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Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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Appendix 4

**Systematic Review:
PET as a Diagnostic Test in
Colorectal Cancer**

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*Appendix 4***Systematic Review:
PET as a Diagnostic Test in Colorectal Cancer**

The final literature database searches for the systematic reviews were performed on September 10, 1996; the assessment represents peer-reviewed literature published and indexed as of that date.

This Appendix to the PET assessment presents the results of the systematic review of PET in colorectal cancer. A general rationale for the use of PET in oncology is supplied by Hawkins, et al. (1994) and Hoh, et al. (1994):

- many forms of cancer characteristically perturb tissue biochemical and physiological processes and PET imaging can be expected to detect the resulting abnormalities;
- reliance on tumor histology and anatomy limits the oncologist's tools for selecting optimal treatment;
- the ability to monitor metabolic responses to treatment could allow the early re-direction of therapy in patients who fail to respond to the first attempt at radiation or chemotherapy.

These and other authors (e.g., Price and Jones, 1995) report that PET studies in cancer are emerging as a major focus of the technology, both in basic research and in clinical investigations. Information gathered by the MDRC Technology Assessment Program from VA PET facilities corroborates that perception (see *Appendix 9: Experience With PET in VHA*).

Fluorine-18-fluorodeoxyglucose (FDG) is the most commonly employed radiopharmaceutical in PET cancer studies. Many neoplasms have high glycolytic rates, resulting in intracellularly trapped phosphorylated FDG that can be imaged with PET. Hawkins, et al. (1994), note that tumor-specific biochemical characteristics of glucose transport and phosphorylation may affect quantitative estimates of tumor glucose metabolism with FDG PET, and that investigations are under way to define these characteristics. However, these uncertainties may be of less concern with qualitative or semiquantitative FDG PET cancer studies because the primary intent of such studies is to detect and map tumor foci, not to rigorously quantify tumor glycolytic rates.

In some instances, PET imaging techniques have been modified to meet the needs of cancer diagnosis. Most PET systems allow axial fields of view (the length of the body encompassed by a series of cross sectional images) of approximately 10 cm. Cancer is frequently distributed beyond this field of view, and whole body image acquisition procedures have been developed (Hoh, et al., 1993). Since it is impractical to apply standard transmission scanning attenuation correction methods to these procedures, whole body PET imaging is primarily useful as a qualitative indicator of disease distribution.

Nieweg (1994) and Price and Jones (1995) define a number of potential applications for PET in oncology. These include:

- tumor detection (although PET images offer insufficient structural detail and should not be used to visualize anatomy; registration techniques to combine PET and anatomic imaging into a single image are under development to circumvent this limitation);
- staging (particularly using whole-body imaging methods) although there is a lower limit to the size of metastases that can be detected by PET;
- detection of local recurrence of disease, since anatomically-based imaging is often limited by the effects of treatment;
- prediction of tumor response to chemotherapy;
- treatment monitoring.

I. BACKGROUND

A. General sources

The material in this section, unless otherwise noted, is based on information in the National Cancer Institute's Physician Data Query (PDQ) system (retrieved in September, 1996).

B. Epidemiology

Colorectal cancer is recognized as a major source of morbidity and mortality, and a significant public health problem, for both men and women in the United States. Among cancer death rates, those for colorectal cancer are second only to lung cancer. These rates have fallen 29% for women, but only 7% for men, in the last 30 years.

Approximately 134,000 incident cases (10% of incident cases of all types of cancer) and 55,000 deaths (10% of all cancer related deaths) are estimated for the United States in 1996 (American Cancer Society, 1996). Within the Veterans Administration health care system, malignant neoplasms of the digestive organs and peritoneum (which include colorectal cancer) accounted for a total of 10,000 patients discharged (1% of all patients discharged within the system) with an average length of stay of 19.4 days (Annual Report of the Secretary of Veterans Affairs, 1994) during 1994.

Risk factors for colorectal cancer include age over 50 years, hereditary syndromes (familial polyposis of the colon and non-polyposis syndrome), and inflammatory bowel disease. There is some evidence that high fat and/or low fiber diets may also contribute to risk. The median age of colorectal cancer patients at diagnosis is 70 years, with less than 4% of cases occurring in patients younger than 50 years (Donald and Burhenne, 1993; US Preventive Services Task Force, 1996).

C. General description

Colorectal cancers are primarily of a single histologic type, adenocarcinoma. Metastases to the liver, abdominal cavity, and extra-abdominal areas at diagnosis are common, as is recurrent disease after surgical resection of the primary tumor. Prognosis is closely related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases.

Most colon cancers are thought to develop from adenomas, but most adenomas do not progress to cancer. Potential approaches to the control of colon cancer include primary prevention by screening for and removing benign adenomatous polyps, and secondary prevention by screening for early cancer that might be removed with curative intent. Accordingly, a number of screening strategies are available, and continuing research into the efficacy of the various strategies is under way (US Preventive Services Task Force, 1996).

D. Staging, treatment, and survival

The prognostic variables noted in the paragraph above are incorporated into the Dukes staging system (Table 1). Unless gross evidence of metastatic disease is present, it is virtually impossible to determine accurately disease stage prior to surgical resection and pathologic analysis of operative specimens (Fengler and Pearl, 1994). Current surgical

practices support more thorough intraoperative and pathologic staging than did previous practices; prognosis appears to be more precisely assessed not only through the presence or absence of metastatic nodes, but the number of involved nodes (i.e., 1 to 4 versus > 5).

The initial diagnosis of colorectal cancer is made on the basis of endoscopic or radiographic findings. Pre-operative evaluation includes: determination of carcinoembryonic antigen (CEA) levels [elevated titers (> 5.0 ng/mL) are associated with a high risk of metastatic disease and eventual tumor recurrence]; physical examination; a chest radiograph; and biochemical assessment of liver function. A colonoscopic evaluation of the entire large bowel may be performed to identify synchronous tumors or suspicious polyps. Computed tomography (CT) is widely used to determine the extent and location of lesions preoperatively. CT relies on anatomic changes to detect disease, and, like many other diagnostic tests, is most accurate when patients have advanced disease (Falk, et al, 1994). Other methods that may contribute to pre-operative staging include magnetic resonance imaging, transrectal ultrasound, laparoscopic exploration, and laparoscopic ultrasound (Falk, et al., 1994).

Table 1 summarizes the treatment options that are currently available to patients with colorectal cancer. As a general rule, surgical resection is the primary therapy. Various forms of adjuvant chemotherapy and radiation therapy are under investigation; some regimens, like combination chemotherapy with fluorouracil and levamisole after surgery for stage III disease, have been shown to be of benefit in certain settings. There is no standard treatment for advanced colorectal cancer; radiation therapy is under investigation. Chemotherapy appears to be of limited benefit in patients with advanced disease, and is associated with only a 15 to 20% chance of partial response or short-term palliation.

E. Follow-up after primary treatment

Most recurrences after surgical resection of colorectal cancer occur within the first 4 post-operative years; 80% of recurrences occur within 2 years (Bruinvels, et al., 1994). Therefore, many physicians observe patients carefully for up to 5 years by semiannual physical examinations, imaging studies, and yearly blood chemistry determinations, including CEA levels. A number of recent articles (Steele, 1993; Nelson, 1994; Kronborg, 1994) review the known costs, risks, and unquantified benefits of intensive follow-up strategies.

Two recently published randomized controlled trials found no survival benefit with intense follow-up versus no follow-up (with patients instructed to report for evaluation when they became symptomatic) (Ohlsson, et al., 1995) or with intense follow-up versus conventional follow-up (Makela, et al., 1995). An additional large-scale randomized trial to document the efficacy of a standard, postoperative monitoring program is in progress; the investigators hope to define any benefit associated with follow up strategies, and to define the subgroups of patients who would be most likely to benefit (Kronborg, 1988; Nelson, 1996).

Table 1 Modified Dukes classification of colorectal cancer, standard treatment options, and survival

Stage	Pathologic description	Colon		Rectum	
		Treatment	5-year survival	Treatment	5-year survival
A	Cancer limited to mucosa and submucosa	<ul style="list-style-type: none"> • wide surgical resection and anastomosis 	> 90%	<ul style="list-style-type: none"> • wide surgical resection and anastomosis • selected patients may receive local resection with or without radiation plus chemotherapy 	75-100%
B	Cancer extends into muscularis or serosa; uterus, parametria, ovaries, or prostate often involved	<ul style="list-style-type: none"> • wide surgical resection and anastomosis • patients should be considered for entry into carefully controlled trials evaluating the use of systemic or regional chemotherapy, radiotherapy, or biological therapy • adjuvant therapy not indicated unless patient participates in clinical trial • subgroups of patients at high risk for recurrence may be considered for adjuvant therapy 	70-85%	<ul style="list-style-type: none"> • wide surgical resection and anastomosis when followed by chemotherapy and postoperative radiation • other surgical /adjuvant approaches within clinical trials • preoperative radiation with or without chemotherapy followed by surgery with attempt to preserve sphincter function with subsequent adjuvant chemotherapy, within a clinical trial 	50-80%
C	Cancer involves regional lymph nodes	<ul style="list-style-type: none"> • wide surgical resection and anastomosis • patients who are not protocol candidates should receive postoperative chemotherapy (fluorouracil and levamisole) • eligible patients should be considered for entry into controlled trials comparing various postoperative chemotherapy regimens, radiation, or biological therapy, alone or in combination 	30-60%	<ul style="list-style-type: none"> • wide surgical resection and anastomosis when followed by chemotherapy and postoperative radiation, preferably through participation in a clinical trial • other surgical /adjuvant approaches within clinical trials • preoperative radiation with or without chemotherapy followed by surgery with attempt to preserve sphincter function with subsequent adjuvant chemotherapy, within a clinical trial 	30 - 60%
D	Distant metastases (liver, lung, etc.)	<ul style="list-style-type: none"> • surgical resection/anastomosis or bypass of obstructing lesions • surgical resection of isolated metastases to liver, lung, ovaries • palliative radio- or chemotherapy • clinical trials of new drugs and biologic therapy 	< 10%	<ul style="list-style-type: none"> • surgical resection/anastomosis or bypass of obstructing lesions • surgical resection of isolated metastases to liver, lung, ovaries • palliative radio- or chemotherapy • clinical trials of new drugs and biologic therapy 	<10%
Recurrent		<ul style="list-style-type: none"> • treatment depends on sites of recurrent disease demonstrated by physical examination and radiographic studies • isolated liver and lung metastases may be resected • palliative radio- or chemotherapy • patients candidates for phase I and II trials 	5-year cure rate for resection of solitary or combination metastases > 20%; otherwise, prognosis poor	<ul style="list-style-type: none"> • treatment depends on sites of recurrent disease demonstrated by physical examination and radiographic studies • isolated lung or ovarian metastases may be resected • palliative radiotherapy • patients candidates for phase I and II trials of palliative chemotherapy 	5-year cure rate for resection of up to 3 liver metastases > 20%, with some long-term cures; otherwise, prognosis poor

F. Potential roles for PET

The first report of potential roles for PET in colorectal cancer management was published by Yonekura, et al., from Brookhaven National Laboratory and the Memorial Sloan-Kettering Cancer Center, in 1982. These authors performed FDG PET studies on 3 patients with biopsy proven advanced liver metastases from colon cancer. All of the patients showed markedly increased accumulation of FDG in their liver tumors in images acquired late in the scan period (50 minutes after injection). FDG activity increased continuously in tumors following injection, while it decreased in normal liver tissue (tumor to normal liver ratios of 3.3 to 4.7). Yonekura, et al., concluded that FDG may be useful as an imaging agent for the detection and characterization of liver tumors.

Other authors (Beets, et al., 1994; Lai, et al., 1996; Vitola, et al., 1996) concur that estimating the resectability of liver metastases may be an area in which PET can have a significant clinical impact. In patients with apparently limited recurrent colorectal cancer (to the liver or lungs) 5-year survival rates of 20-30% can be obtained by resection with curative intent. Since these rates are only 20-30%, many of the patients who undergo surgery for resection must have unrecognized tumor foci. The morbidity (and costs) associated with surgery in patients who do not have genuinely resectable recurrent tumor could be avoided by improved methods of tumor detection.

Other potential roles for PET in colorectal cancer imaging have been identified. These include:

- pre-operative staging of disease (Falk, et al., 1994);
- postoperative monitoring of patients for recurrent disease (Strauss, et al., 1989; Ito, et al., 1992).

Other new nuclear medicine tests, such as monoclonal antibody imaging are also felt to be particularly useful in patients who have rising CEA levels during post-treatment monitoring, but no evidence of recurrence on conventional imaging studies such as CT or MRI, or in patients who are suspected to have an isolated, resectable recurrence and for whom surgery with curative intent is planned (Goldenberg, 1993; Peterson, et al., 1993; Tempero, et al., 1995).

II. RESULTS

Seventeen articles identified through MEDLINE and other database searches and from the bibliographies of initially retrieved articles were selected as meeting the screening criteria. After review, twelve (71%) met inclusion criteria: 5 met the definition of technical efficacy (listed in Section VII; full data abstraction tables for technical efficacy studies are on file with the MDRC Technology Assessment Program); and 5 met, to some extent, the evidence-based medicine criteria for diagnostic accuracy evaluations (Table 3). An additional 2 studies were classified at both the diagnostic accuracy and therapeutic efficacy levels (Table 4). A single study addressed only the effect of PET on treatment decisions and was also classified as a therapeutic efficacy study (Table 4).

The extent to which the potential applications of PET in colorectal cancer are supported by published evidence is indicated in Table 2, which details the methodologic quality of the evidence according to the potential role played by PET in colorectal cancer, and in Tables 3 and 4, which abstract data from studies classified at the diagnostic accuracy and therapeutic efficacy levels. PET

appears to have very good face accuracy in distinguishing recurrent colorectal cancer from treatment artifacts such as scars, and in documenting hepatic or more distant metastases that might preclude surgery with curative intent. However, the methodologic limitations of the studies published to date should be taken into account when interpreting the accuracy data.

The studies in Tables 3 and 4 that address the detection of hepatic metastases may be associated with work-up bias, as PET and other imaging studies were used to direct biopsies to confirm the presence of malignancy in suspicious liver lesions. Sensitivity calculations (for both PET and alternative technologies) in such settings may be problematic and may overestimate accuracy, as the number of false negatives may not be accurately determined (Valk, 1996). While most authors made attempts to compensate for work-up bias (e.g., Lai, et al., reported that 20/34 patients had received intraoperative ultrasound to confirm the completeness of lesion identification and biopsy), there are limitation to the extent to which bias can be eliminated in this clinical setting (Stark, et al., 1987).

All of the studies in Table 3 were classified as case series, since patients were accrued as they presented for evaluation. Although the case series included some patients with benign (rather than malignant) lesions who could serve as internal controls, there was a lack of balance (sometimes of the order of 2 to 1) between numbers of cases and controls. Predictive values based on these case series would have substantial potential for bias. The small numbers of patients in the PET studies and the lack of documentation of disease severity among the cases would also argue for caution in interpreting and generalizing sensitivity and specificity data.

While the studies in Table 4 were classified at the therapeutic efficacy level, their results should also be interpreted and generalized with caution. These studies were retrospective case series that did not appear to have been specifically designed to document changes in treatment, methods for documenting such changes were not made explicit, and data tended not to be systematically analyzed or presented. The studies generally enrolled highly selected patients whose previous work-up was not clearly specified, nor was the size or composition of the referral base from which the patient sample was drawn. Information from PET studies resulted in more appropriate treatment for some patients. However, the published studies tended to give inadequate details about what happened to patients whose PET studies did not accurately reflect their disease status.

The potential role of PET in postoperative monitoring of patients for recurrent disease has not been addressed in the published literature, and would need to be evaluated in the context of the uncertain benefits of such monitoring (Kievet and Bruinvels, 1995; Makela, et al., 1995; Ohlsson, et al., 1995; Nelson, 1996). Finally, the MDRC Technology Assessment Program was unable to locate any studies that addressed the effect of incorporating PET into diagnostic strategies on patient outcomes or costs of care.

III. ALTERNATIVES TO PET AND DISCUSSION

Bruinvels, et al., (1994), note that the intensive follow-up strategies reported in the literature include a range of diagnostic technologies (physical examination, blood chemistry studies including CEA determinations, colonoscopy, barium enema, sigmoidoscopy, fecal occult blood, and liver ultrasound). Once a patient with a potential recurrent cancer has been identified by monitoring or by symptoms, other diagnostic tests, including PET and other nuclear medicine tests such as immunoscintigraphy (which uses a SPECT or gamma camera to image sites of localization for radio-labeled monoclonal antibodies directed against tumor cell antigens) have recently been identified as ways to estimate an individual patients suitability for potentially curative resection. Table 5 provides accuracy data for some of these tests for comparison with the information on PET (Table 3). All of these technologies should be evaluated in the context of the lack of evidence

supporting intensive follow-up and the small percentage of patients for whom any second attempt at cure would be effective (Nelson, 1996).

In the context of the general uncertainty regarding postoperative screening and additional operations to treat recurrent disease, the published studies on PET provide only preliminary information. At the diagnostic accuracy level, PET studies have also failed to address the marginal benefits in accuracy obtained by PET relative to other technologies included in complex diagnostic strategies.

The MDRC Technology Assessment Program was unable to locate any studies that addressed the effect of incorporating PET into diagnostic strategies on patient outcomes or costs of care. Since a major rationale for using PET in evaluating patients with potentially resectable recurrent or metastatic disease is the avoidance of unnecessary surgery, impact of PET on survival and quality of life and on costs may be a particularly fertile area for future research.

IV. SUMMARY

Table 2 summarizes published findings on the diagnostic accuracy efficacy of PET and some of its alternatives for the diagnosis of colorectal cancer. All of the PET studies are retrospective case series, which provide Level V (the weakest) evidence regarding an association between the use of PET and improved patient outcomes.

Five diagnostic accuracy efficacy studies in Table 2 (Strauss, et al., 1989; Schlag, et al., 1989; Ito, et al., 1992; Vitola, et al., 1995; Lai, et al., 1995) met evidence-based medicine criteria for diagnostic test evaluations. These studies addressed the role of PET in differentiating recurrent cancer from scar and in diagnosing liver metastases. They were classified as “C” using other methodologic criteria, due to their relatively small numbers of cases, lack of equivalence between numbers of cases and internal controls, retrospective nature, incomplete descriptions of the “filters” through which patients passed to participate in the studies and severity of disease, and the presence of work-up bias. The lack of methodologic rigor in these studies, and its potential association with overestimation of PET’s diagnostic accuracy, would also apply to the alternative technologies to which PET was compared in the same studies. Diagnostic accuracy reports for alternative technologies that have been investigated using stronger study designs (e.g., the randomized study comparing CT and MRI in diagnosing liver metastases reported by Stark, et al., 1987) would be less subject to bias.

While data on other uses of PET are also included in Table 2, the MDRC Technology Assessment Program was unable to locate any published studies that met evidence-based medicine criteria for evaluations of diagnostic tests for the use of PET in these settings. Alternative technologies have been investigated for these settings with greater rigor; examples of more rigorous studies are included in Table 2.

Three studies (Table 4) have made attempts to address the role of PET in changing treatment decisions. These studies would be considered preliminary, due to their designs (retrospective case series that had not been specifically designed to document changes in treatment); methods for recording changes in treatment plans were not specified, and results data tended not to be systematically analyzed or presented. The studies generally enrolled highly selected patients whose previous work-up was not clearly specified, nor was the size or composition of the referral base from which the patient sample was drawn. Information from PET studies resulted in more appropriate treatment for some patients. However, the published studies tended to give inadequate details about what happened to patients whose PET studies did not accurately reflect their disease status.

Table 2 Summary of the literature: Diagnostic accuracy efficacy of PET and alternatives in colorectal cancer

Notes The PET studies in this table were retrospectively analyzed case series; internal controls (cases with benign, rather than malignant, conditions) allowed the calculation of specificity as well as sensitivity.

Some studies analyzed results separately according to the clinical role of PET for subsets of patients; these studies appear in the table more than once, and may have received different methodologic quality grades for each subset analysis.

Role	Study	N	Operating characteristics*				Evidence-based medicine criteria**			Methodologic quality grade***
			PET	CT	MRI	Other	controls	standard	blinding	
Detecting or staging primary or recurrent disease	Falk, et al., 1994	16 patients: 15 malignant lesions; 3 benign lesions	Se = 87% Sp = 67%	Se = 47% Sp = 100%			+	+	partial	D
	Nattinger, et al., 1991 (ACP review)					colonoscopy Se = 94% Sp = 100%	(review)	(review)	(review)	(review)
	Hernandez-Socorro, et al., 1995	40 cases 64 controls				colonoscopy Se = 94% Sp = 100% hydrocolonic ultrasound Se = 97% Sp = 97%	+	+	+	B
Diagnosing recurrent tumor vs scar	Strauss, et al., 1989	29 patients: 21 malignant lesions; 8 scar	Se = 95% Sp = 100%				+	+	+	C
	Schlag, et al., 1989	18 patients: 11 malignant lesions; 6 scar	Se = 92% Sp = 100%			immunoscintigraphy Se = 40% Sp = 50%	+	+	+	C
	Ito, et al., 1992	15 patients: 11 malignant lesions; 4 scar	Se = 100% Sp = 100%		Se = 91% Sp = 100%		+	+	+	C
	Schiepers, et al., 1994	6 patients: 5 malignant lesions; 1 scar	Se = 100% Sp = 100%				+	+	-	D
Diagnosing recurrent tumor vs scar	Hawes, et al., 1993	85 with disease 408 without disease (review with weighted average of results from 7 studies)				endoscopic ultrasound Se = 99% Sp = 88%	(review)	(review)	(review)	(review)

Role	Study	N	Operating characteristics*				Evidence-based medicine criteria**			Methodologic quality grade***
			PET	CT	MRI	Other	controls	standard	blinding	
Diagnosing liver metastases	Schiepers, et al., 1994	80 studies: 34 malignant lesions; 46 benign lesions	Se = 94% Sp = 100%			CT and/or ultrasound Se = 85% Sp = 98%	+	+	-	C
	Vitola, et al., 1996	55 sites: 39 malignant; 16 benign 24 patients: 19 malignant disease; 5 benign	Se = 90% Sp = 100% Se = 95% Sp = 100%	Se = 86% Sp = 58%		CT portography Se = 97% Sp = 9% Se = 100% Sp = 33%	+(internal)	+	+(semiquantitative analysis)	C
	Lai, et al., 1996	34 patients: 27 malignant disease; 7 benign or no disease	Se = 93% Sp = 57%	Se = 100% Sp = 14%	Se = 100% Sp = 80%		+(internal)	+	+	C
	Stark, et al., 1987	57 cases; 72 controls: 21 benign liver disease; 51 with normal livers		Se = 80% Sp = 94%	Se = 82% Sp = 99%		+	+	+	B
	Panzer, et al., 1991 (ACP review)	review		Se = 90% Sp = 90% LR + = 8 LR - = 0.11		ultrasound, adequate studies Se = 80% Sp = 90% LR + = 9 LR - = 0.22	(review)	(review)	(review)	(review)
Diagnosing liver metastases	Rafaelsen, et al., 1995	295 patients: 64 with liver metastases 231 without liver metastases				liver enzymes Se = 9-47% (ALT 9%, AKP 31%, LDH 47%) Sp = 92-98% preop US Se = 70% Sp = 94% surgical exploration Se = 84% Sp = 97% intraop US Se = 97% Sp = 98%	+(internal)	+	+	B

Abbreviations

CT, computed tomography
MRI, magnetic resonance imaging
neg, negative for disease
pos, positive for disease
LR, likelihood ratio
AKP, alkaline phosphatase

PPV, positive predictive value
NPV, negative predictive value
US/FNA, ultrasound/fine needle aspiration
ACP, American College of Physicians
ALT, alanine amino transferase
LDH, lactate dehydrogenase

*operating characteristics defined in Appendix 2: Assessing Diagnostic Technologies, page 5-7

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V. SUGGESTIONS FOR FUTURE RESEARCH

Existing research supplies a preliminary indication of PET's potential benefit in the diagnosis and management of colorectal cancer patients. The studies that have been published had design limitations and enrolled small numbers of patients. These studies have made preliminary attempts to define the operating characteristics of PET as a diagnostic test, particularly in the setting of follow-up strategies to detect recurrent disease, and to document changes in treatment based on PET results.

- 1) Contributions from larger patient populations and stronger study designs are needed to refine the characteristics of PET as a diagnostic test in colorectal cancer, and to establish a base for further research.
- 2) A PET registry could provide a range of data on demographic and clinical characteristics of patients on whom PET studies are performed, and on their clinical outcomes in a variety of settings
- 3) The use of PET to avoid unnecessary surgery by detecting unresectable recurrent disease in patients who are scheduled for surgery based on other imaging and blood chemistry studies should be documented more systematically and in larger patient samples.
- 4) If the ongoing randomized clinical trial (Kronborg, 1988) indicates that postoperative follow up in colorectal cancer patients reduces mortality, the marginal gains attributable to PET when it is incorporated into a multi-test follow-up strategy should be quantified.

Table 3 **Data abstraction table:**
Diagnostic accuracy efficacy of FDG PET and alternative technologies in colorectal cancer

Notes: Studies in this table were designed to evaluate the use of PET in diagnosing primary or recurrent colorectal cancer (Falk, et al.) or in distinguishing recurrent cancer from treatment artifact (e.g. scar). All of the studies met, to some degree, the evidence-based criteria for diagnostic test evaluations. All would be classified as case series, since they accrued subjects as patients were referred for evaluation of suspected cancer. However, the cases included patients with benign (as opposed to malignant) masses, and these patients can serve as internal controls. Other methodologic limitations are discussed in the text and noted for each study.

Unless otherwise noted, the studies in this table compared PET and CT or MRI to the "gold standard" of histopathology of surgical specimens, which is the reference test for the operating characteristics reported in the "Results/Comments" column.

Study	Patients/Methods	Results/Comments
Strauss, et al., 1989 German Cancer Research Center, Heidelberg	<p>Purpose to differentiate recurrent colorectal cancer from scar tissue</p> <p>Cases 29 patients with suspected local recurrence of colorectal cancer (21 malignant lesions/8 nonmalignant)</p> <p>Methods</p> <ul style="list-style-type: none"> • all subjects examined with both FDG and ¹⁵O-water PET • due to limited resolution of PET, only patients with lesions exceeding 1.5 cm diameter on CT were included • final diagnosis based on biopsy and FU • PET examinations were performed after a final diagnosis had been obtained by means of biopsy and/or consistency of sequential CT findings • PET images analyzed quantitatively by means of ROIs and DAR with gluteal muscles serving as normal reference tissue <p>Study design limitations</p> <ul style="list-style-type: none"> • numbers of cases and internal controls not equivalent (high prevalence of malignancy) • cut off values for normal/abnormal tests not specified 	<p>FDG uptake</p> <ul style="list-style-type: none"> • rapid FDG uptake by tumor, followed by slight decrease in DAR for up to 40 minutes after administration; FDG concentration in tumor at 1 hour post-injection was > 2x that in scar • FDG uptake at 60 minutes was low in nonmalignant lesions • tumor/scar FDG uptake ratio was best at 60 minutes after injection • DAR values for normal tissues were constant for 50 minutes, beginning at 10 minutes post-injection <p>DAR values</p> <ul style="list-style-type: none"> • recurrent tumor = 1.14 - 4.17 • scar = 0.56 - 1.15 <p>Lesion/soft tissue FDG uptake ratios</p> <ul style="list-style-type: none"> • recurrent tumor median ratio = 2.08 • scar median ratio = 0.96 <p>Recurrent tumor vs scar based on FDG DAR and lesion/soft tissue ratio values PET: *Se = 95%, *Sp = 100%</p>

Study	Patients/Methods	Results/Comments
<p>Schlag, et al., 1989 German Cancer Research Center, Heidelberg</p>	<p>Purpose investigate the feasibility and utility of PET and immunoscintigraphy in distinguishing recurrent rectal cancer from scar tissue</p> <p>Cases 18 patients with clinically suspected recurrence of rectal cancer <ul style="list-style-type: none"> • lesions 1.5 cm on CT • 11 malignant/6 nonmalignant </p> <p>Methods <ul style="list-style-type: none"> • all subjects received PET • 14/18 had elevated CEA levels and received immunoscintigraphy with radioactive-labelled CEA/Ca 19-9 • PET images analyzed quantitatively using ROIs and time-activity curves; DAR calculated with gluteal muscles as normal soft tissue reference </p> <p>Study design limitation numbers of cases and internal controls not equivalent (high prevalence of malignancy)</p>	<p>PET <ul style="list-style-type: none"> • mean FDG tumor to normal soft tissue ratio = 2.7 • differentiation best at 57.5 minutes after FDG injection • Se = 92%; Sp = 100% for tumor vs scar </p> <p>Immunoscintigraphy with CEA/Ca 19-9 <ul style="list-style-type: none"> • Se = 40%; Sp = 50% for tumor vs scar • less accurate than other reports; attributed to binding and specificity (for colorectal cancer) of the antibodies and using histopathology as gold standard </p> <p>Authors' comment PET could improve selection of patients for invasive procedures</p>
<p>Ito, et al., 1992 Nagoya University School of Medicine, Japan</p>	<p>Purpose <ul style="list-style-type: none"> • to compare the value of PET and MRI in differentiating recurrent rectal carcinomas from scars • to investigate the role of PET in determining response to therapy </p> <p>Cases 15 patients with suspected (abnormal CT) local recurrence of rectal cancer (11 malignant/4 nonmalignant)</p> <p>Methods <ul style="list-style-type: none"> • final diagnosis obtained by surgery in 2 patients, biopsy in 7 patients, CT of bone destruction in 2 patients, and sequential CT in 2 patients • procedures to minimize FDG activity in urinary bladder used • 7 patients received sequential PET studies after treatment • MRI obtained and superimposed on all PET images • FDG uptake quantified by DAR in ROIs </p> <p>Study design limitations <ul style="list-style-type: none"> • numbers of cases and internal controls not equivalent (high prevalence of malignancy) • cut off values for normal/abnormal tests not specified </p>	<p>PET <ul style="list-style-type: none"> • mean DAR values significantly different for recurrent tumor vs scar ($p < .01$) </p> <p>MRI <ul style="list-style-type: none"> • lesion/muscle signal intensity ratios for recurrent tumors and scars were significantly different ($p < .01$) • DAR and signal intensity ratios correlated ($r = .603$; $p < .05$) </p> <p>Distinguishing recurrent rectal tumor from mature scar <ul style="list-style-type: none"> • PET: *Se = 100%; *Sp = 100% • MRI: *Se = 91%; *Sp = 100% (1 patient who was positive for disease at surgery misclassified by both MRI and biopsy) </p> <p>Treatment monitoring <ul style="list-style-type: none"> • 6/7 patients had decrease in DAR by completion of radiation therapy; in 4 of the 6 tumor did not decrease in size • 1/7 patients did not respond to treatment, and both DAR and tumor size increased during treatment • no longer term follow up results noted </p> <p>Authors' conclusion PET and MRI are complementary, particularly where the results of MRI are atypical</p>

Study	Patients/Methods	Results/Comments
<p>Falk, et al., 1994 Creighton University School of Medicine, Omaha, and West Virginia University School of Medicine</p>	<p>Purpose to determine the sensitivity, specificity, and predictive accuracy of PET and CT preoperatively in patients with colorectal cancer</p> <p>Cases 16 patients with suspected or biopsy-proven primary or recurrent colorectal cancer • 15 malignant lesions confirmed at biopsy (12 sites in colon and rectum, 2 liver metastases, 1 mesenteric metastasis) • 3 nonmalignant lesions</p> <p>Methods • all subjects received PET and CT after at least 4 hours of fasting • qualitative analyses performed • image reviewers blinded to results of other imaging studies; blinding to other test results not noted</p> <p>Study design limitation numbers of cases and internal controls not equivalent (high prevalence of malignancy)</p>	<p>PET • detected 12/12 malignant lesions in colon and rectum and 1/2 liver sites • 1 false positive scan attributed to inflammation • 2 false negative scans; 1/2 attributed to lack of clear demarcation between liver and right colon • Se = 87%; Sp = 67%; accuracy = 83%</p> <p>CT • lesions missed generally quite large (≥ 25 mm) • Se = 47%; Sp = 100%; accuracy = 56%</p> <p>Other findings/authors' conclusions • no PET or CT related complications observed • PET and CT are complementary; PET may be especially useful if CT findings equivocal • PET costs approximately twice those of CT but may be justified if unnecessary surgery prevented or unexpected early lesion detected</p>
<p>Schiepers, et al., 1995 University Hospital Gasthuisberg, Belgium</p>	<p>Purpose to evaluate contribution of whole-body PET to detecting and localizing local recurrence and metastatic disease, compared to CT-pelvis and CT/ultrasound-liver</p> <p>Cases 74 consecutive patients presenting for evaluation of suspected recurrent disease at median 1 year post surgery (45 with recurrent disease, 29 with benign conditions) • final diagnosis by biopsy in 63% • final diagnosis by FU 14 months in 37%</p> <p>Methods • work up after recurrence suspected included CEA/CA 19.9, CT-pelvis, ultrasound or CT-liver, chest x-ray, colonoscopy • 83 PET studies in 74 patients • PET interpreted qualitatively • operating characteristics calculated by site (not patient)</p> <p>Study design/reporting limitations • blinding not noted • validation of tumor in liver and distant sites dependent on imaging results</p>	<p>All recurrences: PET vs CT (74 studies: 45 malignant, 29 benign) • PET: Se = 93%; Sp = 97%, accuracy = 95% • CT: Se = 60%; Sp = 72%, accuracy = 65% • 1% of PET and 15% of CT studies equivocal; equivocal studies counted as false positives or false negatives in accuracy calculations</p> <p>Local fibrosis vs recurrence: PET vs CT (6 patients: 5 recurrent, 1 scar) PET: Se = 100%; Sp = 100%</p> <p>Liver involvement: PET vs CT and/or ultrasound (80 studies: 34 malignant, 46 benign) • PET: Se = 94%; Sp = 100%, accuracy = 97% • CT/ultrasound: Se = 85%, Sp = 98%, accuracy = 92%</p> <p>Distant extrahepatic disease: PET • PET detailed 25 unexpected lesion locations in 20 patients; 14 (56%) lesions confirmed with biopsy or other imaging • absence of disease in all false positives (all in thorax) confirmed with long term FU • 1 false negative confirmed at surgery</p>

Abbreviations: DAR, differential absorption ratio
FU, follow up
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value
ROI, region of interest
SUV, standardized uptake value
T/B, target-to-background ratios
CEA, carcinoembryonic antigen

* indicates calculated by MDRC TA Program from data supplied in published article

Table 4 **Data abstraction table:**
Therapeutic efficacy of FDG PET in colorectal cancer

Notes: Studies in this table provide both diagnostic accuracy and some therapeutic efficacy results. The degree to which the studies meet evidence-based criteria for diagnostic test evaluations and other methodologic criteria is variable (see Table 2).

All of the studies listed here are retrospectively analyzed case series. However, the cases included patients with benign (as opposed to malignant) masses, and these patients served as internal controls.

Sensitivity, specificity, and accuracy data presented here should be interpreted with caution, since validation of tumor in liver and distant sites was dependent on imaging results.

Therapeutic efficacy results are based on highly selected patients who had received a variable number and type of other diagnostic tests prior to PET (PET was complementary to, rather than an alternative to, other diagnostic tests); neither the number of patients who entered the diagnostic process at each institution nor the size of the referral base for the institution are specified, making generalization of the results presented here problematic. "True" PET results made positive contributions to treatment in these studies. False negative and false positive PET results may also have had negative impacts on some patients.

Study	Patients/Methods	Results/Comments
Vitola, et al., 1996 Vanderbilt University Medical Center	<p>Purpose to compare whole-body PET, CT, and CT portography in detecting hepatic metastases</p> <p>Cases 24 patients presenting for evaluation of suspected (increasing CEA levels or abnormal CT) colorectal ca recurrence > 1 year after surgery (19 with recurrent ca, 5 with benign lesions) • 55 intrahepatic sites (39 malignant, 16 benign) • 5 extrahepatic sites (4 malignant, 1 benign) • diagnosis confirmed by histopathology in 19 patients, 1 year FU in 5 patients</p> <p>Methods • 17 patients had CT, 18 had CT portogram, 11 had both • all patients had PET, which was analyzed semiquantitatively using ROIs, T/B ratios and SUV • if PET showed extrahepatic lesion, additional CT in that area performed • selection of liver biopsy sites based on CT portography, which detected the greatest number of lesions</p> <p>Study design/reporting limitations • extrahepatic lesion analysis not presented here due to work up bias in selecting patients for CT or other diagnosis on the basis of PET • validation of tumor in liver and distant sites dependent on imaging results • operating characteristics calculated completely only for site (not patient) as unit of analysis; clinical decisions made on patient basis • high prevalence of recurrent ca • treatment impact of false negative PET studies not discussed</p>	<p>Diagnostic accuracy efficacy</p> <p>PET cut points: SUV = 3.5; T/B = 2 • by site: Se = 90%; Sp = 100% • by patient: *Se = 95%; *Sp = 100%</p> <p>CT • by site: Se = 86%; Sp = 58% • by patient: insufficient information for calculations</p> <p>CT portography • by site: Se = 97%; Sp = 9% • by patient: *Se = 100%; *Sp = 33%</p> <p>Therapeutic efficacy: alterations to treatment based on PET diagnosis • 4/24 (17%) patients with hepatic metastases: - negative PET led to avoiding unnecessary laparotomy in 2 patients - positive PET led to partial hepatectomy in 2 patients who would not otherwise have received the procedure (other studies were false negative) • 2/5 (40%) patients with extrahepatic metastases</p>

Study	Patients/Methods	Results/Comments
<p>Lai, et al., 1996 <i>Royal Prince Alfred Hospital, Australia</i></p>	<p>Purpose to compare PET with abdominal CT, chest CT, chest x-ray in identifying operable colorectal ca metastases to liver</p> <p>Cases 34 consecutive patients referred for evaluation of suspected metastases to liver • 27 malignant, 7 benign or no disease • diagnosis confirmed by histopathology in surgical specimens, percutaneous biopsy, serial CT (median FU, 18 months), intraoperative ultrasound of liver</p> <p>Methods • all patients had staging by abdominal CT, and plain film chest x-ray (15) or CT (19) • patients whose metastases were considered operable received MRI (24) or CT angiography (3) • conventional imaging studies interpreted by 2 senior radiologists blinded to PET results • PET performed after conventional imaging • PET interpreted qualitatively by single observer blinded to conventional imaging results</p> <p>Study design/reporting limitations • data insufficient to reproduce comparison of CT vs PET for extrahepatic metastases • number of cases and internal controls not equivalent: high prevalence of disease and inability to calculate predictive values • data insufficient for analysis of subset of patients who received intraoperative ultrasound for confirmation of imaging results separately from other patients • work up bias in selecting patients for MRI • validation of tumor in liver and distant sites dependent on imaging results • methods of evaluating changes from pre- to -post-PET treatment plans not specified</p>	<p>Diagnostic accuracy</p> <p>Detection of hepatic metastases • PET: *Se = 93%; *Sp = 57%; - one case of multiple metastases not detected on MRI was identified by PET - false positives in liver cysts • CT: *Se = 100%; *Sp = 14% • MRI: *Se = 100%; *Sp = 80%</p> <p>Authors' comments • PET is more sensitive than CT in detecting extrahepatic metastases (below), and has become the initial examination of choice for patients with presumed recurrent colorectal metastases to the liver at this institution • cost of PET is justified if unnecessary tests, hospital admissions, and surgery are avoided • semiquantitative (vs qualitative) whole body PET analysis may improve accuracy</p> <p>Therapeutic efficacy</p> <p>Detection of extrahepatic metastases • PET identified previously unsuspected lesions (missed by conventional imaging) in 11 patients • clinical management influenced by PET in 10 patients (29% of total evaluated) • 1 false positive PET (retroperitoneal nodes) • 1 false negative PET (para-aortic nodal metastases apparent at repeat PET in 1 year) • 3 equivocal PET findings (poorly localized FDG uptake in area of left hepatic lobe)</p>
<p>Beets, et al., 1994 <i>University Clinic Gasthuisberg, Belgium</i></p>	<p>Purpose to evaluate clinical impact of whole-body PET in detecting and localizing recurrent colorectal ca</p> <p>Cases 35 patients with suspected recurrent disease who had received the following diagnostic battery below, up to and including PET</p> <p>Methods after surgery: • 6 monthly FU with clinical exam, serum CEA determinations, US liver, chest x-ray; colonoscopy at 1 year and then every 3 years • if recurrence suspected or identified, patients then had CT of pelvis, US and/or CT of liver, chest x-ray, colonoscopy, endorectal ultrasound • if recurrence still suspected or identified, patients then had pelvic MRI and CT of thorax • if results still equivocal, patients had PET</p> <p>Study design/reporting limitations • referral base of institution and number of patients screened or entered into diagnostic work up not specified • reported as 35 individual case reports; data not systematically analyzed • incomplete details on patients who had false positive or false negative PET results: treatment received/not received?</p>	<p>Therapeutic efficacy:</p> <p>16 patients considered before PET to have resectable liver (15 or lung (1) metastases) • 9 patients: no additional information supplied by PET • 3 patients with equivocal CT (local anastomotic recurrence not ruled out): PET negative and patients had surgery to resect metastases • 4 patients: PET positive for advanced liver involvement and resection not attempted</p> <p>8 patients considered before PET to have resectable local recurrence; PET used to detect additional sites which would rule out surgery • PET correctly identified all local recurrences • 1 patient: surgery avoided due to unexpected pulmonary metastases on PET • 5 patients: PET had no therapeutic impact • 2 patients: false negative PET studies for metastases (metastases detected at surgery)</p> <p>8 patients with presacral mass equivocal on CT • 5 patients: diagnosis with PET accurate (1 true negative, 4 true positives) • 1 patient: false negative PET (malignancy discovered later) • 2 patients: false positive PET</p> <p>3 patients with increasing CEA but no other evidence of recurrence • 2 patients: PET correctly identified pelvic recurrence and patients had treatment • 1 patient: false negative PET (biopsy confirmed recurrence later)</p>

Abbreviations: DAR, differential absorption ratio
FU, follow up
Se, sensitivity
Sp, specificity

PPV, positive predictive value
NPV, negative predictive value
ROI, region of interest
SUV, standardized uptake value

* indicates calculated by MDRC TA Program from data supplied in published article
T/B, target-to-background ratios
CEA, carcinoembryonic antigen

Table 5 **Summary of the literature**
Diagnostic accuracy of alternative technologies to PET in colorectal cancer

Note: This table includes information from review performed for the American College of Physicians (ACP), as well as studies reporting primary data. The ACP reviews provide an overview of the accuracy of commonly used diagnostic tests for colorectal cancer. Many of these studies also provide models of more methodologically rigorous study designs than those that have been used in evaluating PET (see Table 2).

Study/design	Patients/Methods	Results/Comments
Diagnosing and/or staging primary colorectal cancer		
Nattinger, 1991 <i>ACP</i>	review	<p>Flexible sigmoidoscopy</p> <ul style="list-style-type: none"> • 60 cm scope: Se for cancer = 30 - 50%; Se for adenoma = 50 - 60%; Sp (any neoplasia) = 97% • 35 cm scope: Se for cancer = 40 - 50%; Se for adenoma = 40 - 50%; Sp (any neoplasia) = 100% <p>Air contrast barium enema Se for cancer = 82 - 92%; Se for adenoma = 50%; Sp (any neoplasia) = 95%</p> <p>Colonoscopy Se for cancer = 94%; Se for adenoma = 94%; Sp (any neoplasia) = 100%</p>
Hernandez-Socorro, et al., 1995 <i>Hospital del Pino, Canary Islands, Spain</i> diagnostic accuracy efficacy case series (Level V evidence)	<p>Purpose to determine sensitivity and specificity of hydrocolonic sonography (transabdominal sonography after retrograde instillation of water into the colon) in detecting and staging colon cancer</p> <p>Cases 104 subjects referred for evaluation of colorectal disease</p> <ul style="list-style-type: none"> • 40 malignant tumors (35 primary colorectal, 2 recurrent, 1 metachronous, 1 synchronous, and 1 metastatic uterine cancer) • 64 nonmalignant <p>Methods</p> <ul style="list-style-type: none"> • all subjects received conventional abdominal or endorectal sonography and hydrocolonic sonography prior to colonoscopy and single- or double-contrast barium enema • disease status verified by histology of resected surgical specimens • image interpreters blinded to colonoscopy, barium enema and histology results 	<p>Hydrocolonic sonography (40 cases, 64 controls)</p> <ul style="list-style-type: none"> • primary or recurrent colon cancer: Se = 97.5%; Sp = 98.4%; PPV = 97.5%; NPV = 98.4% • tumor staging: 100% of T1, T2, T4 tumors and 96% of T3 tumors correctly classified • presence or absence of peritumor metastatic lymph nodes 4 mm: Se = 50%; Sp = 100% <p>Colonoscopy (36 cases, 45 controls) Se = 94.4%; Sp = 100%; PPV = 100%; NPV = 95.7%</p> <p>Barium enema</p> <ul style="list-style-type: none"> • single (32 cases, 64 controls): Se = 93.7%; Sp = 98.4%; PPV = 96.7%; NPV = 96.8% • double (11 cases, 19 controls): Se = 100%; Sp = 94.7%; PPV = 91.6%; NPV = 100% <p>Conventional ultrasonography (40 cases, 64 controls) Se = 40%; Sp = 98.4%; PPV = 94.1%; NPV = 72.4</p>
Evaluating suspected recurrent disease		
Hawes, 1993 <i>Indiana University Hospital</i>	<p>Purpose review of endoscopic ultrasound accuracy in distinguishing recurrent rectal cancer from scar</p> <p>Methods summary Se and Sp from 7 studies (85 cases/408 controls) using weighted averages</p>	<p>Endoscopic ultrasound Se = 99% Sp = 88%</p>

Study/design	Patients/Methods	Results/Comments
<p>Gasparini, et al., 1994</p> <p>diagnostic accuracy efficacy</p> <p>case series (Level V evidence)</p>	<p>Purpose to compare immunoscintigraphy with anti-CEA monoclonal antibody to CT, ultrasonography, and MRI in patients with suspected local recurrence of colorectal cancer</p> <p>Cases 59 patients referred for evaluation of suspected recurrence (2 consecutive increases in CEA levels) <ul style="list-style-type: none"> • 45 with recurrence by histology or endoscopy • 14 with benign lesions by follow up or histology </p> <p>Methods <ul style="list-style-type: none"> • whole body and multiple regional spot gamma camera scintigraphic images obtained at 4, 24, 48, and 72 hours after antibody injection • SPECT images obtained at 48 - 72 hours • only pelvic sites analyzed </p> <p>Study design limitations <ul style="list-style-type: none"> • not all subjects had histologic confirmation of disease status • blinding of image readers not noted </p>	<p>Immunoscintigraphy Se = 89%; Sp = 78%; accuracy = 86%</p> <p>MRI Se = 93%; Sp = 67%; accuracy = 86%</p> <p>CT Se = 69%; Sp = 67%; accuracy = 68%</p> <p>Ultrasound Se = 41%; Sp = 79%; accuracy = 56%</p>
<p>Corman, et al., 1994</p> <p><i>Sansum Clinic, CA; University of Louisville; University of Chicago; Buffalo VAMC; University of Missouri; CytoGen Corp.</i></p> <p>diagnostic accuracy and therapeutic efficacy</p> <p>case series (Level V evidence)</p>	<p>Purpose to assess diagnostic accuracy, and contribution to diagnostic thinking and subsequent treatment decisions of FDA-approved immunoscintigraphy agent (<i>Oncoscint</i>)</p> <p>Cases 103 patients (84 with confirmation of diagnosis by histology or other tests, 103 supplied data on contribution to diagnostic understanding or to subsequent therapeutic decisions) <ul style="list-style-type: none"> • 46 with rising CEA levels and otherwise negative evaluations • 29 with known recurrence, presumed resectable • 28 with equivocal results after other diagnostic tests </p> <p>Methods <ul style="list-style-type: none"> • gamma camera scintigraphic images of pelvis, abdomen, thorax and other sites obtained at 48 to 72 hours after antibody injection • images analyzed by nuclear medicine physician at each of 10 participating centers before confirmation of diagnosis by other means • clinicians provided description of pre-test management plan and assessed changes in plan due to immunoscintigraphy after surgery or at completion of diagnostic evaluation </p> <p>Study design limitations <ul style="list-style-type: none"> • not all subjects had histologic confirmation of disease status • Se and Sp calculations difficult to reconstruct </p>	<p>Accuracy <ul style="list-style-type: none"> • based on 84 patients with diagnosis confirmed by surgery, other tests, or follow up • scans indeterminate in 19/84 patients (23%); excluded from authors' accuracy calculations • Se = 73%; true negative rate = 100% (no positive scans in patients without other evidence of malignance; indeterminate tests not used in calculations) • if indeterminate scans considered false positive, Sp = 64% (MDRC TA Program calculation) </p> <p>Effect on treatment <ul style="list-style-type: none"> • beneficial in 44% of cases: 17 treatment plans altered due to detection of occult disease (disease not resectable and surgery canceled, surgery changed to radiation or chemotherapy, or surgical plan changed) • detrimental in 2% (test results led to unnecessary surgery in attempt to identify suggested recurrence) </p>

Study/design	Patients/Methods	Results/Comments
Detecting hepatic metastases from colorectal cancer		
<p>Stark, et al., 1987 <i>Massachusetts General Hospital, Boston</i></p> <p>diagnostic accuracy efficacy</p> <p>randomized controlled study (Level II evidence)</p>	<p>Purpose to determine the accuracy of MRI (individual pulse sequences and combined sequences) relative to CT (contrast enhanced) in the diagnosis of liver metastases</p> <p>Cases 57 patients with biopsy-proven primary cancer (24 colon, variety of others) and liver metastases (proven by biopsy in 23 and by FU in 34) • all had both CT and MRI</p> <p>Controls • 27 patients with benign liver disease (17 had MRI only) • 51 subjects with normal livers (11 had CT only, 17 MRI only, 23 both)</p> <p>Methods • 438 MRI and 97 CT studies placed in individual folders, no patient identifiers on films or folders, folders randomized by investigator who did interpret studies • 3 blinded investigators independently interpreted studies • MRI studies reagggregated for 124 patients, rerandomized, and reinterpreted by 3 investigators independently • images analyzed by patient and by lesion and recorded on score sheets • final diagnosis on abnormality and number of lesions by consensus among all investigators with all information available • ROC analysis of test performance using data from patients with metastases or normal livers (not those with benign conditions) • differences between results of several MRI techniques and CT tested statistically</p> <p>Study design/reporting limitations • false negatives and false positives analyzed for both tests, but interobserver variability described but not quantified by kappa statistic • some subgroup analyses based on small numbers of cases and/or controls</p>	<p>ROC analysis • average area under curve for MRI larger than that for CT • all 3 interpreters operated on nearly same curve for both MRI and CT, but dispersion greater for CT (wider range of performance) • for all readers, optimal performance achieved when "probably abnormal" studies scored as negative</p> <p>Performance characteristics using cut points from upper left corner of ROC curves: • Se for abnormalities: MRI = 82%; CT = 80% • Sp: MRI = 99%; CT = 94%</p> <p>Detection of individual metastatic lesions (279 lesions in 39 patients who had both MRI and CT) • Se: MRI = 64%; CT = 51%</p> <p>Detection of benign liver disease • MRI: Se (hemangiomas) = 80%; Se (cysts) = 76% • CT: Se (hemangiomas) = 74%; Se (cysts) = 64%</p> <p>Detection of extrahepatic lesions • pancreatic masses - MRI: Se = 27%; Sp = 99% - CT: Se = 79%; Sp = 96% • renal cyst or mass - MRI: Se = 27%; Sp = 99% - CT: Se = 67%; Sp = 99% • adrenal mass - MRI: Se = 22%; Sp = 100% - CT: Se = 56%; Sp = 99% • focal splenic lesions - MRI: Se = 0%; Sp = 100% - CT: Se = 33%; Sp = 99% • ascites - MRI: Se = 83%; Sp = 98% - CT: Se = 50%; Sp = 98%</p>

Study/design	Patients/Methods	Results/Comments
<p>Rafaelsen, et al., 1995 <i>Odense University Hospital, Denmark</i></p> <p>diagnostic accuracy efficacy</p> <p>prospective cohort study (Level III evidence)</p>	<p>Purpose to compare diagnostic accuracy of liver enzyme determinations, preoperative ultrasound, surgical examination, and intraoperative ultrasound for detection of liver metastases from colorectal cancer</p> <p>Cases 295 consecutive patients (1989 to 1992) admitted for elective surgery for colorectal cancer</p> <p>Methods</p> <ul style="list-style-type: none"> • all patients received preoperative US, liver enzyme measurement, inspection of liver during surgery (findings recorded before intraoperative US), intraoperative US • surgeon, preoperative ultrasonologist, intraoperative ultrasonologist all unaware of each others' findings • disease status confirmed by combination of all tests (after recording of blinded findings), histopathology, and 3 mo postoperative FU (conventional US of liver, biopsy of liver if metastases suspected) • test characteristics calculated by patient and by lesion • differences between test results tested statistically 	<p>Surgical procedures and staging results</p> <ul style="list-style-type: none"> • 216 curative operations, 79 palliative operations • Dukes stages A (35), B (148), C (33), D (64) <p>Detection of liver metastases (295 patients)</p> <ul style="list-style-type: none"> • liver enzymes: Se = 9 - 47%, Sp = 92 - 98%, depending on specific assay • preoperative US: Se = 70%; Sp = 94% • surgical exploration: Se = 84%; Sp = 97% • intraoperative US: Se = 97%; Sp = 98% <p>significant differences: intraoperative US vs all other tests</p> <p>Detection of unresectable metastases (46 patients with bilobar metastases, 35 > 3 lesions)</p> <ul style="list-style-type: none"> • intraoperative US: 91% of patients with bilobar metastases; 89% of patients with > 3 metastases • surgical exploration: 72% of bilobar metastases; 66% of patients with > 3 <p>Analysis by lesions (204 metastatic lesions in 64 patients)</p> <ul style="list-style-type: none"> • preoperative US: Se = 64%; Sp = 92% • surgical exploration: Se = 72%; Sp = 96% • intraoperative US; Se = 94%; Sp = 98%
<p>Panzer, 1991 <i>ACP</i></p>	<p>review</p>	<p>Ultrasound, adequate studies Se = 80%; Sp = 90%; LR positive = 8; LR negative = 0.22</p> <p>Computed tomography Se = 90%; Sp = 90%; LR positive = 9; LR negative = 0.11</p>

Abbreviations:

- ACP, American College of Physicians
- CEA, carcinoembryonic antigen
- FU, follow-up
- Se, sensitivity
- Sp, specificity
- PPV, positive predictive value
- NPV, negative predictive value
- LR, likelihood ratio
- US, ultrasound

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VII. REFERENCES: Technical efficacy studies

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VIII. REFERENCES: Studies reviewed but not included in evidence tables

Exclusion criteria included:

- number of colorectal cancer cases < 12
- radiopharmaceutical other than FDG
- duplicated or superseded by subsequent study from the same institution.

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