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THE NEGLECTED SIDE OF THE COIN: QUANTITATIVE BENEFIT-RISK ANALYSES IN MEDICAL IMAGING

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Abstract

While it is implicitly recognized that the benefits of diagnostic imaging far outweigh any theoretical radiogenic risks, quantitative estimates of the benefits are rarely, if ever, juxtaposed with quantitative estimates of risk. This alone - expression of benefit in purely qualitative terms versus expression of risk in quantitative, and therefore seemingly more certain, terms - may well contribute to a skewed sense of the relative benefits and risks of diagnostic imaging among healthcare providers as well as patients. The current paper, therefore, briefly compares the benefits of diagnostic imaging in several cases, based on actual mortality or morbidity data if ionizing radiation were not employed, with theoretical estimates of radiogenic cancer mortality based on the “linear no-threshold” (LNT) dose-response model.

Keywords

effective dose; risk analysis; risk communication; risk estimates

INTRODUCTION

The introduction of ionizing radiation in medicine revolutionized the diagnosis and treatment of disease and dramatically improved, and continues to improve, the quality of health care. In recent years, however, concern over the radiogenic risks associated with medical imaging has intensified dramatically, largely due to reports of such risks, some alarmist in tone (Redberg and Smith-Bindman 2014), in both the scientific and lay media. Reasonable concern is beneficial in terms of promoting critical evaluation of imaging procedures with technical optimization, elimination of truly unnecessary procedures, and minimization of imaging doses without compromising the diagnostic information being sought. However, the excessive emphasis on radiogenic cancer risk can create the misconception that not only is radiation the *only* risk to be considered in medical imaging but also that the benefit of imaging procedures may be outweighed by the risk.

Patients should, of course, become well informed about the risks and benefits of all aspects of medical care, radiation-related and otherwise. When advising patients about these risks, however, only a perfunctory statement is usually offered to the effect that any theoretical

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risks of the radiation exposures received are far smaller than the direct benefits of the study. Importantly, the word “theoretical” should be used because all risk information is predicated on the “linear no-threshold” (LNT) theory of radiation carcinogenesis, which posits that stochastic, or statistical, risks (primarily of cancer) observed in populations exposed to high doses of radiation can be linearly extrapolated to the much lower doses that are encountered in diagnostic medical procedures and certain other circumstances (NAS/NRC 2006). While the LNT model may be a defensible (i.e., appropriately conservative) basis for formulating population-based radiation dose limits (e.g., for occupationally exposed individuals), its application to *individual* patients and their medical management is unjustified. For example, the LNT-derived risk of a radiogenic cancer associated with a specific diagnostic procedure for an individual patient conceivably may lead the patient and/or the patient’s physician to forego this procedure and, in its place, perform another suboptimal procedure with its own non-radiogenic risks, which may possibly exceed the theoretical radiogenic risk of the procedure originally considered.

Application with certitude of the LNT risk model has led some to derive alarming estimates of excess numbers of cancers as a result of medical imaging (Brenner and Hall 2007). Such exercises largely ignore the considerable uncertainties involved, among other considerations. To the extent that the LNT-derived risk may overestimate the actual radiogenic risk (if any), it undermines a reasonable benefit-risk analysis and may thus adversely impact the patient’s medical management. The LNT model may, in fact, overestimate the actual risks of diagnostic and other low-level exposures, and there is creditable evidence for a threshold for radiogenic cancer induction (Tubiana et al. 2005; Raabe 2011); that is, a non-zero radiation dose below which there is *no* increased risk of cancer. The Health Physics Society has, in fact, issued a position statement advising against estimation of health risks below an individual dose of 50 mSv in 1 y or a lifetime dose of 100 mSv above that received from natural sources (HPS 2010).

As noted above, the point is often made that the benefits of the uses of radiation in medicine are much greater than any theoretical risks, but *quantitative* estimates of the benefits are rarely, if ever, juxtaposed with quantitative estimates of risk. This alone—expression of benefit in purely qualitative terms versus expression of risk in quantitative, and therefore seemingly more certain, terms—may well contribute to a skewed sense of the relative benefits and risks of diagnostic imaging among healthcare providers as well as patients. The current paper, therefore, briefly compares the benefits of diagnostic imaging in several cases, based on actual mortality or morbidity data if ionizing radiation were not employed, with the LNT model-derived (i.e., theoretical) estimates of radiogenic cancer mortality (Balter et al. 2011).

Radiogenic cancer risk

The excess number of cancers in a population exposed to radiation may be estimated using the LNT model as the number of persons exposed $\times$ effective dose (mSv) per person $\times$ excess risk (mSv^{-1}).

The excess risk is the number of excess fatal cancers (excess above the naturally occurring cancer mortality) predicted in a large (and therefore gender- and age-averaged) population

uniformly exposed to a whole-body dose of radiation. A widely cited excess risk value is that recommended by the National Council on Radiation Protection and Measurements (NCRP) Report No. 115 (NCRP 1993), $5 \times 10^{-5} \text{ mSv}^{-1}$. Thus, if a population of a million people were to each receive a dose of 1 mSv, the expected number of excess fatal cancers observed in this population over the balance of the lifetimes of the individuals in this population would be $1 \times 10^6 \times 1 \text{ mSv} \times 5 \times 10^{-5} \text{ mSv}^{-1} = 50$. This compares to the spontaneous, or background, lifetime mortality of ~200,000 (or 20%) otherwise occurring in such a population. Importantly, even if one concedes the accuracy of the LNT model, it cannot be applied reliably to individuals but only to large populations; that is, populations sufficiently large that differences in radiation sensitivity related to gender, age, and intrinsic biology are effectively averaged out.

Medical benefit

While more difficult to quantitate than the (theoretical) risk, the benefit of a diagnostic imaging procedure may be expressed as the lives saved; that is, the number of lives lost by *not* performing the procedure or by performing an alternative, invasive procedure. This benefit was quantified using clinical outcome data gleaned from the literature regarding the actual or hypothetical mortality or morbidity rates in specific instances where a relevant radiological procedure was not performed. There may be other metrics of benefits such as improvements in the quality of life, shortening of hospital stays, and reduction of medical care costs. However, in the current analyses, the emphasis was placed on lives saved as a result of performing the procedure.

The foregoing approach to quantitation of the medical benefit of a diagnostic imaging procedure may be illustrated by the use of scintigraphic perfusion imaging to predict perioperative cardiac events in non-cardiac surgery. The most important cause of perioperative cardiac mortality and morbidity is myocardial infarction (MI) due to occult CAD (coronary artery disease). In a Veterans Administration (VA) series (Gojer and Williams 1995), the incidence and mortality of such events associated with vascular surgery (most commonly, carotid endarterectomy) was 13% and 40–70%, respectively. Based on pre-operative dipyridamole thallium-201 (^{201}Tl) imaging, the incidence of perioperative cardiac events (Gojer and Williams 1995) was 2% for a severity level of 0 and extent of 0 and 100% for a severity level of 3 and extent of 5–6, with 22% of patients having reversible perfusion defects and therefore myocardial ischemia. Thus, perfusion imaging was highly accurate for prediction of perioperative cardiac events. The number of vascular surgeries (from the VA database) is ~9,500 per year, and the number of perioperative cardiac deaths (i.e., fatal MIs) is estimated as 494 per year. Therefore, in the VA system, the gross benefit of preoperative perfusion imaging with ^{201}Tl [that is, the number of predictable perioperative cardiac deaths (fatal MIs) avoided] is 109 (22% of 494) per year.

The effective dose from the ^{201}Tl study is ~24 mSv. In the VA series, the LNT model would predict $9.5 \times 10^3 \times 2.4 \times 10^1 \text{ mSv} \times 5 \times 10^{-5} \text{ mSv}^{-1} = 11$ excess cancer deaths per year, yielding a net benefit of pre-operative myocardial perfusion imaging of $109 - 11 = 98$ lives saved per year or a benefit-to-risk ratio of $109/11 \approx 10$. If one considers a rest/stress myocardial perfusion study using technetium-99 m ($^{99\text{m}}\text{Tc}$) MIBI scan, the effective dose

would be reduced to ~12 mSv, leading to only six theoretical excess cancer deaths per year. Performing cardiac PET with rubidium-82 (^{82}Rb)-rubidium chloride would result in an even lower effective dose of ~7.5 mSv (Health Physics Society 2008), thus resulting in a theoretical risk of only three cancer deaths.

The results of similar benefit-risk analyses for various medical imaging procedures (including the one detailed above) are summarized in Table 1 [see Zanzonico and Stabin (2014) for the references relevant to the respective studies]. In Table 1, and as in the foregoing analysis, the benefit-to-risk ratio is defined as the number of lives saved (i.e., the number of deaths avoided) by performing the procedure divided by the excess number of cancer deaths caused by the procedure, with the latter estimated using the LNT-derived risk factor of $5 \times 10^{-5} \text{ mSv}^{-1}$ unless stated otherwise.

In Table 1, a benefit-to-risk ratio greater than 1 indicates a net benefit of the procedure, and a value less than 1 indicates a net detriment. For four of the five procedures analyzed, there is a net benefit. For the fifth procedure, there is a net detriment; this warrants further discussion. In the U.S., there are 600,000 emergency room visits; 60,000 hospital admissions; and 7,400 deaths annually associated with pediatric head trauma (Faul et al. 2010; Marr and Coronado 2004). CT is the reference standard for emergently diagnosing traumatic brain injuries, and ~50% of children assessed in North American emergency rooms for head trauma undergo CT (Marr and Coronado 2004). Not surprisingly, such a high frequency of CT scanning in a pediatric population has raised concerns regarding long-term effects; namely, an increased risk of cancer. In a study of 42,412 children (including 19,718 younger than 2 y and 31,694 of 2 y and older) presenting to 25 North American emergency rooms within 24 hours of head trauma, Kuppermann et al. (2009) found that the clinical criteria for excluding clinically important traumatic brain injury (ciTBI) (normal mental status, no scalp hematoma except frontal, no loss of consciousness or loss of consciousness for less than 5 s, non-severe injury mechanism, no palpable skull fracture, and acting normally according to the parents) in children younger than 2 y had both a negative predictive value (NPV) and sensitivity for ciTBI of 100%. *Any* non-zero increase in risk of CT-induced cancer, even if theoretical, would not be justified, and therefore CT scanning for diagnosis of ciTBI is contraindicated on the basis of radiogenic cancer risk in children younger than 2 y. In children 2 y and older being evaluated for ciTBI, the foregoing clinical criteria have a NPV of 99.95% and a sensitivity of 98.80%. This NPV means that 0.5 out of 10,000 cases of potentially fatal ciTBI would be missed on the basis of the clinical criteria. Brenner et al. (2001) estimated the excess lifetime risk of brain cancer mortality for head CT among children 2 y and older as 2.5 cases per 10,000 CT scans; in this case, therefore, the appropriate age-specific (rather than the age-averaged) risk factor was used. Thus, at least theoretically, there is *no* net benefit—and actually a net detriment—of CT scanning for ciTBI in children 2 y and older, since there would be $2.5 - 0.5 = 2$ more lives *lost* per 10,000 children with than without CT. This illustrates the potential use of quantitative benefit-risk analyses in clinical decision-making.

CONCLUDING REMARKS

The analyses presented are representative “order-of-magnitude” examples from the literature of the benefits and radiogenic risks of medical imaging procedures. Although it is difficult to identify clinical studies with the necessary outcome data (i.e., outcomes with and without the relevant diagnostic study being performed), the approach presented could be extended to other studies. The current analyses suffer from several limitations. For example, as described, technical aspects of the procedures considered (e.g., the radiopharmaceuticals used, the administered activities, and the CT doses) may be somewhat dated. Further, clinical outcomes and the non-radiogenic mortalities and morbidities in the clinical scenarios considered are specific to the respective studies and are debatable. Despite these and perhaps other limitations, the conclusion is clear: *Overall, the diagnostic use of radiation in medicine saves many thousands of lives every year, while the theoretical risks predicted by the LNT model are typically much lower.*

Importantly, however, there may be clinical scenarios (as illustrated by the analysis of head CT in ciTBI in children) in which the quantitative analysis of benefit vs. radiogenic risk may indicate that a diagnostic imaging procedure is not justified. Thus, focus on the use of radiation in medicine should not be on radiogenic risk exclusively (as is now typically the case) but on reasonable evaluation of benefit as well as risk. Risk-focused analyses (to the exclusion of comparable consideration of benefit) have led to unwarranted concern in many instances about undergoing needed medical examinations that involve ionizing radiation. Patients should be advised of all risks and benefits of any medical procedure, to be sure. Physicians and physicists can speak in general about risks being “low” or “negligible” and are often understandably reticent to provide numerical estimates of risk. Even if requested, it is inadvisable to provide such numerical estimates for an individual patient from an estimated dose of ionizing radiation, although some practitioners may choose to do so. As shown here, however, any numerical estimate of risk from a medical procedure using ionizing radiation, if accompanied by a quantitative estimate of the benefits of these examinations to the medical population, puts the issue in perspective for the patient. The foregoing approach should be extended to additional examinations and the results of such analyses disseminated to the greater medical and radiation protection communities to improve communication of the risks and benefits of medical imaging to patients, their families, and society as a whole.

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Table 1

Benefit-to-risk ratios for various medical imaging procedures.

Imaging procedure	Benefit-to-risk ratio
Scintigraphic perfusion imaging predicting cardiac events in non-cardiac surgery	10
¹⁸ FDG PET in pre-operative assessment and avoidance of surgery and peri-surgical mortality in suspected non-small-cell lung cancer	36
Screening mammography in women 40–49 y of age	4.6
Abdominal CT for diagnosis and avoidance of surgery for suspected appendicitis	1.5
Head CT in diagnosis of clinically important traumatic brain injury after low-risk head trauma in children	0.25