

Moreover, this malignant cell appears to depend on signaling from the surrounding normal cells for its survival. The Reed–Sternberg cell also secretes numerous cytokines, including granulocyte–macrophage colony-stimulating factor, which may attract an assemblage of inflammatory cells to involved lymph nodes. For this reason, the Reed–Sternberg cell has been called the master regulator of the inflammatory response in the lymphoid tissue of Hodgkin's disease.^{4,6}

It was once thought that macrophages, which occur in many kinds of tumors, are a manifestation of an immune response against the tumor. Most of the evidence, however, now links the presence of tumor-associated macrophages with a poor prognosis.⁷ Termed trophic macrophages by Pollard⁸ and Mantovani et al.,⁹ tumor-associated macrophages and the macrophages that are associated with cell migration in the embryo appear to have similar functions.¹⁰ Like embryonic macrophages, tumor-associated macrophages mediate blood-vessel formation by regulating the angiogenic switch through the secretion of vascular endothelial growth factor and hypoxia-inducing factor.¹¹

The migration of macrophages to tumors appears to be a late event in Hodgkin's disease. It is not very difficult to imagine how an abundance of trophic macrophages can lead to tumor progression in light of the cytokine-rich microenvironment of the Reed–Sternberg cell. It is more difficult, however, to explain the association between the number of tumor-associated macrophages and a poor response to treatment, unless their abundance signals the deregulation of a critical pathway to apoptosis in Reed–Sternberg

cells that inhibits cell death in response to cytotoxic agents.

Nonetheless, the data provided by Steidl et al. appear to be the breakthrough we have been looking for by enabling the selection of patients with a particularly poor prognosis (regardless of stage) for aggressive treatment, which can bring more logic to the treatment of this curable cancer.

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Medical Imaging in the 21st Century — Getting the Best Bang for the Rad

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In the United States, the average radiation dose to which we are exposed has doubled in the past 30 years.^{1,2} The average dose from natural background sources has not changed, but what has changed is that there has been an increase by a factor of more than 6 in the average radiation dose from medical imaging.^{1,3} In 1980, medical imaging was responsible for only about 15% of

the total radiation exposure to the U.S. population from all sources; now the proportion is about 50%.

Up to 30% of the radiation exposure to the U.S. population that is associated with medical diagnostic imaging now comes from cardiac imaging,³ so it is appropriate to ask whether current coronary imaging techniques are being

used optimally. Specifically, are they providing us with the maximum information relative to the population exposure that they involve — the best possible “bang for the rad”? A study in this issue of the *Journal* suggests that we still have some way to go. Patel and colleagues⁴ suggest that only 38% of patients who undergo invasive coronary angiography for diagnostic purposes actually have obstructive coronary artery disease — a decidedly low proportion considering both the adverse events⁵ and the radiation exposure³ associated with invasive coronary angiography.

The most common sequence of events for evaluating persons with suspected coronary artery disease is performing a “gatekeeper” test, which is typically a functional test such as myocardial perfusion scintigraphy, followed by invasive coronary angiography if the results of the gatekeeper test are positive. Currently, approximately 9 million myocardial-perfusion-scintigraphic imaging studies are performed each year in the United States, and this test represents one of the single largest man-made contributors to radiation exposure in the U.S. population.³ Patel and colleagues rightly suggest that we need to optimize the application of gatekeeper tests such as myocardial perfusion scintigraphy, in order to decrease the disturbingly large proportion of invasive coronary angiographic procedures that yield negative results. Ironically, there

is evidence that, in many situations, a better gatekeeper test may be yet another radiographic imaging technique — namely, multidetector-row computed-tomographic (CT) angiography. For example, in a recent prospective trial of 64-row multidetector CT,⁶ the negative predictive value in the case of persons referred for nonemergency invasive coronary angiography was 99% — making it a very promising gatekeeper test for invasive coronary angiography. Several clinical trials are under way.⁷

These considerations raise the more general question of whether other medical-imaging tests that involve ionizing radiation are being used optimally.¹ Of course when a radiologic imaging procedure is clinically appropriate, the benefit almost always far outweighs the risk of the procedure. But the key here is “clinically appropriate.” For example, of the more than 70 million CTs being performed in the United States this year, how many of them are actually clinically justified?

For many scenarios we can answer this question quite well, because of the burgeoning number of available clinical decision guidelines (e.g., decision rules and appropriateness criteria). These decision guidelines, which are based on a combination of clinical data and expert judgment, provide scenarios in which a given imaging procedure is medically justified. The American College of Radiology (ACR), the Royal College of Radiologists, and the European Commission have all published decision guidelines for the appropriate use of CT in different settings, as have various organizations associated with specific subspecialties.

These decision guidelines can be used to assess current CT usage. For example, in a study⁸ involving 200 patients who underwent some radiographic imaging on arrival at a level 1 trauma center, and for whom the imaging decisions were made without the use of decision rules, CT prescription patterns were retrospectively analyzed: of the 200 patients, 169 underwent CT scanning, resulting in a total of 660 scans. If ACR appropriateness criteria had been applied (which they were not), 44% of these CT scans would not have been performed, but none of the patients with clinically significant injuries would have been excluded from CT imaging. Results from other, larger retrospective⁹ (Table 1), prospective,¹⁰ and modeling¹¹ studies also suggest that 20 to 40% of CT scans could be avoided if

Table 1. Percentage of Computed Tomographic (CT) Scans That Could Be Avoided if Decision Guidelines for CT Scanning of Mild Traumatic Brain Injury Were Followed.*

CT Decision Guideline	CT Scans That Could Be Avoided
	percent
Scandinavian Neurotrauma Committee	50
Nexus-II (National Emergency X-Radiography Utilization Study-II instrument)	44
New Orleans Criteria	31
NCWFNS (Neurotraumatology Committee of the World Federation of Neurosurgical Societies instrument)	45
Canadian CT Head Rule	45

* Data are from Stein et al.⁹ A total of 8000 patients with mild head trauma were included in these retrospective estimates. Mild traumatic brain injury was defined as a score of 14 or 15 on the Glasgow Coma Scale, which ranges from 3 to 15, with lower scores indicating reduced levels of consciousness; in U.S. emergency rooms, CT scans are typically performed on 75 to 100% of all patients with mild head injury. The five CT decision guidelines shown had sensitivities for detecting surgical hematoma of at least 99%.

decision guidelines are followed, without compromising patient care.

That being said, reducing the number of CT scans that are not clinically justified is a hard task, because there are other very real considerations pushing in the other direction, including legal and economic factors and patient preference.¹² But when decision guidelines are used, they have the potential to “trump” some, though not all, of the factors that result in CT being overprescribed and so represent a potentially powerful tool for optimizing the use of CT. A recent initiative by the Food and Drug Administration to reduce unnecessary radiation exposure from medical imaging (www.fda.gov/Radiation-EmittingProducts/RadiationSafety/RadiationDoseReduction/UCM199904), although only advisory with regard to decision guidelines, is most welcome.

Naturally, decision guidelines are not useful if they are not applied, and this is too often the case.¹³ A successful approach to increasing the use of CT decision guidelines has been to incorporate them into computerized systems that are used for entering orders for imaging.¹⁴ To date, incorporating decision guidelines into a managed care preauthorization system has not been successful in changing the patterns of CT use, at least in the United States.¹⁵

Of course, the factors that feed into a decision guideline are complex, and the available data are often incomplete or contradictory. It follows that guidelines need to be constantly reassessed to take new evidence into account. The increased emphasis on, and funding for, comparative-effectiveness research represent a valuable opportunity to extend and improve current decision guidelines for medical imaging.¹⁶

These considerations also have financial implications. In the retrospective study involving trauma patients that was discussed above,⁸ if the ACR appropriateness criteria had been applied, there would have been an estimated 38% decrease in imaging costs in addition to the 44% decrease in CT use and the associated decrease in radiation exposure.

In summary, it is impossible to imagine the current practice of medicine without modern-day imaging. It is also axiomatic that, in the final analysis, the clinician is in the best position to assess the imaging needs of his or her patient. But with so many high-tech imaging tools currently available, it is essential to optimize

their use. Clinical-decision guidelines represent a proven methodology in this regard. This is not easy to implement on a national level, but it can be done and it should be done.

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