Cancer Imaging (2007) **7,** 189–194
DOI: 10.1102/1470-7330.2007.0027

CI

e-med
www.e-med.org.uk

ARTICLE

PET/CT and hepatic radiation injury in esophageal cancer patients

Revathy B. Iyer[a], Aparna Balachandran[a], John F. Bruzzi[a], Valen Johnson[b], Homer A. Macapinlac[c] and Reginald F. Munden[a]

[a]Department of Diagnostic Radiology, [b]Department of Biostatistics and [c]Department of Nuclear Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

Corresponding address: Revathy B. Iyer, MD, Department of Diagnostic Radiology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd. Unit 368, Houston, TX 77030, USA.
Email: riyer@mdanderson.org

Data accepted for publication 17 October 2007

Abstract

This paper evaluates the imaging appearance of radiation injury in the liver on positron emission tomography (PET)/computed tomography (CT) in patients with distal esophageal cancer who underwent pre-operative chemoradiation therapy. Twenty-six patients with distal esophageal cancer who received chemoradiotherapy before esophagectomy were included. All patients had baseline and follow-up PET/CT. Fluorodeoxyglucose (FDG) uptake in both left and right lobes of the liver was evaluated. CT findings suggesting radiation damage were documented. Abnormal FDG uptake in the liver was observed in 5 (19%) patients after therapy. These abnormalities were in the left lobe (12%) and right lobe (12%) of the liver. In the irradiated left lobe, FDG uptake increased focally greater than 50% over baseline in two patients (54% and 133%); in one of these patients, biopsy confirmed radiation injury. In the non-irradiated right lobe, standard uptake values (SUV) increased diffusely in two different patients. In one patient, SUV decreased by at least 50% in both the right and left lobes. In the remaining patients, there were no significant changes in FDG uptake. Atrophy and attenuation changes of irradiated liver on CT were found in 15 (58%) patients. In patients receiving chemoradiotherapy, PET/CT may identify metabolic abnormalities in irradiated liver. Such abnormalities should be correlated with other imaging, clinical and laboratory findings to avoid confusion with hepatic metastases.

Keywords: *Esophageal cancer; radiation therapy; PET/CT; liver metastases; hepatotoxicity.*

Introduction

Esophageal cancer has a high mortality rate and is rising in incidence in the western world. In 2006 there were an estimated 15,000 new cases of esophageal cancer in the United States with almost 14,000 deaths[1], representing 4% of all cancer deaths. Most patients present with unresectable or Stage IV disease and the median survival of those with Stage IV disease who undergo palliative therapy is less than one year. If diagnosed at an earlier stage, esophagectomy is potentially curative but is associated with a high morbidity and high rate of distant recurrence. There is evidence that neo-adjuvant chemo-radiotherapy prior to surgery can improve the 3-year survival and radiation can reduce local-regional cancer recurrence[2–9]. Because the most favorable results are in those patients who have a pathologic response to pre-operative chemoradiation therapy, optimal patient selection is critical.

Positron emission tomography (PET)/computed tomography (CT) can be helpful in identifying the subset of patients who are responders to pre-operative therapy and can also detect distant metastases, thereby excluding those patients who will not benefit from esophagectomy. Radiation treatment of distal esophageal cancers may include the adjacent liver parenchyma, which can appear on PET/CT as an area of increased fluorodeoxyglucose (FDG) uptake within the liver parenchyma that mimics metastatic disease. The objective of this study was to evaluate the imaging appearance of radiation injury in the liver on PET/CT in patients with distal esophageal

1470-7330/07/000001 + 06

cancer who underwent pre-operative chemoradiation therapy.

Materials and methods

We performed a retrospective review of consecutive patients with distal esophageal cancer, who underwent neoadjuvant chemoradiotherapy prior to surgery between January 2004 and February 2005 after obtaining institutional review board approval. All patients received 50.4 Gy of radiation therapy to the distal esophagus using a 3D conformal technique. All patients underwent baseline PET/CT prior to treatment, followed by a repeat PET/CT scan performed 6 weeks following completion of chemoradiotherapy for the purposes of assessing local tumor response and for detection of new distant metastases. Patients were excluded if they had liver metastases, fatty liver, liver cirrhosis or had undergone previous hepatic surgery.

All PET/CT examinations were performed on an integrated PET/CT scanner (Discovery ST-8, General Electric Medical Systems, Milwaukee, WI). Patients underwent fasting for at least 6 h prior to scanning. Blood glucose was checked approximately 4 h prior to scanning and was less than 165 g/dl; no patients in our study had hyperglycemia requiring deferment of their scans. One hour prior to scanning, patients were injected with a mean of 15 mCi (range 12–20 mCi) of radioactively-labeled FDG. PET studies were acquired from the skull base to the upper thighs in two-dimensional mode for 3 min per bed position. PET images were reconstructed using standard vendor-provided reconstruction algorithms which incorporated ordered subset expectation maximization (OSEM). Attenuation correction of PET images was performed using attenuation data from the CT component of the exam; emission data were corrected for scatter, random events and dead-time losses using the manufacturer's software.

The CT component of the study comprised a non-contrast multidetector CT examination from the base of the skull to the upper thighs (120 mA, 140 kVp, table speed 13.5 mm/rotation). Axial CT images were reconstructed with a slice thickness of 3.75 mm.

Images from the PET/CT scans were reviewed by consensus at a combined interpreting session by two diagnostic radiologists with experience in interpreting PET/CT scans. The CT, PET and fused PET/CT images were reviewed together in multiple planes (axial, sagittal, and coronal) on a GE Advantage Windows workstation. On CT, images of the liver were examined using both soft tissue (center, +40 HU, width, 300 HU) and liver (center, +50 HU, width, 150 HU) windows. In each patient, maximum standard uptake values (SUV_{max}) were measured in the liver using 3D region of interest cursors placed over the left and right lobes of the liver on PET/CT scans performed before and after radiotherapy; the regions of interest were drawn to include the maximum amount of liver tissue in each lobe without including adjacent tissues. On the CT images, changes such as atrophy and decrease in attenuation of the liver were subjectively evaluated and also documented on scans performed before and after radiotherapy. Lastly, the results of laboratory liver function tests were documented at baseline and at 6 weeks following completion of radiotherapy.

Statistical analysis

Descriptive analyses were used for patient age, sex, time intervals between scans and imaging findings. To test for differences in the detection probability for radiation injury between PET and CT, we used McNemar's test for paired binomial observations.

Results

A total of 26 patients with distal esophageal cancer were included in the study (24 men, 2 women; mean age 54 years, age range 41–78 years). Histology of the esophageal tumors was 24 adenocarcinomas and 2 squamous cell carcinomas.

On baseline PET/CT imaging, there was homogenous FDG uptake within both lobes of the liver with a mean SUV_{max} of 3 (range 2–6). There were no significant differences in FDG uptake between the left and right lobes of the liver. No abnormal imaging findings were seen on the CT images.

On PET/CT following radiotherapy, 5 (19%) patients demonstrated changes in the pattern and intensity of FDG uptake. In 2 (8%) of these patients, focal areas of increased FDG uptake were found in the left lobe of the liver adjacent to the irradiated esophageal tumor; in both of these patients, the SUV_{max} increased by over 50% compared to their baseline scan (by 54% and 133%, respectively). No significant change in the level of FDG uptake was seen within the right lobe of the liver in these two patients. On the CT of these two patients, there was no liver abnormality to indicate metastasis, but there was a well defined diffuse low attenuation characteristic of radiation injury. In one patient a focal area of increased FDG uptake was thought to represent radiation injury and a biopsy at the time of esophagectomy confirmed the presence of radiation injury and the absence of metastatic disease.

The remaining three patients demonstrated either diffuse increase in FDG uptake (>50% over baseline) in the right lobe of the liver with no abnormality in the left lobe ($n = 2$) or decreased FDG uptake (>50% over baseline) in both the left and right lobes of the liver ($n = 1$).

On CT, characteristic findings of decreased attenuation and atrophy were seen within the left lobe of the liver in 15 (58%) patients. Two of these patients also had greater than 50% increase in FDG uptake in the left lobe of the liver. Abnormalities in liver function tests were

seen in only 3 (12%) patients at the time of re-evaluation following chemoradiotherapy, all three of whom demonstrated increases in alkaline phosphatase by over 200%. Two of these three patients had corresponding increases in FDG uptake within the left lobe of the liver (>50% over baseline).

The 95% confidence interval for the PET detection probability of radiation injury as manifested by focal changes in SUV_{max} is (0.024, 0.302) based on 3/26 detections using the Clopper–Pearson confidence interval. For CT, the 95% Clopper–Pearson interval for detection of the characteristic well-defined low attenuation of radiation injury is (0.369, 0.766), based on 15/26 detections. When comparing the probability of detecting radiation injury on CT versus PET at this time point after radiotherapy, the *p*-value for McNemar's test of no difference in detection probability is less than 0.003 (i.e., $p < 0.003$).

Discussion

Clinical radiation injury in the liver may occur in 6–66% of patients depending upon the volume of hepatic tissue irradiated and the dose used[9–11]. Factors that increase the likelihood of hepatic toxicity include whole-liver irradiation and doses greater than 30 Gy.

In esophageal cancer patients undergoing neo-adjuvant therapy, three-dimensional (3D) conformal therapy or intensity modulated therapy (IMRT) is employed to increase the radiation dose to the primary tumor while limiting damage to surrounding healthy tissue. Using such techniques, doses in excess of 70 Gy can be employed[12]. However, given the anatomical location of the lateral segment of the left lobe of the liver adjacent to the distal esophagus, radiation injury to the liver is difficult to avoid.

The CT appearance of radiation injury of the liver has been well described[13–16]. The irradiated liver appears hypodense on non-contrast CT scans and can be seen in patients who receive more than 45 Gy to a portion of the liver, regardless of whether they develop symptoms or other signs of radiation-induced hepatotoxicity. In the acute phase of radiation-induced liver injury, CT demonstrates a well-demarcated area of low attenuation within the hepatic parenchyma that corresponds to the radiation ports used, likely due to edema or fatty infiltration[13,14]. Such abnormalities were seen on CT in 58% of patients in our group.

The FDG-PET findings in radiation injury to the liver have been less well described. Antoch *et al.*[17] reported their findings of the utility of PET/CT in the assessment of liver tissue after intraoperative radiation therapy in a pig model. They found that PET/CT showed a decrease in the uptake of FDG in the irradiated field at 2 and at 4 weeks following completion of intraoperative therapy using 20 Gy. At 8 weeks the distribution of the tracer in the irradiated pigs did not differ from that in non-irradiated animals[17]. In our study of patients with esophageal cancer, at 6 weeks after completion of therapy, changes in FDG uptake in the irradiated portion of the liver were seen in 12% (three patients) and were somewhat variable (two patients demonstrating increased FDG uptake and one patient showing decreased uptake) while characteristic CT changes of atrophy and decreased attenuation were seen in 58% (15) of patients. The variable FDG uptake at 6 weeks suggest that PET imaging may be less sensitive than CT in detection of established liver injury after therapy is completed. Metabolic changes in the liver may have been detected more often if PET imaging had been performed earlier. Two additional patients in our study were also noted to have alteration in FDG uptake diffusely in the non-irradiated right lobe of the liver without corresponding CT abnormalities and this finding is more difficult to explain. Vascular changes resulting from radiotherapy could cause differential flow to the irradiated and non-irradiated portions of the liver resulting in changes in FDG distribution. These more diffuse metabolic changes in the right lobe might relate to systemic changes from the concurrent chemotherapy that was also administered.

Clinically, acute radiation hepatitis generally occurs between 2 and 6 weeks after therapy and is characterized by ascites and right upper quadrant discomfort with associated elevation of liver function tests, typically doubling of the alkaline phosphatase, which subsequently returns to normal[9]. Patients usually remain asymptomatic if the non-irradiated liver is healthy. On CT, imaging findings of established liver injury are not usually found in these patients until a later stage, some 2–3 months after completion of radiation therapy. However, the results of our study suggest that mild sub-clinical forms of radiation hepatitis can be detected by PET/CT earlier; in the two patients in our group who demonstrated increased FDG uptake in the left lobe of the liver 6 weeks after completion of radiation therapy, there were accompanying abnormalities in alkaline phosphatase. However, both patients were asymptomatic and did not subsequently develop radiation induced liver disease.

It is also important to remember that patients with locally advanced esophageal cancer are also at risk for developing distant metastatic disease. Distant sites of hematogenous dissemination are seen most frequently in the liver and lung. When patients present for re-evaluation after neo-adjuvant therapy, it is important to exclude metastatic disease in order to prevent futile surgeries. Pre-operative whole body PET/CT is particularly useful in the re-evaluation of esophageal patients to determine treatment response and exclude metastasis. Given the propensity of hepatic metastases in these patients, it is important to recognize FDG avid lesions in the liver that may be metastatic. However, any FDG avid areas in the liver should be correlated for associated anatomic abnormality in the liver on CT. The appearance

of radiation injury on CT is quite characteristic and generally shows sharp, straight margins that correspond to the portals used (Fig. 1). Metastatic lesions, on the other hand, are generally more mass-like and rounded in contour on CT (Fig. 2). As noted in our data, radiation injury to the liver may be FDG avid in a small number of cases and should not be confused with FDG avid hepatic metastatic disease.

Limitations of our study stem from its retrospective nature and from the fact that histological confirmation of radiation-induced liver damage was not obtained in all cases. However, it seems reasonable to assume that,

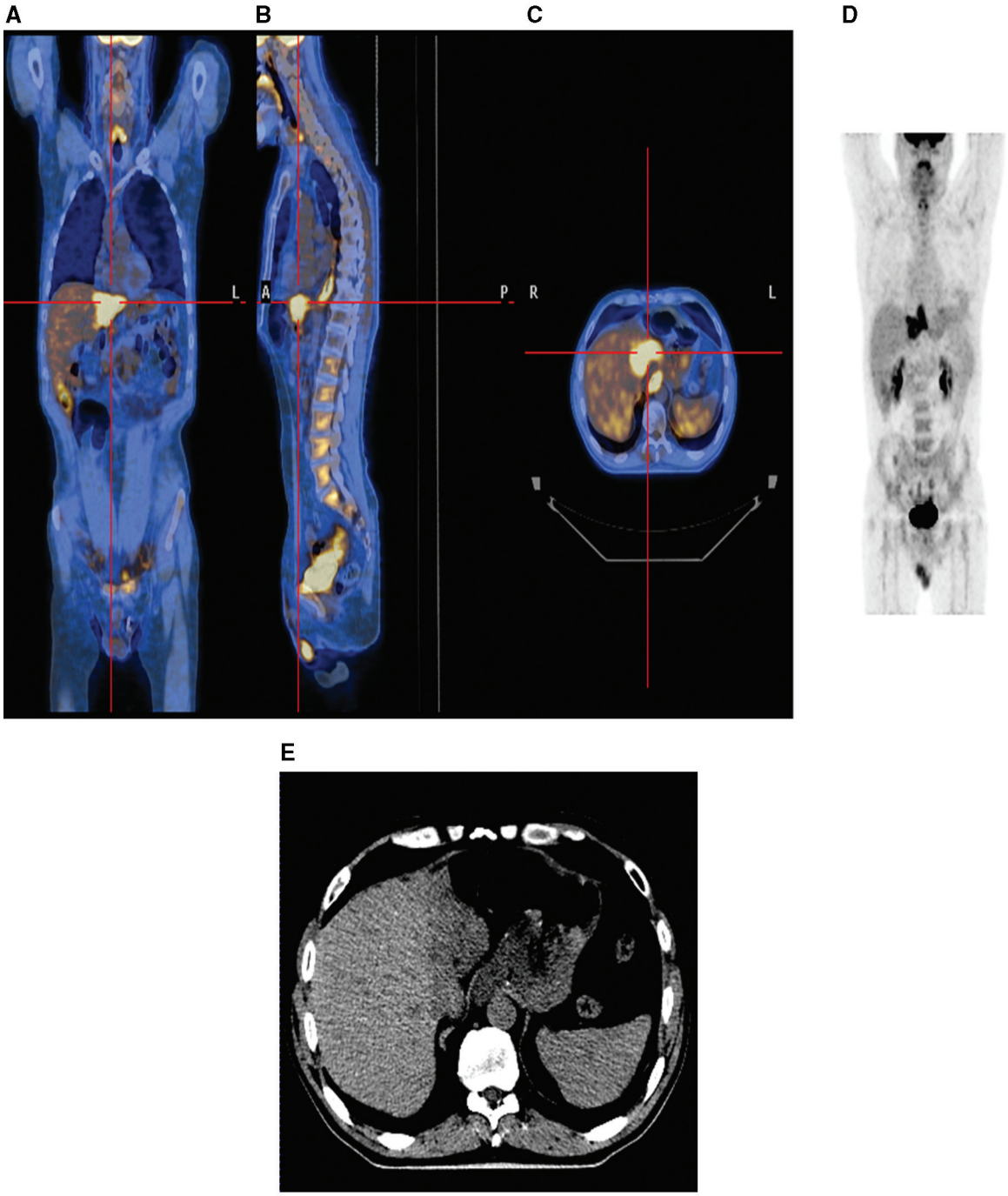

Figure 1 **A 63-tear-old male with adenocarcinoma of distal esophagus treated with 50.4 Gy with 3D conformal technique 6 weeks earlier. Baseline PET showed FDG avid primary tumor only. Fused PET/CT coronal (a), sagittal (b) and axial (c) images and coronal MIP (d) image show increased FDG uptake focally (arrow) in the left lobe of the liver and an FDG avid primary distal esophageal tumor (arrowheads). Axial non-contrast CT (e) shows well demarcated low attenuation (curved arrow) compatible with radiation injury subsequently proven by biopsy.**

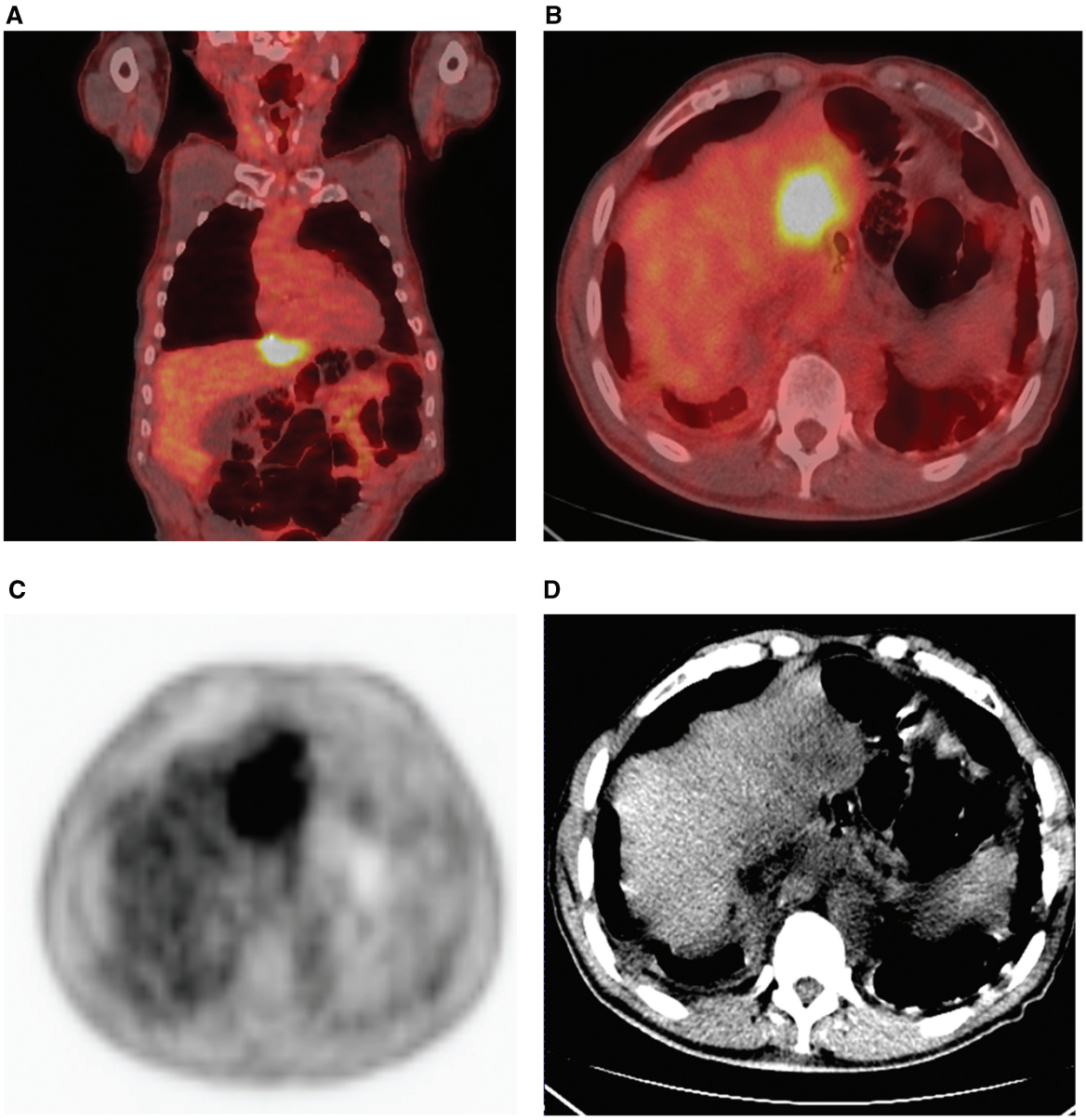

Figure 2 **A 71-year-old male status post chemoradiation and esophagectomy 18 months ago, now with FDG avid liver metastasis (arrow) to the left lobe of the liver as seen on coronal (a), axial (b) fused PET/CT images as well as axial (c) PET and axial non-contrast CT (d).**

in the absence of metastatic liver disease (as confirmed by subsequent follow-up) and the location of increased FDG uptake in the left lobe of the liver in most cases, the abnormalities observed on PET/CT were indeed due to radiotherapy. Another limitation of this study was that the liver was imaged with PET/CT at only one time point (6 weeks) after neoadjuvant therapy and any changes in FDG uptake before this time point would not have been detected.

Conclusion

In patients with distal esophageal cancer receiving neoadjuvant chemoradiotherapy, PET/CT can detect metabolic abnormalities in the adjacent liver parenchyma due to its inclusion in the radiation therapy port. Such abnormalities should be correlated with other imaging, clinical and laboratory findings in order to avoid confusion with hepatic metastases.

References

[1] Jemal A, Siegel R, Ward E, *et al.* Cancer statistics 2006. CA Cancer J. Clin 2006; 56: 106–30.

[2] Bosset J, Gignoux M, Triboulet J, *et al.* Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997; 337: 161–7.

[3] Swisher SG, Ajani JA, Komaki R, *et al.* Long-term outcome of phase II trial evaluating chemotherapy, chemoradiotherapy, and

surgery for locoregionally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 2003; 1: 120–7.

[4] Roth JA, Pass HI, Flanagan MM, *et al.* Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg 1988; 2: 242–8.

[5] Walsh TN, Noonan N, Hollywood D, *et al.* A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996; 7: 462–7.

[6] Donington JS, Miller DL, Allen MS, *et al.* Tumor response to induction chemoradiation: influence on survival after esophagectomy. Eur J Cardiothorac Surg 2003; 4: 631–6 (discussion 36–7).

[7] Urba SG, Orringer MB, Turrisi A, *et al.* Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001; 2: 305–13.

[8] Kelsen DP, Ginsberg R, Pajak TF, *et al.* Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998; 27: 1979–84.

[9] Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003; 185: 538–43.

[10] Brucher BL, Weber W, Bauer M, *et al.* Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001; 233: 300–9.

[11] Westerterp M, van Westreenen HL, Reitsma JB, *et al.* Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy – systematic review. Radiology 2005; 3: 841–51.

[12] Wieder HA, Brucher BL, Zimmermann F, *et al.* Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J Clin Oncol 2004; 5: 900–8.

[13] Flamen P, Van Cutsem E, Lerut A, *et al.* Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 2002; 3: 361–8.

[14] Kato H, Kuwano H, Nakajima M, *et al.* Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. Am J Surg 2002; 3: 279–83.

[15] Downey RJ, Akhurst T, Ilson D, *et al.* Whole body ^{18}FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003; 3: 428–32.

[16] Weber WA, Ott K, Becker K, *et al.* Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001; 12: 3058–65.

[17] Antoch G, Kaiser GM, Mueller AB, *et al.* Intraoperative radiation therapy in liver tissue in a pig model: monitoring with dual-modality CT-PET. Radiology 2004; 230: 753–60.

[18] Song SY, Kim JH, Ryu JS, *et al.* FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys 2005; 4: 1053–9.

[19] Swisher SG, Maish M, Erasmus JJ, *et al.* Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg 2004; 4: 1152–60(discussion 52–60).

[20] Swisher SG, Erasmus J, Maish M, *et al.* 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer 2004; 8: 1776–85.

[21] Yamasaki SA, Marn CS, Francis IR, Robertson JM, Lawrence TS. High-dose localized radiation therapy for treatment of hepatic malignant tumors: CT findings and their relation to radiation hepatitis. AJR 1995; 165: 79–84.

[22] Cheng JC, Wu JK, Huang CM, *et al.* radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: dosimetric analysis and implication. Int J Radiat Oncol Biol Phys 2002; 54: 156–62.

[23] Robertson JM, Lawrence TS, Walker S, *et al.* The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. Int J Radiat Oncol Biol Phys 1995; 32: 445–50.

[24] Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995; 31: 1237–48.

[25] Webb S. Advances in three-dimensional conformal radiation therapy physics with intensity modulation. Lancet Oncol 2000; 1: 30–6.

[26] Bluemke DA, Fishman EK, Kuhlman JE, Zinreich ES. Complications of radiation therapy: CT evaluation. Radiographics 1991; 11: 581–600.

[27] Jeffrey RB, JrMoss AA, Quivey JM, Federle MP, Wara WM. CT of radiation-induced hepatic injury. AJR 1980; 135: 445–8.

[28] Charnsangavej C, Cinqualbre A, Wallace S. Radiation changes in the liver, spleen, and pancreas: imaging findings. Semin Roentgenol 1994; 29: 53–63.

[29] Wallace S. Liver, spleen, and pancreas. Diagnostic roentgenology of radiotherapy change. Baltimore: Williams and Wilkins; 1979, p. 101–9.