

Contents

1-3 Pet Scanning in Oncology: Does a Better Diagnostic Test Make a Difference?

3-6 Avastin (Bevacizumab) Therapy in Oncology

7 Magnetic Resonance Imaging for Breast Screening and Diagnosis

8 Avastin Treatment for Glioblastoma

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3-Minute Impact Movie

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Oncology Special Edition

Pet Scanning in Oncology: Does a Better Diagnostic Test Make a Difference?

Ed Clark, M.D.

Computed tomography (CT) and magnetic resonance imaging (MRI) are high resolution, computer-based anatomic imaging techniques used generally in medicine and specifically in oncology. CT uses X-rays to discriminate between different tissues based on X-ray density. MRI uses radio waves to discriminate between different tissues based on hydrogen proton density.

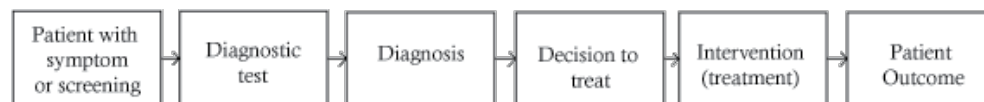
Positron emission tomography (PET) is a computer-based imaging method using a positron emitting a radioactive tracer that accumulates in abnormal tissue. PET creates low-resolution images causing areas of abnormality to appear as “hot” and stand out from normal background tissues. Since PET images are low-resolution, PET is often combined with CT to give high-resolution CT images of “hot” spots identified by PET.

While an MRI has no radiation dose, radiation dose from a CT is approximately 200 to 400 chest x-ray equivalents (CXREs) — that is, the amount of radiation exposure equivalent to undergoing 200 to 400 chest X-rays. The radiation dose from a PET scan is approximately 150 CXREs. From a combined PET/CT, it is approximately 350 to 550 CXREs.

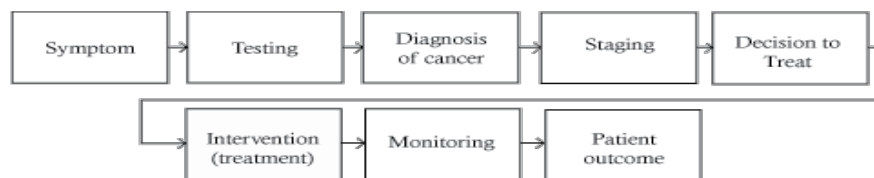
The approximate costs for each of these procedures is \$400 for a CT, \$900 for MRI, \$1,800 for PET and \$2,100 for PET/CT.

Clinical decision-making in oncology

A typical patient encounter can be represented schematically as:



For cancer, this scheme needs to be expanded. After the diagnosis of cancer is made, current standards of care require that the provider determine what stage the cancer has reached (whether it's localized, has spread to nearby tissues or has spread widely to other parts of the body) prior to finalizing treatment decisions. In addition to a staging step, treatment is often monitored for effectiveness or cancer recurrence. Imaging is often central to diagnosis, staging and treatment monitoring in many types of malignancy.



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Although it seems obvious that better diagnostic performance will result in better treatment decisions and patient outcomes, this is not always the case. (1, As an example, CT of the abdomen and pelvis for the diagnosis of appendicitis has not reduced the number of negative surgeries or ruptured appendices [1-4]). In addition to diagnostic information, a number of factors influence treatment decisions — patient preferences, other existing medical conditions, physician preference or specialty and anecdotal physician experience. A test might be quite good at distinguishing cancer from non-cancer, but not result in changes in treatment, or there might be no difference in benefit between any of the treatment options.

Patients, doctors and insurers would like to use tests that result in improved patient outcomes and avoid the radiation dose, side effects and costs of tests that do not. However, establishing the link between a diagnostic test and improved patient outcomes is very difficult because of multiple intervening steps and factors (decision to treat, type of treatment, variability in individual patient responses, effectiveness of treatments, etc.). The evidence for improved clinical outcomes from most diagnostic tests is lacking. This is also true for PET scanning in oncology.

Current coverage for PET (PET/CT) in Oncology

The Center for Medicare and Medicaid Services (CMS) currently approves PET for coverage for the following conditions:

| Clinical Condition | Effective Date | Coverage |
|------------------------------|----------------|---|
| Solitary Pulmonary Nodule | 7/1/98 | Characterization |
| Lung Cancer (Non Small Cell) | 7/1/01 | Diagnosis, Staging and Restaging |
| Esophageal Cancer | 7/1/01 | Diagnosis, Staging and Restaging |
| Colorectal Cancer | 7/1/01 | Diagnosis, Staging and Restaging |
| Lymphoma | 7/1/01 | Diagnosis, Staging and Restaging |
| Melanoma | 7/1/01 | Diagnosis, Staging and Restaging; not covered for evaluating regional nodes |

| | | |
|--------------------------|---------|---|
| Head and Neck Cancer | 7/1/01 | Diagnosis, Staging and Restaging |
| Cervical Cancer | 4/18/05 | Staging of new, locally advanced cancer with no extra-pelvic metastases on conventional imaging tests |
| Brain Cancer | 4/18/05 | Coverage with evidence development (enrolled in a qualifying clinical trial) |
| Ovarian Cancer | 4/18/05 | Coverage with evidence development |
| Pancreatic Cancer | 4/18/05 | Coverage with evidence development |
| Lung Cancer (Small cell) | 4/18/05 | Coverage with evidence development |
| Testicular Cancer | 4/18/05 | Coverage with evidence development |

Coverage with evidence development is a strategy undertaken by CMS to develop evidence of the effect of diagnostic tests on patient outcomes. There are ongoing clinical trials investigating the effect of PET on patient outcomes for the last six cancers in the above table and multiple additional cancers. The National Oncology PET Registry is collecting data from multiple sites across the United States on multiple cancers and is beginning to publish its findings (5). CMS is evaluating the results.

To simplify the research question, the National Oncology PET Registry is investigating the effect of PET on treatment decisions (change in decisions before and after PET) rather than actual patient outcomes. This is an intermediate step that is much easier and quicker to answer than actual patient outcomes. The initial published data suggest that PET does change treatment decisions for many cancers.

A number of commercial carriers cover PET scans for on-
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cology. As an example, Regence Blue Cross (6, <http://blue.regence.com/printFriendly.jsp>) covers PET (or PET/CT) for diagnosis when PET may avoid an invasive procedure. It also covers PET for staging either when the stage remains in doubt after conventional imaging or when PET could potentially replace conventional imaging studies that are expected to provide insufficient information and the clinical management of the patient would differ depending on the stage of the tumor.

Evidence of diagnostic effectiveness

In 2004, the Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review of the evidence on PET in six cancers: brain, cervical, small-cell lung, ovarian, pancreatic and testicular (7). For each cancer, there were key questions related primarily to comparative effectiveness of PET to CT or MRI in diagnosis, staging and re-staging after treatment. In most cases, PET had marginally higher sensitivity, specificity, positive predictive values and negative predictive values than CT or MRI in diagnosis and staging. This systematic review noted the absence of evidence on the effectiveness of PET on patient outcomes. It was this AHRQ review that led the CMS decision to begin coverage with evidence development in 2005.

Caveat

There is an important distinction between the lack of evidence for effect on clinical outcome and evidence of lack of effect. The case for PET is that there is lack of evidence of effect, meaning that there may be a positive or negative effect of PET on patient outcomes. Therefore, the question about the improving patient outcomes remains to be answered.

Conclusion

PET is a high tech, low-resolution imaging method that uses a radioactive tracer to localize areas of tumor. It is normally combined with CT to give high-resolution anatomic information. It is expensive and has a high radiation dose. It has marginally better diagnostic efficacy (sensitivity, specificity, etc.) than CT or MRI for many tumors. The role of PET in changing treatment decisions and improving patient outcomes has yet to be determined and CMS is currently investigating and considering this.

References

1. McDonald GP, Pendarvis DP, Wilmoth R, Daley BJ. Influence of preoperative computed tomography on patients undergoing appendectomy. *Am Surg.* 2001. 67 (11): 1017-21.
2. Huynh V, Lalezarzadeh F, Lawandy S, Wong DT, Joe VC. Abdominal computed tomography in the evaluation of

acute and perforated appendicitis in the community setting. *Am Surg.* 2007. 73 (10): 1002-5.

3. Musunuru S, Chen H, Rikkers LF, Weber SM. Computed tomography in the diagnosis of acute appendicitis: definitive or detrimental? *J Gastrointest Surg.* 2007. 11 (11): 1417-21.
4. McGory ML, Zingmond DS, Nanayakkara D, Maggard MA, Ko CY. Negative appendectomy rate: influence of CT scans. *Am Surg.* 2005. 71(10): 803-8.
5. Hillner BE, Siegel BA, Liu D, Shields AF, Gareen IF, Hanna L, Stine SH, Coleman RE. Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. *J. Clin Oncol.* 2008; 26 (13): 2155-2166.
6. The Regence Group. Medical Policy Manual. Oncologic Applications of PET Scanning. Seattle, WA. 2008.
7. Matchar DB, Kulasingam SL, Havrilesky L, Mann LO, Myers ER, McCrory DC, Patwardhan M, Prosnitz R. Positron Emission Testing For Six Cancers (Brain, Cervical, Small Cell Lung, Ovarian, Pancreatic and Testicular) Agency for Healthcare Research and Quality, Rockville, Maryland 20850. February 2004.

Avastin (Bevacizumab) Therapy in Oncology

Jonathan Eneman, M.D.

Bevacizumab (Genentech brand name Avastin) is a targeted drug therapy with a growing number of indications in oncology. It is a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). Increased VEGF serum levels correlate with lower survival rates and tumors require new blood vessel growth (neovascularization) to grow and metastasize, which the drug inhibits.

Single-drug therapy with bevacizumab has shown limited benefit in most studies. However, studies have seen significant benefit for a variety of tumors when bevacizumab is given in combination with chemotherapy. The FDA has approved bevacizumab for the management of colon cancer, lung cancer and breast cancer.

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Although oncologists do not know exactly how bevacizumab works or its optimal dose, more than 400 clinical trials of bevacizumab are underway because of its promise in treating many cancers. As oncologists strive to provide optimal therapy for patients, a thorough understanding of what currently is known about the benefits of this drug is critical – particularly in light of its potential medical risks and significant financial cost (roughly \$100,000 for an average woman with metastatic breast cancer during one year of therapy). Due to the vast uncertainties regarding this drug, questions are likely to be debated among oncologists for some time.

This article reviews bevacizumab's current FDA approved uses, commonly accepted off-label uses, and current areas for research and treatment risks. This discussion will be limited to bevacizumab's oncology uses, but it is also used in non-oncologic conditions, such as macular degeneration.

FDA approved indications

Bevacizumab is currently indicated for the treatment of metastatic colorectal cancer, metastatic non-squamous non-small cell lung cancer, and, most recently, first-line metastatic therapy in combination with paclitaxel for her-2 negative breast cancer.

For metastatic colorectal cancer, there is considerable clinical-trial data supporting bevacizumab given with multiple different regimens, including fluoropyrimidines with or without oxaliplatin or irinotecan. Additionally, combination antibody therapy with cetuximab (directed against the epidermal growth factor receptor, EGFR) has also demonstrated efficacy, though the combination of bevacizumab with cetuximab is currently the subject of CALGB 80405 when given in combination with chemotherapy (a strategy that was not effective with the EGFR inhibitor panitumumab in the PACCE trial). While most of the data with bevacizumab has been in the first line setting, ECOG 3200 demonstrated a significant benefit for the addition of bevacizumab in a second-line oxaliplatin containing regimen. In addition to using a higher dose (10 mg/kg every two weeks instead of the more standard 5mg/kg every two weeks in first-line colorectal cancer), patients in this study did not receive prior bevacizumab. Continuation of bevacizumab following progression on a bevacizumab containing regimen is a separate question (See "research questions" below).

Palliative therapy for non-squamous, non-small cell lung cancer has been significantly improved by adding bevacizumab in combination with carboplatin and paclitaxel (ECOG 4599) or cisplatin and gemcitabine (the AVAiL trial). The dose of bevacizumab was similar to that for first-line colorectal cancer

trials at 15 mg/kg every three weeks (averaging 5 mg/kg/week), but the AVAiL trial included an arm with a reduced bevacizumab dose (7.5 mg/kg/three weeks) which also appears efficacious. However, at present, most oncologists favor the higher dose.

ECOG 2100 demonstrated a dramatic progression free survival (PFS) advantage for the addition of bevacizumab chemotherapy in the first-line therapy of breast cancer when combined with weekly paclitaxel. Though the PFS lengthened from roughly six months to 12 months, overall survival was not improved. This was probably due to the multiple lines of palliative therapy available for the management of metastatic breast cancer. Nonetheless, bevacizumab recently received FDA approval for this indication.

In the above trials, bevacizumab was continued as a single agent until disease progression in cases where the chemotherapy was planned to discontinue (as in the ECOG 4599 and AVAiL). Currently, the benefit of bevacizumab alone is unknown. The drug is also commonly continued with fluoropyrimidine therapy if oxaliplatin or irinotecan is discontinued to minimize toxicity in colorectal cancer management (such as with the OPTIMOX strategy, De Gramont, 2005).

Common standard off-label uses for bevacizumab

There are several ongoing clinical trials including bevacizumab for different tumor types and chemotherapy or radiation therapy combinations. Given the uniformly grave prognosis for cancer patients, oncologists have a long tradition of providing palliative off-label treatments and using a sensible amount of safety and efficacy data. While enrollment in a clinical trial is always preferred, it is not always appropriate, available or desired for a patient. Additionally, given the relatively slow and expensive progress of FDA approval for new indications, oncologists often offer treatments prior to FDA endorsement.

Gray areas exist between what is experimental and what is a reasonable off-label use for a medication. Often this is resolved with consensus expert opinion. But specific insurance plan language is sometimes critical in making this distinction. Current off-label indications for bevacizumab include renal cell cancer, ovarian cancer and glioblastoma multiforme.

Renal cell cancer (clear cell) has seen a recent explosion of effective targeted therapies. These tumors commonly are characterized as having a loss of heterozygosity in the von Hippel-Lindau gene resulting in a significant up-regulation of VEGF in these vascular tumors. Phase II study has demonstrated a

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prolongation of PFS with single-agent bevacizumab versus placebo (Yang JC, et al 2003). Preliminary results of a recent phase III study of alpha interferon therapy with or without bevacizumab (the AVOREN trial) reported that with a median follow-up of 13 months there was a significant improvement in response rates and PFS with the addition of bevacizumab.

While the optimal combination and sequencing of these agents is debated and researched, many experts will now integrate bevacizumab at some point in cancer treatment. Similar issues have been raised by positive reports using bevacizumab in the management of advanced or refractory ovarian cancer and glioblastoma multiforme (GBM). Although the use of bevacizumab to treat these tumors has not received FDA approval, they have become sufficiently supported by the oncology community for inclusion in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines.

Risks and warnings

Although there are no “contraindications” listed for bevacizumab, there are several concerns regarding its use that require great care regarding patient selection and continued treatment. While common side effects include hypertension, headache, nosebleeds, and proteinuria, most of these are mild and manageable with anti-hypertensives. However, the long-term effects of these are not known and are an important consideration as oncologists move toward using these therapies to prevent cancer from recurring. As with other antibody therapies, infusion reaction can occur (in less than three percent of cases) and may require premedication or drug discontinuation. Also, other serious adverse reactions have been seen and can limit the appropriateness of bevacizumab therapy.

Early lung cancer trials reported significant and sometimes fatal pulmonary hemorrhaging. Hemorrhaging occurred with greater frequency in patients having squamous cell histology. Such patients were subsequently excluded from clinical trials and excluded from the FDA indication. This safety concern should not be overlooked. While oncologists still do not know the mechanism with certainty, the reason appears to be related to tumor histology rather than the common central location of these tumors. For this reason, there is a “black box” warning for bevacizumab use with patients who have recently coughed up more than half a teaspoon of blood or in whom hemoptysis develops.

Clinical trials also have excluded patients with recent arterial thromboembolic events (heart attack and stroke) as well as patients with brain metastasis. Although there are ongoing trials including bevacizumab usage in patients with brain tumors (including NCCN guidelines supporting its use in the

treatment of GBM) and irradiated brain metastasis, as well as patients on chronic anticoagulation, these are situations in which the managing physician must discuss carefully the risks and benefits with the patient. Additionally, operative complications have been seen with bevacizumab, including wound complications. Clinical trials have excluded patients with incomplete wound healing due to its half-life of nearly three weeks. The trials have also required patients to have completed major surgery four to six weeks before receiving bevacizumab and to withhold bevacizumab for a similar period before elective surgery.

Other “black box” warnings include concerns for gastrointestinal perforation (less than four percent) and wound dehiscence (one percent). The significance of these known, as well as additional unknown side-effects, are underscored by the continued reporting of rare, but unanticipated complications in ongoing trials, such as reversible posterior leukoencephalopathy syndrome (less than one percent) that can occur anywhere from less than a day to one year after therapy. Recent studies of patients with lung cancer and esophageal cancer have noted tracheoesophageal fistula formation when the drug was provided in combination with chemotherapy and radiation therapy.

Research questions

There are several unanswered questions for which additional research may provide future direction. For instance, can bevacizumab provide similar benefits in the management of the tumors noted, but with different chemotherapeutic agents or with radiation therapy? Will it add to therapy in the adjuvant or neoadjuvant setting? What is the most appropriate dose, schedule and treatment duration? Researchers debate that targeted therapies may not be optimally dosed by the standard Phase I trial design and the expense may be significantly modified if trials such as the AVAiL study have evidence supporting the benefit of lower dosages. At present, continuation of bevacizumab into second-line therapy is not supported by the NCCN guidelines.

Still, many oncologists feel that the drug’s efficacy is in making chemotherapy more effective (perhaps by “normalizing” blood flow to tumors and improving chemotherapy delivery). If this were true, oncologists would want to continue bevacizumab even after progression with one chemotherapeutic to combine it with another. The BRiTE registry data demonstrating a survival advantage for metastatic colon cancer patients with continued bevacizumab treatment supports this view. Unfortunately, observational studies can have significant bias

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and most experts would still strongly favor enrollment onto the SWOG 0600 iBET trial for patients who received first line bevacizumab with an oxaliplatin containing regimen, and who are interested in randomization to continuation with irinotecan and cetuximab.

A separate area of off-label or research use includes changing the treatment line use or combining bevacizumab with alternative chemotherapies already approved. For example, first-line therapy for breast cancer has a significant PFS when bevacizumab is combined with paclitaxel, but many physicians might favor capecitabine as first-line chemotherapy for its oral administration and side effect profile. This presents the three questions: (1) Would paclitaxel and bevacizumab be as effective if provided in second-line therapy after capecitabine? (2) Could bevacizumab be provided with capecitabine? (3) Would the substitution of nab-paclitaxel (Abraxane, Abraxis; a proprietary "nanoparticle albumin-bound" formulation of paclitaxel that requires no premedications, allows higher paclitaxel doses, and may be more efficacious) be acceptable if infusional therapy is pursued during first line?

Although some of these questions may be answered in ongoing trials, many oncologists do not feel that research resources (including a limited number of eligible patients) should be devoted to answer some of these questions for practical reasons. Instead, they favor empiric treatment. Others may utilize subset analysis as in a recent trial of first-line bevacizumab and capecitabine (Sledge, et al, 2007) which showed improvement in response rate but no PFS or OS improvement feeling that this combination is reasonable in the hormone receptor positive subset that did appear to have some incremental benefit. At present, the NCCN guidelines only provide paclitaxel as a "preferred" agent to combine with bevacizumab.

In the interest of patient safety and benefit, as well as controlling health care costs, physicians need to be mindful of the limits of their knowledge regarding bevacizumab therapy. This will become a greater issue as this fascinating therapy continues to find more uses.

References

1. Baselga J, Taberner J. Combined Antiangiogenesis and Antiepidermal Growth Factor Receptor Targeting in the Treatment of Cancer: Hold Back, We Are Not There Yet. *J Clin Oncol* 2007; 25: 4516-4518.
2. De Gramont A, Cervantes A, Andre T, et al. OPTIMOX study: FOLFOX 7/LV5FU2 compared to FOLFOX 4 in patients with advanced colorectal cancer. *ASCO Meeting Abstracts* 2004; 22:3525.
3. Escudier, B, Pluzanska, A, Koralewski, P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2008; 370:2103-2111.
4. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol* 2008; 26:76-82.
5. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25:1539-1544.
6. Grothey, A, Sugrue, M, Hedrick, E, et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival in patients with metastatic colorectal cancer (mCRC): Results from a large observational study (BRiTE) (abstract). *J Clin Oncol* 2007; 25:172s.
7. Manegold, C, von Pawl, J, Zatloukal, P, et al. Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (abstract). *J Clin Oncol* 2007; 25:967s.
8. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
9. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial - E4599. *J Clin Oncol* 2005 ASCO Annual Meeting Proceedings. 2005; 23: LBA4
10. Sledge G, Miller K, Moisa C, et al. Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2007; 25:1013
11. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007; 25:4722-4729.
12. Yang, JC, Haworth, L, Sherry, RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; 349:427-434.

Magnetic Resonance Imaging for Breast Screening and Diagnosis

Richard Karchmer, M.D.

As a screening or diagnostic tool, mammograms can detect breast cancer during its early stages and reduce mortality rates if the appropriate treatment follows diagnosis. However, new 2007 screening guidelines from the American Cancer Society and another article published in the *New England Journal of Medicine* also call for expanded use of magnetic resonance imaging (MRI) in addition to mammography to detect breast cancer. MRI is a diagnostic procedure that uses magnets and radio waves to produce images of the breast that can be more sensitive than mammography.

MRIs for screening

The American Cancer Society (ACS) organized a Breast Advisory Group and published recommendations for breast screening using MRI in addition to routine mammography. Based on evidence, the ACS recommended annual MRI screening for anyone with a lifetime breast cancer risk of 20 percent or greater based on predictive models. This included anyone with a BRCA gene mutation or an untested, first-degree relative of a BRCA carrier. The panel also recommended an annual MRI screening for anyone who received radiation to the chest between the ages of 10 and 30, as well as patients and their first-degree relatives with Li-Fraumeni, Cowden or Bannayan-Riley-Ruvalcaba syndromes.

The panel felt there was insufficient evidence to recommend for or against MRI screening for women with a 15 to 20 percent risk of breast cancer, lobular carcinoma in situ, atypical ductal hyperplasia or women with dense breasts shown on mammography or a personal history of breast cancer. Physicians must make these decisions on a case-by-case basis.

The panel recommended against annual MRI screening for women with less than a 15 percent lifetime risk of breast cancer. The increased sensitivity of MRI scans can produce false positive readings that can lead to further tests, unneeded biopsies and patient anxiety. Screening women at low risk would find very little cancer and the current efforts focus on MRI screening for women at higher risk.

Using MRIs for diagnosis

MRI can also be very useful in women with diagnosis of breast cancer. A study in the *New England Journal of Medicine* (2007, vol. 356: 1295-1303) found that for women with a diagnosis of cancer in the breast, MRI screening could detect

cancer missed by a mammogram in the contralateral breast. In the study, MRIs detected 30 cancers in 969 women missed by mammography. Other indications may include looking for cancer foci elsewhere in the breast when planning a breast conserving procedure.

MRI may also be useful in other diagnostic situations. It can help differentiate scar tissue from cancer recurrence after a lumpectomy and radiation therapy. MRI also helps diagnose possible implant ruptures. However, MRI is not intended as a procedure to avoid a biopsy recommended by other modalities.

MRI screening has a higher sensitivity and finds small tumors missed by mammography. In the future, it is reasonable that finding smaller cancers will prove to lead to reductions in mortality. However, physicians must inform women about the benefits and limitations of breast MRI. Only experienced providers using high quality machines with the ability to provide MRI guided biopsy, if needed, should perform MRI exams.

Case evaluation

The "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography" published in 2007 (*CA: A Cancer Journal for Clinicians* 2007; 57: 75-89) is the gold standard for the use of MRI for breast cancer screening. Other articles also document the usefulness of MRI in diagnosis to determine treatment approaches, like conservative surgery, or if there is concern about the other breast.

Case managers reviewing a patient's file calling for a screening MRI should look at the guidelines to determine on a case-by-case basis if the patient is an MRI candidate. Sometimes this may mean a phone call to the physician to clarify the physician's thinking.

AVASTIN TREATMENT FOR GLIOBLASTOMA

Mark Levin, MD

Although glioblastoma multiforme is a type of a brain tumor that can occur at almost any age, it is most common after age 50. In general, treatment of this brain tumor depends on the specific tumor characteristics, for example, its rate of growth, how rapidly it causes symptoms and its location. Until recently, glioblastoma was a disease for which there were few options available. Traditional treatments include surgery, radiation therapy and chemotherapy, which can benefit some patients with these tumors. The Food and Drug Administration (FDA) recently approved Temador for use after initial surgery and in combination with radiotherapy. BCNU is an older drug that has been shown to also be useful in older studies, but now is rarely used because it is quite toxic.

With the emergence of new biologics and molecularly-based treatments, many new treatments are being investigated. Two of the more promising candidates are bevacizumab (Avastin) and irinotecan (Camptosar). Dr. Virginia Stark-Vance recently reported that, among 21 patients with recurrent malignant glioma treated with bevacizumab plus irinotecan, one patient achieved a complete response, eight achieved partial responses, and 11 achieved stable disease. Overall, patients reported tolerating the regimen well, although two died during treatment, including one patient with an intracranial hemorrhage and one patient with bowel perforation.

The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center is performing a formal, single-arm Phase II study of bevacizumab plus irinotecan for patients with recurrent malignant glioma. Preliminary analyses of the results of this trial reveal that malignant glioma patients tolerate this regimen well and demonstrate a highly exciting rate of radiographic response. Several centers have undertaken further investigation of the bevacizumab-plus-irinotecan regimen. Eleven sites nationwide are participating in the pivotal clinical trial of bevacizumab and irinotecan in recurrent glioblastoma. One small study reported this combination shrinks tumors in 63 percent of patients with recurrent glioblastoma.

In late November 2007, Genetech announced preliminary results of a randomized Phase II study with two arms, Avastin versus Irinotecan/Avastin. The latter arm has a higher time-to-progression and response rate. The study is ongoing. There are no reported Phase III trials or guideline recommendations for Avastin or Camptosar plus Avastin. Avastin alone is in an ongoing Phase II trial.

Resources:

1. A. Reardon, Patrick Y. Wen. Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents *The Oncologist*, Vol. 11, No. 2, 152-164, February 2006.
2. J. J. Vredenburgh, A. Desjardins, J. E. Herndon II, J. M. Dowell, D. A. Reardon, J. A. Quinn, J. N. Rich, S. Sathornsumetee, S. Gururangan, M. Wagner, D. D. Bigner, A. H. Friedman, and H. S. Friedman. *Clin. Cancer Res.*, February 15, 2007; 13(4): 1253 - 1259.
3. J. J. Vredenburgh, A. Desjardins, J. E. Herndon, J. Quinn, J. Rich, S. Sathornsumetee, H. S. Friedman, D. Reardon, S. Gururangan, A. Friedman. "Phase II Trial of Bevacizumab and Irinotecan in Recurrent Malignant Glioma." *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 1506.
4. Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. *Neurooncol* 2005;7:369.