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# Diagnostic imaging methods in metastatic disease

**KEYWORDS: Medical Oncology; Neoplasm Metastasis; Diagnostic Imaging; Radiography; Ultrasonography; Magnetic Resonance Imaging; Tomography, X-Ray Computed; Positron-Emission Tomography**

## INTRODUCTION

During last three decade extremely rapid development of technology in diagnostic imaging has been achieved. These innovations became available for application in oncology. Specific indications of imaging methods in oncology are: 1) early detection of malignant disease, 2) diagnosis and staging, 3) imaging guided biopsy, 4) guidance for tumoricidal techniques (radiofrequency ablation, embolotherapy, catheter-derived therapy), 5) radiotherapy planning, 6) monitoring of treatment response, 7) disease follow-up, 8) clinical trials with specific demands, and 9) research in oncology.
Regarding the important role of radiology in oncology, it is essential that oncologists understand the contribution and limitations of diagnostic imaging methods and be aware of new developments in this field.

## GENERAL CONSIDERATIONS

Diagnostic imaging methods are divided into two categories: anatomic imaging (conventional X-ray, computed tomography [CT], magnetic resonance imaging [MRI], ultrasonography [US]) and functional imaging (positron emission tomography [PET]), i.e. "spatial localized and/or temporally resolved sensing of molecular and cellular process *in vivo*" (1).
An image in medicine represents properties of the tissues that are obtained by one of two ways: a) the interaction of tissue with applied energy (conventional X-ray, CT, MRI, ultrasonography) and b) the emission of energy from exogenous administered radioactive tracers (PET). Each of these diagnostic imaging methods describes different tissue properties and operates at different level of the energy spectrum. Ultrasound uses low-energy sound waves, MRI are at the low-energy (radiofrequency) electromagnetic spectrum, whereas conventional X-ray, CT and PET operates in high-energy part of the electromagnetic spectrum. The image quality is additionally improved using contrast agents: nonspecific, delivered by blood stream and specific, targeted to particular tissues and cells. Proper combination of the imaging methods gives the complete information about cancer status (and function) *in vivo* (2).

## CONVENTIONAL X-RAY

Conventional X-ray is widely available and most cost-effective diagnostic tool. The X-ray image represents a map of the tissues depending on absorption of X-ray photons in the medium. Conventional X-ray image is valuable only if the tumor absorbs or attenuates X-ray beam more or les than surrounding tissues. Consequently, the application of the method is useful in the case of lung and bone metastases.
Apart from limited contrast for differentiation various soft tissues, the main disadvantage of the method is that all anatomical structures are projected in one plane, leading to superimposition of a metastatic nodule with normal anatomic structures. The chest X-ray, the traditional screening radiology exam for lung nodules/masses, frequently produces false-negative results. The sensitivity for the detection of lung nodules is low and the mean diameter of the missed lesion is 1.6 cm (3,4).
In the late 1990s, digital chest radiographs was introduced in the practice and partially resolved these problems. A digital image can be manipulated on a computer screen to enhance contrast, magnify image, invert gray-scale, to use computer-aided diagnosis (CAD), and subtract one lung from another to reveal subtle asymmetric opacities. However, it is unlikely that technical improvements in the chest X-ray will produce similar lesion detectability to CT (5).

## ULTRASONOGRAPHY

Ultrasonography exploited reflected sound waves to form the image, owing to the fact that the returning sound waves give the information about the separation of tissue planes with different acoustic properties. The advantages of ultrasonography are: excellent characterization of cystic and solid masses, good soft tissue contrast, availability, relatively low cost and absence of ionizing radiation. The method provides real-time images with possibilities for biopsy guidance. The limitations of ultrasonography are: operator dependency (subjectivity of the method), low reproducibility and dependency on the body habitus of the patient (6).
The main role of ultrasonography in metastatic disease is the detection of liver metastases, enlarged nodes in the neck, axillary, para-aortic and inguinal region, the further characterization of these masses and ultrasound guided biopsy. The reported sensitivity of ultrasound for detecting liver metastases is 56.3% and specificity 63% (7). The sensitivity and specificity of axillary ultrasonography is 67.6% and 80%, and in the patients with suspected neck lymph node metastases is 95% and 40% (8).
Further improvement of image is obtained by contrast-enhanced ultrasound (CEUS), recently introduced in clinical practice. The ultrasound contrast agents are microbubbles of gas encapsulated in lipid/lipoprotein shells, smaller than 7 $\mu$m. After intravenous administration they are entirely remain in the vascular system. The microbubbles are strong reflectors of sound and enhance brightness of the small liver or kidney lesion relative to the background tissue. CEUS improves the sensitivity of ultrasound for detecting of liver metastases to 83.8%. In particular, the CEUS led to an improvement in detection in the cases of nodular hepatic metastases smaller than one centimeter, after adjuvant chemotherapy and for lesions near the surface of the liver (7).

## CT

The principle of CT is the projection of X-rays from multiple angles, generating tomographic, axial images. Since introduction of CT in the mid 1970s, there has been continuous evolution of the technology, from devices that acquire a single slice at a time, through single spiral scanning to the multidetector spiral scanning. Current clinical CT scanners contain up to 64 detector rows and acquire 64 slices at a time. The spatial and temporal resolution of CT has increased

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to the level which provides images of submillimeter structures and rapid acquisition of data, without motion artifacts and volume-averaging effects. All tissues can be visualized three-dimensionally in highly reproducible, investigator-independent way. The rapid scanning provides acquisition of the entire image during the peak of the bolus of intravenous contrast, enhancing the effects of contrast agents and creating 3D CT angiography. CT angiography provides "vascular mapping" for surgery, especially important in the cases of limited, minimal invasive surgery. Furthermore, 3D image data are processed to generate images of virtual colonoscopy and bronchoscopy, as well as CT urography (2). The main disadvantage of CT is the radiation in relatively high dosages. For example, CT examination of abdomen delivers 16 mSv, compared with 0.7 mSv of abdomen conventional X-ray (6).

Nevertheless, because of mentioned advantages, at present, CT is the most frequently used imaging diagnostic method in developed world for diagnosis, staging, detection of nodal and distant metastases, monitoring and follow-up in oncology. Reported sensitivity of pulmonary nodule detection on thin-section thoracic CT scans is 67%, while the sensitivity and specificity of CT for detecting metastatic mediastinal nodes in lung cancer staging is 70% and 69%. Several CAD software packages that calculate lung nodule volume are currently available. They provide more reproducible measurements than manual nodule measurement that is particularly important in the following of the response to lung metastatic disease therapy (9,10). Sensitivity and specificity of hepatic metastases diagnosis for contrast-enhanced CT is 89% and 89%. Particular quality is the visualization of specific pathology of liver, such as a differentiation of hypovascular metastasis in the portal venous phase from hypervascular hepatoma in the late arterial phase (7).

## MRI

MRI is using magnetic fields and radiofrequency waves to induce and detect a signal from various body tissues that is then converted to a gray-scale image. Signal strength is determined by the amount of hydrogen nuclei in the tissue. Advantages of MRI are: method is nonionizing; high resolution and high soft tissue contrast; possibility to obtain direct images in any plane; possibility to further enhance inherent high sensitivity for tissue characterization by the use of different MR-contrast agents. Increased signal on T1-W MR images after intravenous administration of extracellular MRI contrast gadolinium is highly suspicious for tumor activity, with relatively low percentage of false-negative results. Contrast enhanced total-body MRI is potential first-line modality for screening for metastases (6). New MRI contrast has developed, such as mangafodipir trisodium for the detection of hepatic metastases, or LHRH-conjugated magnetic iron oxide, specific contrast for detection of breast cancer metastases in lymph nodes, bones and peripheral organs (11,12). Disadvantages of MRI are: long examination time, relatively high cost, limited availability and, until now, the lack of a uniform technique and reproducibility. Consecutively, MRI is rarely used as the first diagnostic modality, except for brain and soft tissue tumors. Indications for MRI are usually specific problems and difficult clinical cases that are no resolved after conventional X-ray, US or CT examinations (6).

## PET

PET images represent the distribution of radiopharmaceuticals labeled with positron emitters. Emitted radioactivity is detected by camera to generate an image. Different positron-emitting isotopes are incorporated into biologic molecules, and their uptake in the patients reflects specific cellular process, which are usually increased in tumors. Commercially available positron emitter, Fluorine-18 deoxyglucose (FDG) is analog of glucose. Increased FDG uptake in tumor cells and intracellular accumulation give the high contrast between tumor and normal tissues and proper sensitivity for tumor detection and staging. The main indication for FDG-PET is presurgical staging of the patient with non-small cell lung cancer, colorectal liver metastases, esophageal cancer and metastatic melanoma. Limitations of FDG-PET are: lack of anatomical details that is solved by the introduction of integrated PET-CT scanners, false positive results because of the accumulation of FDG in inflammatory foci and limited availability of PET scanners (2,6,13).

## CONCLUSION

Continuous development of complementary imaging methods and the increasingly availability of functional imaging (PET, PET/CT) in recent years has provided a remarkable possibility to define human anatomy and cell function *in vivo*. Sensitivity and specificity of these methods in detection of metastatic disease are mainly defined. Nevertheless, the role of imaging methods in diagnostic algoritms are modified by availability and cost effectiveness of imaging, as interesting and complex question in oncology practice.

## REFERENCES


**1.** Thrall JH. ACR primer on molecular imaging. J Amer Coll Radiol 2004;1:32.

**2.** Schnall M, Rosen M. Primer on imaging technologies for cancer. J Clin Oncol 2006;24:3225-33.

**3.** Lobrano M. Partnerships in Oncology and Radiology: The Role of Radiology in the Detection, Staging, and Follow-up of Lung Cancer. Oncologist 2006;11:774-9.

**4.** Woodard K, Slone M, Sagel S, et al. Detection of CT-proved pulmonary nodules: comparison of selenium-based digital and conventional screen-film chest radiographs. Radiology 1998;209:705-7.

**5.** Tsukuda S, Heshiki A, Katsuragawa S, et al. Detection of lung nodules on digital chest radiographs: potential usefulness of a new contralateral subtraction technique. Radiology 2002;223:199-203.

**6.** Barentsz J, Takahashi S, Oyen W, et al. Commonly used imaging techniques for diagnosis and staging. J Clin Oncol 2006;24:3234-44.

**7.** Quaia E, D'Onofrio M, Palumbo A, Rossi S, Bruni S, Cova M. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. Eur Radiol 2006;16:1599-609.

**8.** Meller B, Sommer K, Gerl J, et al. High energy probe for detecting lymph node metastases with 18F-FDG in patients with head and neck cancer. Nuklearmedizin 2006;45:153-9.

**9.** Rubin G, Lyo J, Paik D, et al. Pulmonary Nodules on Multi–Detector Row CT Scans: Performance Comparison of Radiologists and Computer-aided Detection. Radiology 2005;234:274-83.

**10.** Shim S, Lee K, Kim B, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. Radiology 2005;236:1011–9.

**11.** Regge D, Campanella D, Anselmetti GC, et al. Diagnostic accuracy of portal-phase CT and MRI with mangafodipir trisodium in detecting liver metastases from colorectal carcinoma. Clin Radiol 2006;61:338-47.

**12.** Leuschner C, Kumar CS, Hansel W, Soboyejo W, Zhou J, Hormes J. LHRH-conjugated Magnetic Iron Oxide Nanoparticles for Detection of Breast Cancer Metastases. Breast Cancer Res Treat 2006;99(2):163-76.

**13.** Weng E, Tran L, Rege S, et al. Accuracy and clinical impact of mediastinal lymph node staging with FDG-PET imaging in potentially resectable lung cancer. Am J Clin Oncol 2000;23:47–52.

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# Current controversies in intraperitoneal chemotherapy

**KEYWORDS: Ovarian Neoplasms; Antineoplastic Agents; Injections, Intraperitoneal**

Ovarian cancer is the most lethal gynecological malignancy and patients frequently present at advanced-stage disease. Epithelial ovarian cancer appears to arise from the epithelial surface of the ovary and spread by local extension and peritoneal hydrodynamics from the right pelvic sidewall then along the right paracolic gutter, across the right and left diaphragmatic surfaces and then down the left paracolic gutter into the left pelvis leaving tumor deposits in multiple peritoneal sites. A second mode of spread is via lymphatics into both pelvic and para-aortic nodes in the retroperitoneum (1). As the primary tumor develops, cells shed from the tumor, circulate within the peritoneal cavity, and implant on peritoneal surfaces within the abdomen and/or pelvis. This can happen even when the primary tumor is undersized in volume, which contributes to the difficulties in diagnosing cancer when cancer remains confined to the ovary. In the hands of experienced and skilled surgeons, most patients are undergone to optimal cytoreductive surgery. In such case disease is surgically removed so that no implant greater than 1 cm remains (2,3). Because the disease is predominantly within the peritoneum, treatment approaches that target the peritoneal cavity may have the twofold advantages of maximizing the concentration and the duration of exposure of intraperitoneal (IP) tumor to anticancer agents, and minimizing the exposure of normal tissues, such as the bone marrow, to the unwanted toxic effects of these agents. Ovarian cancer is unique among solid tumors in its propensity and inclination to remain localized to the peritoneal cavity. Recognizing that, investigations reached over 20 years have explored the potential efficacy of cytotoxic chemotherapy administered into this cavity after debulking surgery to obtain higher concentrations of drugs in the area of residual tumor. The goal of primary surgery is to reduce the burden of ovarian cancer to no- or minimal residual disease. The definition of minimal disease burden has changed over the years, but it is now generally considered as no single nodule in size 1 cm or more at the end of surgical treatment. There are also data suggesting that patients who have the lowest tumor burden, only microscopically visible, have the better outcome, and are the best candidates for a regional therapy. Recognizing that, IP administration of chemotherapy was first proposed nearly three decades ago by Dedrick (4). Studies that have evaluated the peritoneal to plasma ratio of drugs find at multiple time points that peritoneal concentrations far exceed the plasma concentrations (5).

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## TOXICITY OF INTRAPERITONEAL THERAPY

Toxicity from IP therapy is significant. It is the best reflected in the fact that typically fewer than two-thirds of patients are able to complete all scheduled cycles of therapy by the IP route. Many toxicities with the IP therapy are related to pain associated with the IP infusion itself. Finally, systemic toxicities clearly related to the cytotoxic agents themselves are also more common in the group receiving IP therapy (6). More patients in the IP therapy group had clinically significant fatigue and hematological, gastrointestinal, renal, and neurological adverse effects than the intravenous group.

## COMPLICATIONS OF INTRAPERITONEAL THERAPY

Some of above toxicities are related to mechanical problems with the IP catheter, and some of these issues have been solved by using catheters without a Dacron cuff that enhances the ingrowths of fibrinous material leading to catheter occlusion (3).
Walker et al reported that among 205 eligible patients randomly assigned to IP therapy on GOG protocol 172, 119 patients (58%) did not complete the prescribed six cycles of treatment (7). Forty patients, representing 19% of all randomly assigned patients and 34% of those who failed to complete the prescribed treatment program, discontinued IP therapy primarily because of catheter complications. Catheter complications included infection (10.2%), blockade (4.9%), access problems (2.4%), and leakage (1.9%).%). In general, bowel complications associated with IP catheters have been reported to occur at a rate of 3% to 5% and include fistulae, catheter migration into the bowel lumen, bowel obstruction, and bowel perforation (8).

## SURGICAL QUESTIONS IN INTRAPERITONEAL THERAPY

There are many clinical data demonstrating a survival advantage for patients with International Federation of Gynecology and Obstetrics (FIGO) stage III ovarian cancer treated with intraperitoneal (IP) chemotherapy compared with the standard intravenous treatment route. Survival determinants are multifactorial: the survival outcome associated with cytoreduction of bulky tumor to small-volume residual disease does not result in equal survival to patients with initial small-volume disease and extensive cytoreductive surgery that leaves a maximal diameter of residual disease of 2 cm or more has no appreciable effect on survival. The maximal diameter of residual disease correlates with subsequent survival outcome according to classification in three distinct groups: no macroscopic residual disease (5-year survival, 60%), residual disease 2 cm or less (5-year survival, 35%), and residual disease more than 2 cm (5-year survival, 20%). The survival benefit associated with IP chemotherapy as front-line treatment of advanced ovarian cancer will only be realized by ensuring that the majority of patients are submitted to a primary surgical effort that leaves minimal residual disease.
The feasibility of improving ovarian cancer surgical care was represent in a report by Chi (9) who described the impact of change in surgical approach incorporating extensive upper abdominal debulking procedures, on the rate of optimal primary cytoreductive surgery in patients with advanced ovarian cancer.

## IP CATHETERS

The original Tenckhoff peritoneal dialysis catheters showed two major problems if are used for ovarian cancer chemotherapy (10). Firstly, the catheter fenestrations tend to cause a fibrous sheath formation, which lead to adhesions within the peritoneal cavity. The second, they have a Dacron cuff, which

has been reported to migrate into the peritoneal cavity and result in bowel obstruction. Currently, the use of a semi-permanent subcutaneous venous-access port connected to a single-lumen venous catheter, such as 9.6 French polyurethane venous access tubing, is recommended by most authorities with expertise in the administration of IP chemotherapy. IP ports may be placed at the time of primary cytoreductive surgery or delayed for several weeks and placed as an interval surgical procedure, usually via laparoscopy. It is unclear whether resection of the rectosigmoid or left colon represents a contraindication to concurrent IP catheter insertion.

A recent publication in the *New England Journal of Medicine* about a Gynecologic Oncology Group (GOG) study (Protocol 172) to evaluate IP versus intravenous (IV) cisplatin and paclitaxel chemotherapy for stage III epithelial ovarian cancer has produced controversy (3). The authors reported that patients who received IP treatment had better rates of survival than those who received IV therapy, with a median survival of 15 months longer. The National Cancer Institute (NCI) issued a bulletin suggesting that, in women in stage III epithelial ovarian cancer, IP cisplatin should be considered for their treatment.

Mauriae Markman, MD forcefully encouraged that IP cisplatin should be considered the standard therapy in women with advance stage of ovarian cancer, and he argues that there are now three independent GOG trials that showed survival advantage to IP cisplatin therapy (11).

Robert F. Ozols, MD, PhD, expressed concern that in these trials, there was no direct comparison with IV carboplatin and paclitaxel, which has been considered the standard treatment for patients with ovarian cancer and noted his concern that only 42% of women randomly assigned to the IP arm actually completed six cycles of the treatment because of toxicity and catheter complications (12). Patients selection will obviously be the cornerstone of the decision regarding these therapeutic alternatives.

IP therapy has been studied for more than two decades. Despite several clinical trials, no survival advantage has been reported compared with standard IV carboplatin/paclitaxel in patients with optimal stage III disease. It seems judicious that before IP therapy, with its formidable and difficult toxicity, will be recommended for routine use, it should be prospectively compared with a much less toxic, more convenient regimen of IV carboplatin/paclitaxel, which in a forceful, exploratory cross-trial comparison appears to have very similar efficacy (13).

In conclusion patients with suboptimal residual extensive carcinomatosis, those with stage IV disease, and those with serious co-morbid conditions, low performance status, and advance age might not tolerate the added morbidity of IP therapy or derive any significant benefit over IV therapy.

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## REFERENCES

**1.** Bristow RE, Tomacruz RS, Armstrong DK, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol 2002;20:1248-54.

**2.** Bristow RE, Zahurak ML, del Carmen MG, et al. Ovarian cancer surgery in Maryland: Volume-based access to care. Gynecol Oncol 2004;93:353-60.

**3.** Armstrong D, Bundy B, Wenzel L, et al. Phase III randomized trial of intravenous cisplatin and paclitaxel versus an intensive regimen of intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in stage III ovarian cancer: A Gynecologic Oncology Group study. N Engl J Med 2006;354:34-43.

**4.** Dedrick R, Myers C, Bungay P, et al. Pharmocokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 1978;62:1-11.

**5.** Cannistra SA. Intraperitoneal chemotherapy comes of age. N Engl J Med 2006;354:77-9.

**6.** Francis P, Rowinsky E, Schneider J, et al. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: A Gynecologic Oncology Group pilot study. J Clin Oncol 1995;13:2961-7.

**7.** Bilsel Y, Balik E, Bugra D, et al. A case of protrusion of an intraperitoneal chemotherapy catheter through the rectum. Int J Gynecol Cancer 2005;15:171-4.

**8.** Walker JL, Armstrong DK, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group study. Gynecol Oncol 2006;100:27-32.

**9.** Chi DS, Franklin CC, Levine DA, et al. Improved optimal cytoreduction rates for stage IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: A change in surgical approach. Gynecol Oncol 2004;94:650-4.

**10.** Jenkins J, Sugarbaker PH, Gianola FJ, et al. Technical considerations in the use of intraperitoneal chemotherapy administered by Tenckhoff catheter. Surg Gynecol Obstet 1982;154:858-64.

**11.** Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001-7.

**12.** Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-200.

**13.** Ozols RF, Gore M, Trope C, Grenman S. Intraperitoneal treatment and dose-intense therapy in ovarian cancer. Ann Oncol 1999;10:(Suppl 1):59-64.