

methods of assessing treatment response to ensure that these agents are being used in a manner that will optimize patient outcomes.

Mary C. Gainford, George Dranitsaris,  
and Mark Clemons

Division of Medical Oncology, Sunnybrook and Women's College Health Sciences Center, Toronto, Ontario, Canada

---

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

### REFERENCES

1. Hamaoka T, Madewell JE, Podoloff DA, et al: Bone imaging in metastatic breast cancer. *J Clin Oncol* 22:2942-2953, 2004
2. Clemons M, Rea D: Perspectives on the future of bisphosphonate use in breast cancer patients. *Semin Oncol* 31:87-91, 2004 (suppl 10)
3. Verma S, Kerr-Cresswell D, Dranitsaris G, et al: Bisphosphonate use for the management of breast cancer patients with bone metastases: A survey of Canadian Medical Oncologists. *Support Care Cancer* 12:852-858, 2004
4. Clemons M, Enright K, Cesta A, et al: Do physicians follow systemic treatment and funding policy guidelines? *Can J Clin Pharmacol* 11:e168-e178, 2004
5. Brown J, Thompson C, Ellis S, et al: Bone resorption predicts for skeletal complications in metastatic bone disease. *Br J Cancer* 89:2031-2037, 2003
6. Clamp A, Danson S, Nguyen H, et al: Assessment of therapeutic response in patients with metastatic bone disease. *Lancet Oncol* 5:607-616, 2004

DOI: 10.1200/JCO.2005.01.3490

**IN REPLY:** We appreciate the supportive comments from Gainford et al. As they noted, the most accurate assessment of bone tumor response may well require use of several measurement techniques, such as imaging, symptom assessments, and measurements of bone turnover and tumor markers. Certainly, reliable ways of assessing bone tumor response would be greatly useful for establishing the optimal duration of bisphosphonate treatment, which has yet to be determined. Although we focused on bone imaging in our review,<sup>1</sup> we recognize that markers of bone turnover such as NTx may be powerful tools for assessing response, and we agree that measuring bone turnover markers in addition to using multiple radiographic imaging techniques may facilitate accurate assessments of bisphosphonate efficacy. Indeed, several reports<sup>2,3</sup> have indicated that bone turnover markers show promise for assessing bone response, including results of a multicenter double-blind, randomized trial conducted by the European Organisation for Research and Treatment of Cancer.<sup>2</sup> In that trial, urinary calcium, hydroxyproline, and NTx and serum CA 15.3 and cancer-associated serum antigen levels were measured at baseline and after 1 month and 4 months of pamidronate. Of those markers, only NTx could reliably distinguish patients whose disease would progress from those whose disease would respond to treatment or not change.<sup>1,2</sup> We highly recommend that these findings be

confirmed in prospective clinical trials involving comprehensive bone tumor assessments with a combination of bone imaging and bone turnover measurements. At The University of Texas M.D. Anderson Cancer Center (Houston, TX), we are now conducting such a trial to verify x-ray, skeletal scintigraphy, and computed tomography scanning for assessing bone tumor response. The end point of this trial is to assess the sensitivity and specificity of each imaging modality and each set of response criteria (ie, those proposed by the World Health Organization, by the International Union Against Cancer, and by us). Unfortunately, this protocol may not be useful for clarifying responses of bone metastases to bisphosphonates because the plan is to analyze response to systemic chemotherapy and hormonal therapy. However, we do believe that measurements of NTx, which have been included in the protocol, will provide some useful information. We hope that the results of this trial will lead to improvements in the assessment of treatment response in bone metastasis.

Tsuyoshi Hamaoka, John E. Madewell, Donald A. Podoloff, Gabriel N. Hortobagyi, and Naoto T. Ueno

The University of Texas M.D. Anderson Cancer Center, Houston, TX

---

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

### REFERENCES

1. Hamaoka T, Madewell JE, Podoloff DA, et al: Bone imaging in metastatic breast cancer. *J Clin Oncol* 22:2942-2953, 2004
2. Coleman RE: Monitoring of bone metastases. *Eur J Cancer* 34:252-259, 1998
3. Vinholes J, Coleman R, Lacombe D, et al: Assessment of bone response to systemic therapy in an EORTC trial: Preliminary experience with the use of collagen cross-link excretion—European Organisation for Research and Treatment of Cancer. *Br J Cancer* 80:221-228, 1999

DOI: 10.1200/JCO.2005.01.4126

## Positron Emission Tomography Paradigm Fuzzier Than Reported

**TO THE EDITOR:** Kovacs et al<sup>1</sup> report an interesting prospective trial evaluating the utility of positron emission tomography (PET) and sentinel node biopsy (SNB) in patients with oral and oropharyngeal squamous cell carcinoma (OOSCC). I agree that their management paradigm results in fewer neck dissections for patients staged with PET and SNB than for patients staged by computed tomography (CT) and SNB. I disagree however with their contention that their new proposed management paradigm is better than the current standard of care for the clinical N0 neck. Many if not most centers use radiation therapy and/or

chemotherapy rather than surgery as the initial therapy in patients with oropharyngeal cancer. Patients with OOSCC and a N0 neck after triple endoscopy, CT scan, and physical exam staging are well served by the strategy developed by Fletcher et al<sup>2</sup> in the 1970s. If the primary tumor is controlled, recurrences after radiation therapy administration at 50 Gy in 5 weeks to an N0 neck are exceedingly rare (less than 3%). This experience is supported by the accepted radiobiologic concept that the small amounts of tumor that are present in roughly one third of the patients with N0 disease can be controlled by a lower nontoxic dose of radiation. PET, SNB, and limited neck dissections bring unnecessary risks and financial burdens to these patients.

In Table 2 of the Kovacs et al article, when comparing the utility of PET versus CT it becomes evident that there are no significant differences between the sensitivity, specificity, accuracy, and positive or negative predictive values of PET and CT in the patients studied.

Our data<sup>3</sup> from the State University of New York Upstate Medical University (Syracuse, NY) on 52 patients with head and neck cancer show similar sensitivity, specificity, and accuracy rates when comparing patients staged with PET plus clinical findings to patients staged by CT plus clinical findings.

In conclusion, triple endoscopy, CT scanning, and physical exam should remain the standard staging method for OOSCC patients. Patients with N0 neck disease do not need a PET scan, a sentinel node biopsy, or a neck dissection if they have received radiation therapy.

#### Surjeet Pohar

State University of New York Upstate Medical University, Syracuse, NY

---

### Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

#### REFERENCES

1. Kovács AF, Döbert N, Gaa J, et al: Positron emission tomography in combination with sentinel node biopsy reduces the rate of elective neck dissections in the treatment of oral or oropharyngeal cancer. *J Clin Oncol* 22:3973-3980, 2004
2. Fletcher GH: Head and Neck: Neck Nodes, in *Textbook of Radiotherapy* (ed 3). Philadelphia, PA, Lea and Febiger, 1980, pp 250-253
3. Pohar S, Brown R, Hsu J, et al: How does PET imaging change the management of patients with head and neck cancer? *Radiother Oncol* 173:S295, 2004 (suppl 1)

DOI: 10.1200/JCO.2004.00.5942

**IN REPLY:** I very much appreciate the comments of Dr Pohar who clearly argues from a radiation-oncologist's point of view.

I cannot agree with his assertion that, "Many if not most centers use radiation therapy and/or chemotherapy rather than surgery as the initial therapy in patients with

oropharyngeal cancers." First, the main portion of the patients evaluated in the discussed article<sup>1</sup> suffered from oral cavity cancer. Second, according to the DÖSAK tumor registry (Giessen University Medical School, Giessen, Germany), approximately 81% of primary cancers of the lip, the oral cavity, and the oropharynx are treated with surgery as first-line therapy in the German-speaking countries (Germany, Austria, and Switzerland), and only 10% are initially treated with radiation.<sup>2</sup> Third, regarding oncologic treatment of oral cavity and oropharyngeal cancer, the German consensus of head and neck surgeons and radiation-oncologists<sup>3</sup> states for oral cavity cancer that "alternatively to an operation, a T1 tumor in the dorsal segment of the mobile tongue may be referred to interstitial brachytherapy. In case of clinical suspicion of lymph node metastases as well as in case of category T2, the necessary combination of brachytherapy and percutaneous radiotherapy leads to higher complication rates and shall be carried out only in case of contraindications to an operation"; and for oropharyngeal cancer that "alternatively to an operation (on presentation of contraindications to an operation), a primary single radiotherapy may be pondered for the stages I and II (T1N0 and T2N0)." For advanced tumor stages of both sites, the consensus recommends chemoradiotherapy "alternatively." Primary radiologic treatment for the neck is not designated. Therefore, surgery has to be regarded as the initial treatment of choice by us. We know, however, that primary irradiation may be successful in some patients, and also in the clinical N0 neck; we nevertheless are mindful of the fact that well known and acknowledged survival statistics are based on surgical treatment whereas there is no prospective randomized study comparing the two modalities with respect to tumor control and functional assessment. Furthermore, we, and surely many other head and neck oncologists, see a problem in primary irradiation when it comes to a local recurrence.

It is true that positron emission tomography (PET) and computed tomography (CT) did not have significant differences concerning the sensitivity, specificity, accuracy, or positive or negative predictive value, which was an assessment based on the final histologic results. However, the consequences for the patients can be very different. For example, let's consider a T2 tumor in the lateral floor of the mouth without midline involvement. When PET demonstrates a spot in the ipsilateral neck, our decision would be ipsilateral modified radical neck dissection. When CT demonstrates suspicious lymph nodes with borderline findings on both neck sides, a surgeon will tend to prefer resection on both neck sides. Granted that if a single metastatic node was found in the pathohistologic examination, the specificity of both diagnostic techniques would have been the same because "it was counted as a correct positive finding when at least one pathologic lymph node was found in the preoperative examination as well as histologically" —but what a

difference for the patient! PET will always be more practical in interpretation as compared with CT—a spot is a spot, and it has been interpreted as a positive node by us, irrespective of the standard uptake value. CT evaluation has many more uncertainties.

Finally, we doubt that triple endoscopy, CT scanning, and physical exam are less straining and less costly for both the patients and the society. A large portion of distant metastases and synchronous second primaries are detected by PET, which cannot be detected by the mentioned tools. In fact, skeletal scintigraphy and abdominothoracic CT have to be added to the mentioned tools resulting in even higher costs. These findings by PET completely change the regimen necessary for the respective patients. However, our main goal pursued in our article was to demonstrate the possibility of reducing the rate of elective neck dissections in oral and oropharyngeal cancer patients with a combination of imaging techniques and sentinel node biopsy. The emphasis lies on the usage of sentinel node biopsy. If other groups are able to demonstrate this using CT and sentinel node biopsy, we will be content. The future, however, belongs to a combination of morphologic and functional diagnostics.

*Adorján F. Kovács*

Department of Maxillofacial Plastic Surgery, Johann Wolfgang Goethe-University Medical School, Frankfurt am Main, Germany

#### Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

#### REFERENCES

1. Kovács AF, Döbert N, Gaa J, et al: Positron emission tomography in combination with sentinel node biopsy reduces the rate of elective neck dissections in the treatment of oral and oropharyngeal cancer. *J Clin Oncol* 22:3973-3980, 2004
2. Reicherts M, Hassek S, Kainz M, et al: Gießen: Zentralregister des Deutsch-Österreichisch-Schweizerischen Arbeitskreises für Tumoren im Kiefer- und Gesichtsbereich, 2000
3. Bootz F, Howaldt HP (eds): Karzinome des oberen Aerodigestivtraktes. Interdisziplinäre kurzgefasste Leitlinien der Deutschen Krebsgesellschaft und ihrer Arbeitsgemeinschaften, der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie und der Deutschen Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) online Web site. <http://leitlinien.net/>

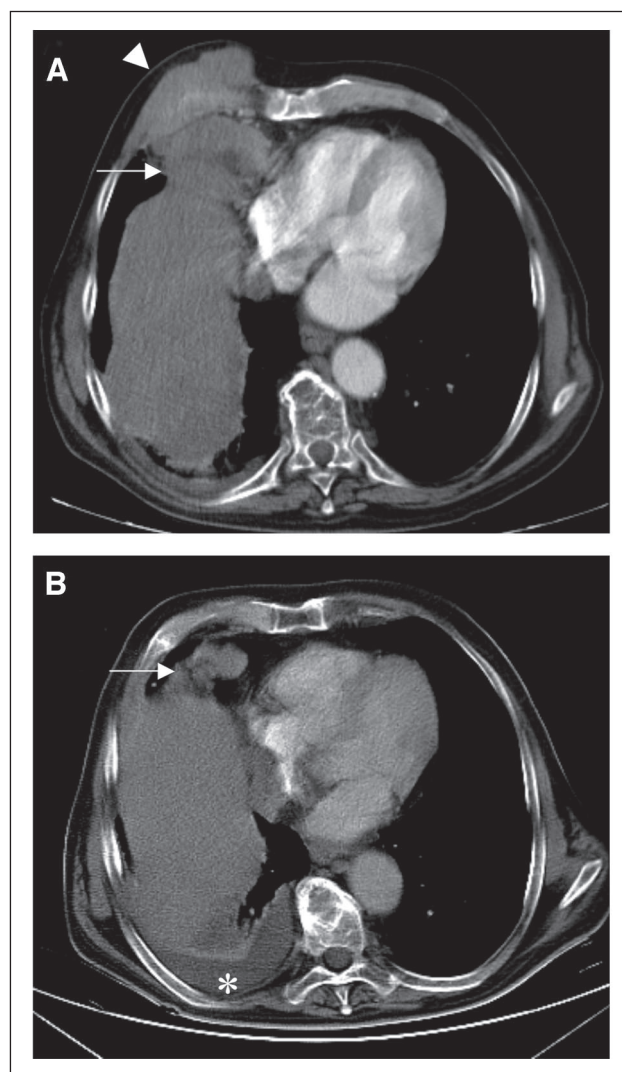
DOI: 10.1200/JCO.2004.01.0603

## Antitumoral Effect of Celecoxib in Hepatocellular Carcinoma

**TO THE EDITOR:** Effective therapeutic options for unresectable hepatocellular carcinoma (HCC) are still lacking. Cyclooxygenase-2 (COX-2), a key enzyme in arachidonic acid metabolism, is overexpressed in many types of malig-

nant tumors, including HCC.<sup>1</sup> Here we report a case of HCC, which dramatically responded to celecoxib, a selective COX-2 inhibitor.

A 76-year-old man underwent a left liver resection for well-differentiated HCC, developed on underlying hemochromatosis and liver cirrhosis. Serum alphafoetoprotein level decreased from 251 ng/mL preoperatively to 5 ng/mL postoperatively (upper limit of normal values, 10 ng/mL). Twenty months later, percutaneous radiofrequency ablation was performed for intrahepatic tumor recurrence. One year later, multifocal intrahepatic recurrence, mediastinal and celiac lymph node metastases, and radiofrequency needle-track peritoneal seeding with visible prehepatic bulging developed (Fig 1A). Two lines of systemic chemotherapy (gemcitabine plus



**Fig 1.** Antitumoral effect of celecoxib in a patient with recurrent hepatocellular carcinoma. (A) Needle-track peritoneal seeding (arrow) with prehepatic bulging (▷) after percutaneous radiofrequency ablation. (B) Three months after starting celecoxib treatment, dramatic tumoral regression (arrow), contrasting with the onset of right pleural effusion (\*), which led to diagnose poorly differentiated large-cell lung carcinoma.