.7±4.2 mm, whereas the average size of tumor-free lymph nodes was 5.1±3.8 mm. Additionally, only 9.3% of all resected lymph nodes measured 10 mm or more in maximal diameter. In the same study, no significant correlation could be found between lymph node size and nodal metastasis (31). Therefore, it is clear that conventional imaging has significant limitations, and the reformatting capability of modern MDCT may be helpful in recognizing the involved nodes by CT and fused images (27).

The combined use of EUS and CT is the classical way of staging in patients with esophageal cancer; however, the results of these modalities in comparison to those of PET imaging are conflicting and sometimes confusing, and, thus, it is difficult to draw solid conclusions. The poor results of EUS have been attributed to tight stenosis in the esophagus and secondary incomplete evaluation, whereas PET has been reported to indicate false positives in some patients with chronic lung disease or previous tuberculosis (32, 33). Small-volume diseases and lymph node obscuration by large tumors are among the causes of false negativity in PET imaging; however, with the use of fusion imaging in combination with the superior resolution and multiplanar imaging of MDCT, these drawbacks may be eliminated, and better results can be achieved. PET-CT has also been reported to be superior to stand-alone PET-only imaging for nodal staging (34). According to the

literature, it appears that there is not any single imaging modality that is clearly superior to all of the available methods, and there will always be a need for combined imaging in order to realize better accuracy in the staging of esophageal cancer. PET-CT appears to be reliable for the evaluation of lymph node metastases in lymph node stations that are far from the primary tumor site but may be limited for locoregional lymph nodes, particularly when they are in close proximity to the primary tumors. In these cases, MDCT and EUS may be extremely helpful in alerting the surgeon to possible metastatic, non-enlarged lymph nodes. In the case of EUS, the biopsy of adjacent lymph nodes may also be possible in selected cases.

Finally, any practicing radiologist should be aware of the fact that esophageal cancers tend to metastasize to lymph nodes, even in T2 disease, at a rate of 60%. This percentage increases to up to 80% in T3 and T4 disease (35), and this characteristic propensity of esophageal tumors is among the major causes of its discouraging treatment results.

M stage

Patients with distant metastases, either in the lymph nodes or solid organs, have a very dismal prognosis, and surgery should not be attempted in these patients. The 30-month survival rates decrease significantly from 60% in patients with local disease to 20% in those with metastatic disease. Unfortunately, metastatic disease is common in the setting of esophageal cancer and is detected in 20%–30% of patients at the time of the diagnosis (25). According to the most recent AJCC classification, the M1a and M1b subclassifications have been eliminated, and distant metastases are simply reclassified as M0 (no distant metastasis) and M1 (distant metastasis) (21).

PET-CT is extremely useful for the detection of metastatic disease that may not be identifiable with other imaging modalities (Fig. 8). PET-CT has been shown to improve pre-operative staging (36, 37). A meta-analysis that was published in 2008 reported that PET has a 71% sensitivity and a 93% specificity in the detection of distant metastases in comparison to 52% and 91% for CT, respectively (38). Another study has revealed that PET detected distant metastasis in 20% of patients who were originally deemed to be amenable to surgical resection (39). This unique ability of PET has a significant impact on patient management. For example, a recent multicenter, prospective study observed that additional disease sites were detected in 41% of patients from a group of 129 patients, prompting significant changes in the disease management strategies in 38% of the subjects (Fig. 9) (40). The identification of an additional occult metastasis with PET is also not rare and has been reported in 8% of patients that have been scanned for the staging of esophageal cancer (41). The most common sites of visceral metastases are the liver, lung, bones, and adrenal glands, whereas metastases to the brain, subcutaneous tissues, thyroid gland, skeletal muscles, and pancreas are rare (Fig. 10) (27). It is important to look at the common metastatic sites in PET-CT images so as to not overlook subtle and small metastatic foci. Diagnostic-quality CT images are also useful for additional information in case of uncertainties in the PET images, and fused images are also extremely useful, again, in the localization of subtle metastases and also for guiding a potential percutaneous biopsy. As mentioned above, a synchronous focus can be detected in 8% of the patients, and this should also be kept in mind during the interpretation

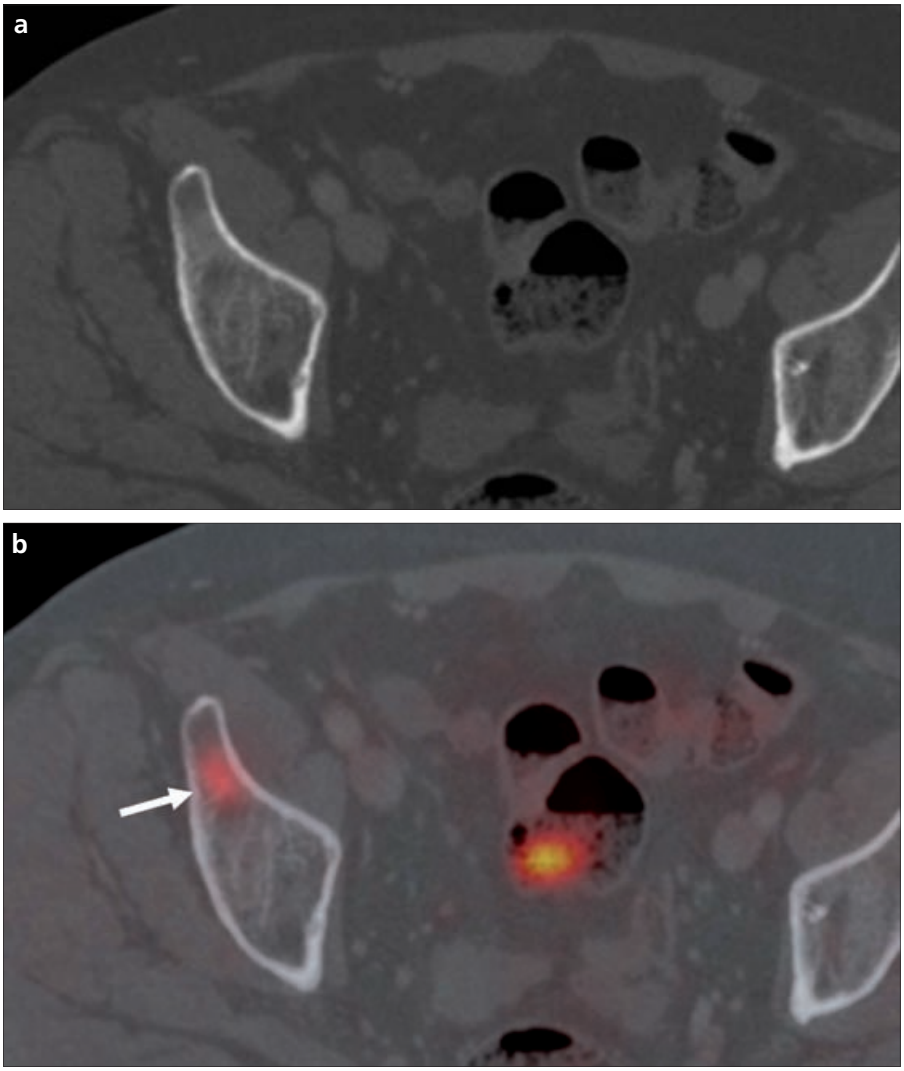


Figure 8. a, b. Biopsy-proven esophageal cancer metastasis in the right iliac bone in a 53-year-old man. An axial CT image on bone windowing only shows questionable sclerotic foci, which are indeterminate with regard to metastatic cancer **(a)**; however, an axial fused PET-CT image indicates a corresponding intense focus of FDG uptake **(b,** *arrow***)** in the right iliac bone that greatly provides increased confidence in making the correct diagnosis of a bony metastasis.

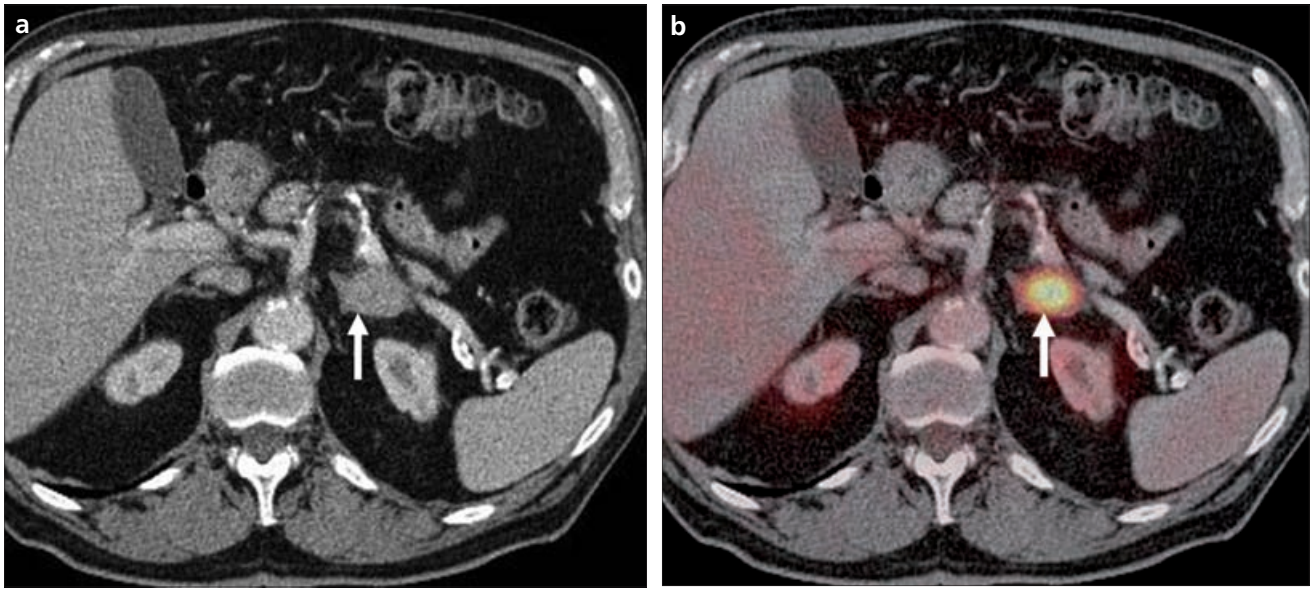
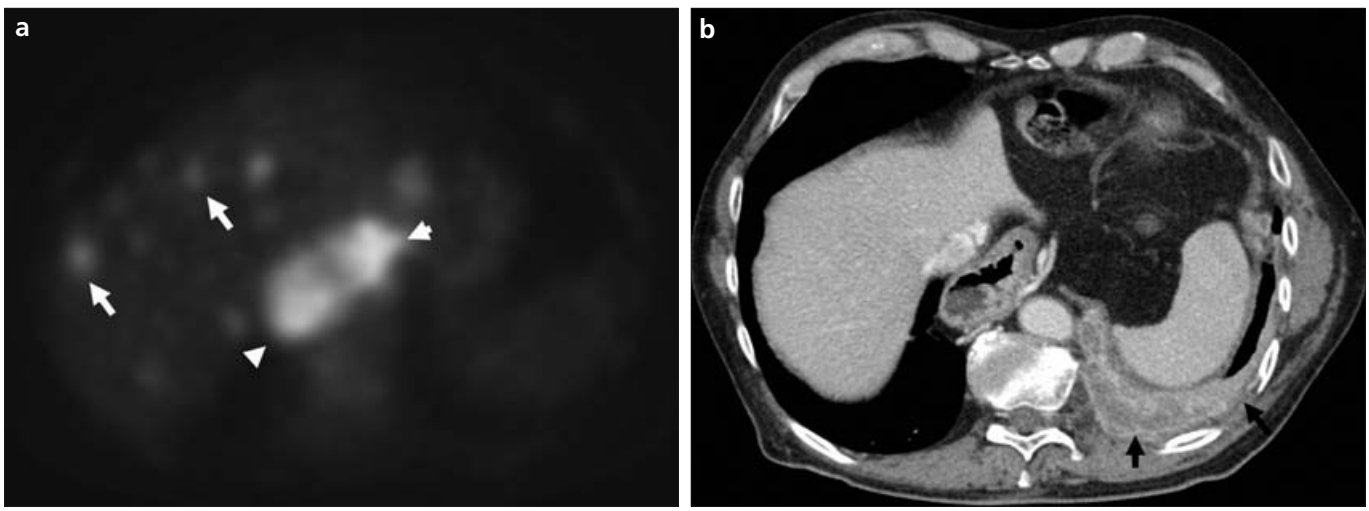


Figure 9. a, b. A 64-year-old man with squamous cell cancer of the thoracic esophagus. An axial CT image shows a focal mass lesion in the left adrenal gland **(a,** *arrow***)**. This lesion shows intense FDG uptake, as shown on the fused PET-CT image **(b,** *arrow***)**, which was confirmed to be a metastatic focus on a subsequent biopsy. This was the only site of metastatic disease in this patient at the time of the diagnosis, which rendered the patient unresectable.



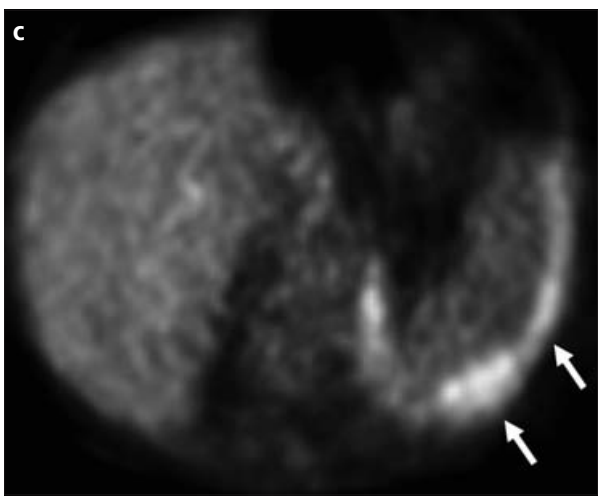


Figure 10. a–c. Metastasis to the liver and pleura in two different patients. An axial PET-CT image **(a)** of a 58-year-old man with newly diagnosed squamous cell cancer in the distal esophagus *(arrowheads)* and multiple liver metastases *(arrows)*. Axial CT **(b)** and PET **(c)** images of a 69-year-old male with pleural metastasis from squamous cell cancer of the esophagus 10 months after Ivor-Lewis surgery **(b, c,** *arrows***)**. One should be aware that a similar FDG appearance on PET might also be normally present after talc pleurodesis.

process; hence, CT images may be helpful in the identification of morphological clues for such unsuspected primaries (Fig. 11).

Assesment of the treatment response

Preoperative chemoradiotherapy (CRT) has become a common practice in both localized (for downgrading) and metastatic disease. The evaluation of the response to treatment is, therefore, of utmost importance to future treatment guidance. A maximum response to neoadjuvant chemotherapy is a good prognostic indicator but is unusual and is typically only observed in 15%–30% of subjects, in whom the resultant three-year survival is

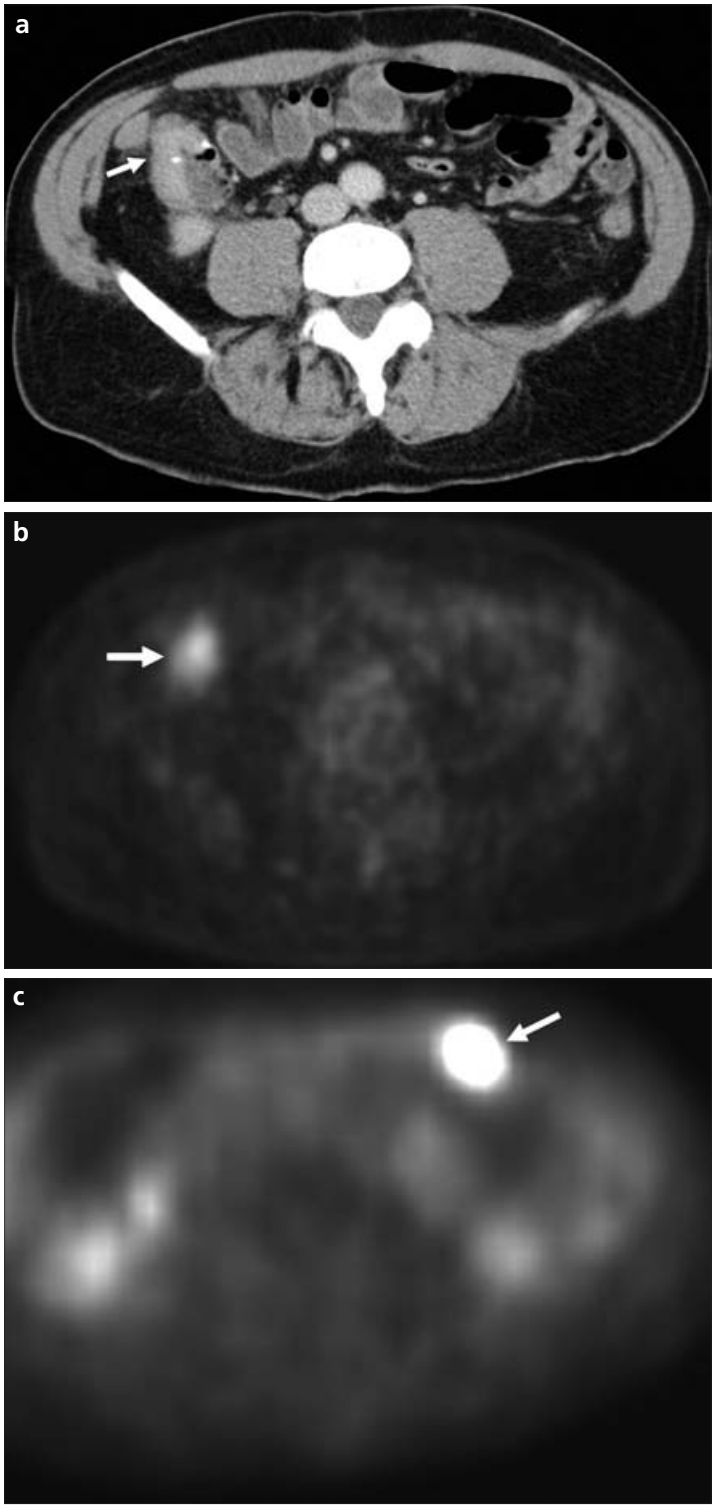


Figure 11. a–c. CT and PET images of unsuspected, biopsy-proven recurrence in the resection margin in a 71-year-old male with newly diagnosed squamous cell cancer of the esophagus. The patient has a remote history of resection of the adenocarcinoma of the colon **(a, b,** *arrows***)**. The incidentally detected mesenteric implant from the colon cancer (biopsy proven) is also noted **(c,** *arrow***)**.

approximately 60% (42). In addition, the patient response to chemotherapy may also be used as a prognostic indicator. The SUV was also evaluated as a predictive indicator for chemotherapy. In a study by Levine et al. (43), which evaluated SUVs in preoperative CRT, a pre-surgical SUV maximum of greater than 15 was associated with a good response in 77.8% of the cases, whereas patients with preoperative SUVs of less than 15 responded less commonly (only 24.4%). A decrease in the SUV of greater than 10 following treatment was also found to be associated with a significant response in 71% of the patients, which was significantly more than the 33% of patients who experienced a significant response when the decrease in the SUV was less than 10 (Fig. 12) (43). The identification of tumor response is important for the implementation of other treatment modalities or surgical planning.

PET-CT is also very helpful in the evaluation of treatment response in comparison to those achievable using CT and EUS due to its unique ability to quantify metabolic response. Both CT and EUS rely on morphological changes and may give false negative results in the case of fibrosis or necrosis in the index lesion or in metastases. The metabolic response may well precede the morphological response. It has been demonstrated that the metabolic response closely correlates with the histopathological response, and the three-year survival is far better in responders compared to non-responders (70% vs. 35%, respectively) (44); however, in another study that primarily focused on adenocarcinomas, PET findings were evaluated before and one-week after the start of the CRT, and the authors did not find any difference in SUV reduction between responders and non-responders. The authors suggested that radiotherapy, which induces inflammation, might be masking the decrease in the SUV, and they recommended that early assessment with PET should be restricted to patients who are undergoing chemotherapy without radiotherapy (45). PET may also be useful for the detection of local recurrences; however, esophagitis, recent biopsy, or early post-surgical changes may mimic recurrence (Fig. 13).

The most important drawback of PET studies is the difficulty in comparing different studies. The non-reproducibility of SUVs between different studies even in the same patient is the major underlying reason for this drawback. FDG uptake quantification depends on multiple technical and patient-related factors, and, therefore, criteria that have been developed in one center in the setting of a carefully planned and

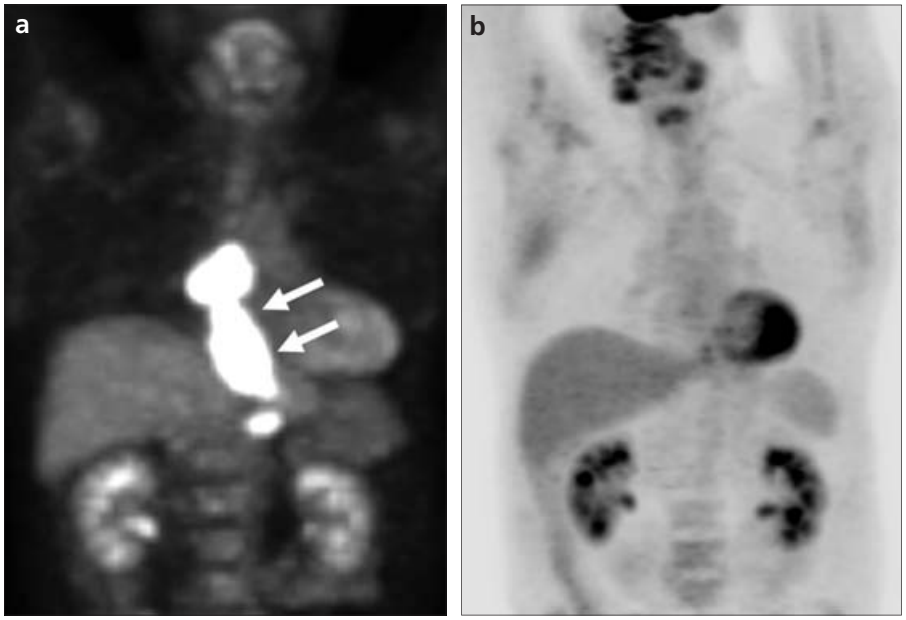


Figure 12. a, b. Pre- **(a)** and post-chemoradiotherapy **(b)** treatment coronal PET images of a 75-year-old patient with extensive squamous cell cancer of the esophagus. The post-treatment coronal PET image indicates an excellent response to treatment. The *arrows* **(a)** indicate the primary tumor.

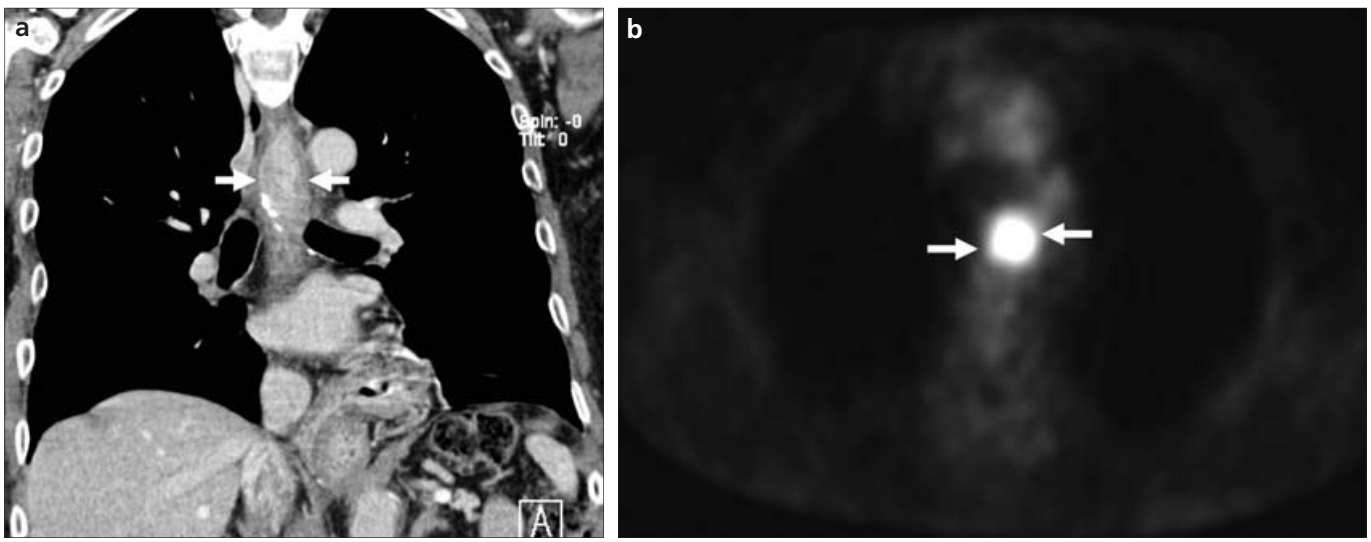


Figure 13. a, b. Biopsy-proven local recurrence at the anastomosis site eight months after surgery in a 75-year-old patient with squamous cell cancer. A coronal reformatted CT image indicates diffuse soft-tissue thickening **(a,** *arrows***)**. An axial PET-CT image shows intense FDG uptake at the same site **(b,** *arrows***)**, which is highly indicative of recurrence.

controlled study may not be applicable to routine clinical practice elsewhere (46, 47). Given all of these reasons, SUV measurements may sometimes be misleading, causing confusion and even misdirection. Respiratory motion artifacts may pose problems, and it has been reported that the maximum SUV may show variations as high as 30%–50% in some patients at the level of the diaphragm (48).

The esophagitis that develops after radiation therapy may also be an important confounding factor on PET. The degree of inflammation and ulceration in the esophagus increases with the duration and dose of radiotherapy and may be observed in 69% of patients after 34 days of chemotherapy and associated radiotherapy (47). The evaluation of these patients in the first two weeks before the development of radiation esophagitis has been, therefore, recommended; however, to the best of our knowledge, there is no currently available data regarding this situation (27). Endoscopic studies and mucosal biopsies during these endoscopies may falsely cause FDG uptake that may be confused with recurrence or residual disease (47), and, therefore, PET-CT imaging has been recommended prior to endoscopy in order to prevent this confusion (27).

Although there is currently a lack of comprehensive and robust research, the medical and imaging literature has demonstrated the promising role of PET in the prediction and differentiation of responders from non-responders in several malignancies (48).

As a conclusion, PET and more recently, PET-CT are being increasingly used for patient diagnosis, initial staging and, potentially more importantly, in the follow-up and treatment response of several malignancies, including esophageal cancer. Another

potential application of PET may be the selection of potential responders for different treatment modalities.

The main role of PET and PET-CT in esophageal cancer is not the primary diagnosis of the disease. EUS, CT, and endoscopy are the primary diagnostic tools. PET is extremely useful during the initial diagnostic work-up in the selection of patients for surgery, given its unique ability to detect non-enlarged metastatic lymph nodes from non-affected ones. Esophageal cancer is notorious for its early lymph node metastases, which is among the top reasons for failure of surgical treatment. The detection of these lymph nodes prior to treatment may prevent unnecessary major surgery, which has significant morbidity and mortality; however, one should bear in mind that the lymph nodes that are in close proximity to the primary lesion may be easily missed on PET because of the relatively low resolution of this modality. In these patients, diagnostic-quality CT images that are acquired as a part of the PET-CT imaging process should be meticulously evaluated by the radiologist.

PET-CT also plays a crucial role in the follow-up of these patients, both for the local effect of treatment and as a strategy for detecting new disease foci elsewhere in the body. PET-CT may also potentially be helpful in the treatment response by differentiating responders from non-responders.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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