and anti-VEGF therapies that are currently being explored in pancreatic cancer.

In conclusion, the EGFR is expressed in different nontransformed cell types of the neoplastic environment that are involved in tumor growth and progression, including endothelial cells. Studying the effects of anti-EGFR agents in the different components of the tumor microenvironment might improve our knowledge of the mechanism of action of these drugs.

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REFERENCES
1. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960-1966, 2007

2. Löhr M, Kloppel G, Maisonneuve P, et al: Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: A meta-analysis. Neoplasia 7:17-23, 2005

3. Moore MJ, da Cunha Santos G, Kamel-Reid S, et al: The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with Erlotinib on National Cancer Institute of Canada Clinical Trials Group trial study PA.3. J Clin Oncol 25:202s, 2007 (suppl; abstr 4521)

4. Pao W, Wang TY, Riely GJ, et al: KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med 2:e17, 2005

5. Massarelli E, Varella-Garcia M, Tang X, et al: KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res 13:2890-2896, 2007

6. Lièvre A, Bachet JB, Le Corre D, et al: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 66:3992-3995, 2006

7. Khambata-Ford S, Garrett CR, Meropol NJ, et al: Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 25:3230-3237, 2007

8. Normanno N, Bianco C, De Luca A, et al: Target-based agents against ErbB receptors and their ligands: A novel approach to cancer treatment. Endocr Relat Cancer 10:1-21, 2003

9. Bruns CJ, Solorzano CC, Harbison MT, et al: Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res 60:2926-2935, 2000

10. Baker CH, Kedar D, McCarty MF, et al: Blockade of epidermal growth factor receptor signaling on tumor cells and tumor-associated endothelial cells for therapy of human carcinomas. Am J Pathol 161:929-938, 2002

11. Weber KL, Doucet M, Price JE, et al: Blockade of epidermal growth factor receptor signaling leads to inhibition of renal cell carcinoma growth in the bone of nude mice. Cancer Res 63:2940-2947, 2003

12. Yokoi K, Sasaki T, Bucana CD, et al: Simultaneous inhibition of EGFR, VEGFR, and platelet-derived growth factor receptor signaling combined with gemcitabine produces therapy of human pancreatic carcinoma and prolongs survival in an orthotopic nude mouse model. Cancer Res 65:10371-10380, 2005

13. Salomon DS, Brandt R, Ciardiello F, et al: Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 19:183-232, 1995

14. Kim SJ, Uehara H, Karashima T, et al: Blockade of epidermal growth factor receptor signaling in tumor cells and tumor-associated endothelial cells for therapy of androgen-independent human prostate cancer growing in the bone of nude mice. Clin Cancer Res 9:1200-1210, 2003

15. Baker CH, Pino MS, Fidler IJ: Phosphorylated epidermal growth factor receptor on tumor-associated endothelial cells in human renal cell carcinoma is a primary target for therapy by tyrosine kinase inhibitors. Neoplasia 8:470-476, 2006

16. Hirata A, Ogawa S, Kometani T, et al: ZD1839 (Iressa) induces antiangiogenic effects through inhibition of epidermal growth factor receptor tyrosine kinase. Cancer Res 62:2554-2560, 2002

17. Sini P, Wyder L, Schnell C, et al: The antitumor and antiangiogenic activity of vascular endothelial growth factor receptor inhibition is potentiated by ErbB1 blockade. Clin Cancer Res 11:4521-4532, 2005

18. Kindler HL, Niedzwiecki D, Hollis D, et al: A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB). ASCO Meeting Abstracts 25:199s, 2007 (suppl; abstr 4508)

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MRI or Bone Scan or Both for Staging of Prostate Cancer?

To the Editor: We read with interest the article entitled "Magnetic Resonance Imaging of the Axial Skeleton for Detecting Bone Metastases in Patients With High-Risk Prostate Cancer: Diagnostic and Cost-Effectiveness and Comparison With Current Detection Strategies" by Lecouvet et al,[1] and are intrigued by the excellent results reported with magnetic resonance imaging (MRI) over bone scan.

We would like to comment on the criteria used in the study to categorize abnormal uptake on radionuclide bone scan as either malignant or equivocal, which might have biased the results of the study. The benefit of bone scan for staging prostate cancer is that it detects metastasis before it is evident on plain radiographs. Conventional wisdom suggests that if the radionuclide bone scan shows uptake that is not explained by a benign lesion on targeted radiographs (TXR), the inference is that it is most likely to represent a malignant process, rather than equivocal, as has been categorized by the authors.[2,3] Additional confirmation with other imaging including MRI may not be required in such instances in routine clinical practice.

We beg to differ when the authors state that the abnormal uptake on the bone scan demonstrated in Figure 1 of the article[1] is equivocal. In fact, it is highly suggestive of skeletal metastasis, given that there is no benign lesion or abnormality in the TXR to account for the increased uptake on bone scan, and this patient does not necessarily require an MRI to clarify the bone lesion as being malignant. Alternately, if there was a benign radiographic explanation for the bone scan uptake, then again the patient may not require an MRI for clarification.

The bias in the reporting of bone scans in the study is shown when the authors state that "MRIa had no false-negative results." Abnormal uptake on bone scan may be due to a malignant process, even though it did not showing up as malignant on other imaging (TXR or axial MRI). In these circumstances, bone scans in this study

seem to have been classified as equivocal, although they are positive, hence the resulting false-negative MRI may have been missed. Furthermore, when the authors state that "none of the patients without axial metastasis (on MRIa) had metastasis elsewhere," has the abnormal uptake on bone scan due to metastasis outside the axial skeleton been categorized as not malignant when it did not show up on TXR? This under-reporting of malignant lesions may have contributed to the low sensitivity (46%) and specificity (32%) attributed to bone scan in the study.

The inclusion criteria of the study also may have biased the results, given that 28 of the 66 patients were already receiving hormonal treatment. In such instances the uptake of radionuclide on bone scan may be diminished because of the response to androgen deprivation. The utility of investigations differs depending on whether they are performed for initial staging before systemic treatment or for imaging while receiving treatment. The benefit of MRI may be for patients who are already receiving systemic treatment, whereas a bone scan without a baseline comparator has its drawbacks.

In the 38 patients with newly diagnosed disease in the study, MRI identified metastasis in three of the 14 patients with normal bone scan/TXR findings and in two of the 12 patients with equivocal bone scan/TXR findings, which were confirmed with investigations and clinical information after 6 months of follow-up. Six months may not be an adequate period of follow-up to determine whether the equivocal bone scan findings may in fact represent metastasis, especially because these patients may have received systemic treatment during this period.

The results of this study may be misleading because they erroneously suggest that MRI, although a more sensitive investigation, could replace bone scan as the initial and sole imaging modality of choice. However, we believe that bone scan, although not perfect, still remains the imaging investigation of choice for the initial staging of prostate cancer patients, with TXR correlation and other imaging including MRI to be used when results are truly equivocal. Bone scan and MRI may be considered as complementary imaging modalities in this clinical setting.

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REFERENCES

1. Lecouvet FE, Geukens D, Stainier A, et al: Magnetic resonance imaging of the axial skeleton for detecting bone metastases in patients with high-risk prostate cancer: Diagnostic and cost-effectiveness and comparison with current detection strategies. J Clin Oncol 25:3281-3287, 2007
2. Jacobson AF, Stomper PC, Cronin EB, et al: Bone scans with one or two new abnormalities in cancer patients with no known metastases: Reliability of interpretation of initial correlative radiographs. Radiology 174:503-507, 1990
3. Citrin DL, Hougen C, Zweibel W, et al: The use of serial bone scans in assessing response of bone metastases to systemic treatment. Cancer 47:680-685, 1981

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In Reply: We appreciate the interest of Dr Venkitaraman and colleagues in our recent article.[1] We wish to address their comments.

Dr Venkitaraman and colleagues seem to be intrigued by the superior results of magnetic resonance imaging (MRI) over bone scan (BS) to detect bone metastases in patients with prostate cancer (PCa) at high risk for metastases, and question our categorization of results.

As detailed in the article, we used the same clear classification system of the results into three well-defined categories (positive, negative, or equivocal), and the same statistical approach (consisting of categorizing the equivocal readings as suggestive for malignancy in patients with no metastasis and categorizing the equivocal readings as benign in patients with metastasis) for all imaging tests (BS, targeted radiographs [TXR], and MRI of the bone marrow).

We do agree that the term "equivocal" covers a wide range of results that could have been termed "possible," "suspicious," "likely," "highly suspicious," "almost certain," and so on. The generic term does not matter: this category encompasses all situations in which imaging findings could not be categorized confidently as positive or negative, regardless of the level of incertitude. This classical approach was used for all imaging techniques. There is no bias there.

We do agree that the example illustrated in the Figure 1 of our article is highly suggestive of skeletal metastasis on the basis of the results of the BS/TXR work-up. However, we do not state that "further confirmation with other imaging including MRI" is required, although it would be requested in clinical routine whenever a consolidate answer is required. We do demonstrate that a one-step noninvasive examination, MRI, results in immediate certitude with regard to the metastatic status of this patient.

We cannot agree with Dr Venkitaraman and colleagues when they invoke conventional wisdom or suggestions to make sometimes life-threatening or invalidating therapeutic decisions. Conventional wisdom may be acceptable in clinical practice to assess a fracture risk—it becomes questionable when it comes to definitive decisions in oncology.

In 1958, Galbraith coined this term "conventional wisdom" to define "the ideas which are esteemed at any time for their acceptability," and pointed out that there may be important differences between what is acceptable (the territory of the conventional wisdom) and what is true. Conventional wisdom is often seen as an obstacle to introducing new theories—a cause of inertia.[2]

Our study demonstrated that a fair proportion of our patient staging using the current BS/TXR work-up was not true according to the gold standard. Is this acceptable?

Let us take examples from our series. The example of a middle-aged man just being diagnosed with localized high risk PCa (Gleason score 8), with a normal abdominal computed tomography and normal BS. Based on conventional wisdom and current work-up, he would undergo a radical prostatectomy, although metastatic status is