HIA framework to investigate additional cancer risk from Ionizing Radiation in Medical Imaging.

Top-Down case study

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Abstract

Computed tomography (CT) was introduced into medical imaging in the 1970s and has grown exponentially particularly in cardiovascular clinical test for a wide variety of cardiovascular conditions. Cardiovascular CT use has recently been tempered by a string of high-impact publications raising concern about the increase in radiation exposure to the population from medical procedures and the potential cancer risk. This report highlights the framework in which integrated assessment of the effect of current cardiovascular imaging procedures on cancer risk is carried out. The analysis is based on the emerging results of a research project called SUIT-Heart (Stop Useless Ionizing Testing in Heart Disease) conducted by the Institute of Clinical Physiology of National Council of Research (IFC-CNR) in Pisa, Italy and funded by the Istituto Toscano Tumori (ITT). Finally it is outlined the chain of elements contributing to cancer incidence attributed to cardiovascular CT use. It is therefore represented an approach that helps the integration of health impact assessment for decision-making in the sector of ionizing radiation protection policies.

Keywords

IONIZING RADIATION
MEDICAL IMAGING
COMPUTED TOMOGRAPHY
CARDIOVASCULAR IMAGING
CANCER RISK
RISK ASSESSMENT
RADIATION PROTECTION POLICY
TUSCANY

Introduction

Focusing on single risk factors is not always satisfactory, as strategies and policies developed to address one risk might increase other risks. To develop effective precautionary policies, policy-makers and stakeholders need evidences based on an integrated risk assessment. To match this need RAPID project have included a case study to develop and test a framework and methodology for a "full chain" health impact assessment. Italian partner selected a topic on useless imaging testing in medical practice, tackling one of main policy focus at local and international level as well. Different policies, focused to the issue of awareness in diagnostic use of ionizing radiation, correspond to changes in individual exposure to cumulative dose and account for the variation of attributable long term cancer risks.

The intermediate level of determinants of health has been particularly posed under study as determinants are modified by policies and in turn they modify exposure to risk factors.

Health Impact Assessment (HIA) framework

Since 2000, the need for a new approach integrating the direct and the indirect effects assessed during health impact assessment has been recognized. In the development of health impact assessment, two broad approaches are usually acknowledged: the biomedical approach and the social determinants of health approach (Morgan, 2003). WHO initially promoted the first approach in the 1980s and defined it as environmental health impact assessment (WHO Regional Office for Europe, 1987). Environmental health impact assessment is based on the biomedical model of health, illustrated in direct effects such as mortality and morbidity. The second approach of health impact assessment evolved from public health considerations and is based on the interrelationships between the population and the environment, including socioeconomic determinants of health and institutional factors. This approach allows the indirect effects of projects and policies on health to be estimated.

More generally health impact assessment provides a structured framework to map the full range of health effects of any proposal and action, whether these are negative or positive (WHO Regional Office for Europe, 2002): "Health impact assessment is a combination of procedures, methods and tools by which a policy, programme or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population" (WHO European Centre for Health Policy, 1999). An integrated assessment, incorporating health impact assessment, allows policy development to ensure that health effects are not overlooked.

In the present case study the health impact assessment is done looking at the interrelationships between the population and the environment, including socioeconomic determinants of health and institutional factors. This document describes the "full chain" assessment of cancer risk from Ionizing Radiation in Medical Imaging with a top–down approach. The analysis goes from present regional regulation and interrelated policies, to the determinants of health, the risk factors and the attributable health outcomes. Available evidence and knowledge are used to highlight the full web of connections that lead health effects of policies to individual and population level.

Aim and relevance of the topic

Aim of this study is to develop a model which include either the risk management and the quantitative assessment of risks, into a framework for the assessment of the full range of health impacts (figure 1). The overall HIA process is aimed to supply qualitative knowledge for better decision making in the sector of diagnostic use of computed tomography for cardiovascular disease, by describing the full scheme of impacts proceeding from current regulatory advice in clinical practice (top) to a selected health outcome (down).

The challenge on research findings transfer from a Clinical Research Centre (performing the empirical research on this topic) to policy decisions is discussed, as well.

The topic selection for the case study has been based on considering that inappropriate use of cardiological ionizing imaging testing, fueled by radiological unawareness, is a significant source of useless radiation exposure of patients (creating a risk without a commensurate benefit). Medical imaging is the largest controllable source of radiation exposure in the population of industrialized countries. One out of two examinations is completely or partially inappropriate (i.e. risk outweighs benefit) and cardiologists are often unaware of the radiological dose of the examination they prescribe or practice (Gibbons et al., 2007; Gibbons et al., 2008; Picano et al. 2007). This avoidable exposure is associated with increased, significant cancer risk at both the individual and population levels and can be minimized through a knowledge-based intervention targeted to increasing radiological awareness of prescribers and practitioners.

Responding to rising concerns in the radiology community and among the public, the Food and Drug Administration (FDA) announced a new initiative (US FDA, 2010) in February 2010 aimed at reducing unnecessary radiation exposure due to medical imaging in US.

In Europe existing guidelines (European Commission, 2001) need duly be reinforced to achieve a more justified and optimized use of Computed Tomography in each country (Picano, 2004).

In Tuscany, Italy, under the Regional Health Plan 2008-2010 (Regione Toscana, 2008) and in accordance with the specific objectives on Clinical Risk Management, the Tuscany Region is committed to promoting initiatives for the prevention and protection of the community, in particular to the proper use of ionizing radiation (IR) and radioactive substances, which have enabled major developments in modern medicine with technological innovations such as tomography (CT), digital angiography and, more recently, Positron Emission Tomography (PET).

The Institute of Clinical Physiology of CNR, in Pisa, has activated in 2008 a collaborative project with the Istituto Toscano Tumori aiming at primary prevention of cancer through reduction of inappropriate ionizing testing (SUIT-HEART). Referring to this research issue, IFC researchers and medical staff represent a multidisciplinary team of experts and a network of practitioners to undergo testing and validation of case studies. In particular, disclosing how different approaches of diagnostic practice, responsible of balancing risks and benefits, are modified from background communication on and knowledge of risks, would lead to strengthen measures for an appropriate use of IR.

Exposure to ionizing radiation in medical practice

Over the last 30 years imaging techniques have become indispensable as an aid in diagnosis, prognosis, monitoring of disease and the implementation of interventional procedures (both diagnostic and therapeutic). Among medical imaging techniques radiological and nuclear medicine examination, based on the use of ionizing energy ("Ionizing Radiations" IR), exposes the patient and the operator to biological hazards and confers a definite (albeit low) long term risk of cancer.

According to a recent report by the National Council on Radiation Protection and Measurements (NCRP, Rep. 160, 2009), the per-capita effective radiation dose of the U.S. population from all sources increased 72% from the early 1980s to 2006, primarily as the result of a 5.7-fold increase from medical imaging. The increase in medical radiation dose is largely related to the increased use of imaging procedures that involve high radiation doses. Overall, all radiographic and conventional and interventional fluoroscopic procedures together represented 25% of the collective dose from nontherapeutic radiation in 2006. CT represented 49%, and nuclear medicine 26%, of the collective dose. The number of CT studies in general increased by 10% to 11% per year between 1993 and 2006. According to the NCRP report, there were 3.1 million cardiac CT studies in 2006, which represented 4.7% of all CT studies and 12.1% of the collective radiation dose from CT. There were 18.1 million nuclear medicine studies in 2006, a 4.6-fold increase from 1982. Cardiac nuclear medicine studies had the greatest growth. In 2005, cardiac studies represented 57% of all nuclear medicine patient visits and 85% of the collective radiation dose received from nuclear medicine studies. A large proportion of this diagnostic (non-therapeutic) medical radiation was delivered in specific settings or specific subgroups. For example, 82% of the CT procedures were performed in hospital laboratories. In 2003, 71% of the cardiac nuclear medicine procedures were performed in patients older than 55 years of age (NCRP, Rep. 160, 2009).

Therefore imaging testing is a significant source of radiation exposure of a not negligible proportion of the general population (Wiest et al., 2002; Lee et al. 2004; Mettler et al., 2009). A CT scan exposes patients to far more radiation than a standard X-ray, yet scans remain largely unregulated. It would not be uncommon for a patient's estimated exposure to exceed 50 millisievert. CT doses can indeed approach or exceed levels that have been shown to result in an increase in cancer (ICRP, 2008). Generally, women, children and young people should try to avoid scans.

As a consequence cardiovascular CT has taken a central role in the discussion about the risk–benefit of ionizing radiation-based diagnostic imaging procedures (Kim et al., 2009). Importantly, this has hastened the development and implementation of dose-lowering tools (Halliburton, 2009) and provided the young field of cardiovascular CT with an opportunity to aggressively incorporate radiation exposure into quality standards. Quality standards must consider applied radiation in the context of the clinical indication, the characteristics of the patient, the availability of alternative diagnostic (imaging) strategies, and the specific CT imaging technique available (Halliburton & Schoenhagen, 2010).

The model

A top-down risk assessment model (figure 1) is herein proposed to answer the following issue:

- How do current or prospective policies, focused to the issue of awareness in diagnostic use of ionizing radiation, correspond to changes in individual exposure to cumulative dose?
- How do they account for the associated attributable long term cancer risk?
- Is currently estimated individual risk comprehensive of cumulative exposures?

With reference to this issue the Tuscany Regional Health Plan 2008-2010 (Regione Toscana, 2008), presides over initiatives to make it more stringent reduction of ionizing radiations in medical practice. This policy acts in accordance with local initiatives conveying towards industrials, physicians and patients awareness with the aim of modifying proximal cultural and socio-economic health determinants (not usually included in view of cumulative life exposure dose) as to cause a substantial change in current exposure models to IR. Main risk factors could be lowered from disseminating at collective and community level a novel understanding of real risks associated with effective dose of ionizing radiations.

Saving use of radiation has a great potential to reduce incidence case of cancer mainly at population level. While policy addressed to screen high risk subjects reduce greatly the individual risk, a policy action modifying exposure model reduce greatly the potential for major populations at risk (it is the case for categories of male, age over 55, children). As to the balance risk-benefit, the gain is calculated over a long term perspective including the overall cancers, attributed to medical imaging.

The following generic methodological steps, validated in a pilot study by IFC-CNR (Regione Emilia Romagna, 2010), are used to test and validate the model for the assessment of the health burden of current regulation on ionizing radiation in medical practice:

- Selection from literature of relevant knowledge and evidences on medical imaging and health effects. They constitute a starting rationale of the study context;
- Expert advice to validate core factors in model building;
- Testing of hypothesis on a real context by a pilot application;
- Consensus-building on the developed model;
- Results, tools and concrete recommendations summed in a written report. This last has the function to vehicles information into policy and regulations.

Last two steps completion including the prevented revision by the Rapid whole group.

In essence this framework is an aspiration for a strategy change in the way that the regional health service provide care as to manage the use of medical imaging optimally, in order to reduce the likelihood of effective dose of radiation for patients.

Policy description

Protecting the patient from ionizing radiation is regulated by Legislative Decree 187/00, issued to implement the European directive 97/43 (D. Lgs. 187/00). The Tuscan Regional Council is committed to monitor the dose to the population and medical workers due to medical examinations, firstly to allow the information to the patients of the received dose in each examination and that accumulated during their clinic history. Among aims there is also to promote either a widespread communication campaign for Tuscan citizens and a training pathway for prescribers on the risks posed by the medical exposure to ionizing radiation. The objectives of the Regional Health Plan are also targeted to propose guidelines and recommendations for the implementation of Legislative Decree 187/2000, to be achieved through the definition of protocols and best practices addressed to regional structures concerned. Funding is allocated by the Tuscan Region for 3 years to develop a project, by the Italian Association of Medical Physics, entitled "Communication of patient dose". The project plans to make automatic the process of measuring the dose and its recording in an electronic health card, in each Tuscany health-care accredited centers. Funding is also allocated to the development of the project entitled SUIT-HEART (Stop Useless Ionizing Testing in Heart Disease) - primary prevention of cancer through reduction of inappropriate ionizing testing, to be carried out by IFC-CNR and Tuscany Cancer Institute, over 3 years. The overarching aim of the SUIT-HEART study is to promote a better appreciation of radiation risks in the cardiology community and in patients, as now unanimously recommended by official documents of the American College of Radiology 2007, International Atomic Energy Agency 2008 and American Heart Association 2009.

Consequences of a comprehensive understanding of radioprotection issues inside medical practice and of the use of advanced health care ionizing radiation technologies, influences different current policy targets such as: training and information for specialists and practitioners, correct information for users, implications of informed consent, political intervention to reduce the dose in the higher risk practices.

Determinants of health

Determinants of health include the range of personal, social, biological, economic and environmental factors which determine the presence and distribution of risk factors in the populations. Interaction between a large variety of these factors and different exposure or baseline health condition, affect the presentation of the outcome. Prescription practice in medical setting is a major determinant of the cumulative individual and collective dose, having an effect on the medical practice. However medical practice is also determined from multiple factors ranging from current regulation, technological updating of devices, type of “license” for medical device use, continuing training for physicians, physician attitude and perception toward risks and health equity, patient awareness and informed consent protocols, working environment regulation and available information on risk-benefit (Figure 2).

Classification of exposed population by gender and young age classes as well as previous exposure story, also interact determining variations of attributable risks. Moreover there are often medical conditions, chronic, serious or even fatal, acting as co-determinants of the final outcome of radiation exposure (Figure 2).

Medical practice and cancer risk

Based on growing clinical experience, guidelines describing appropriate indications for cardiovascular CT have been established, weighing procedural risk, pre-test probability, and expected benefit (Hendel et al., 2006). Procedural risk is defined by the need for vascular access, amount of injected contrast media and level of radiation exposure, and depends on patient specific criteria, including age and sex (Einstein et al., 2007). It is important to note that a significant reduction in radiation dose for CT imaging of a particular indication (e.g., coronary CTA with $<$ 1 mSv) could shift the risk-benefit ratio and subsequently have an impact on appropriateness criteria. However, the relatively noninvasive nature of a test alone does not establish its usefulness for screening, in particular because false positives in patients with low pre-test probability can be associated with untoward outcome (Nissen, 2008).

If CT is determined to be the most appropriate test, it is important to tailor the imaging protocol to the clinical question. The CT imaging protocol should also be tailored to patient characteristics. In addition, X-ray parameters including tube voltage and tube current should be adjusted according to patient size (Halliburton 2009). A 30% decrease in tube current results in a 30% reduction in X-ray exposure (DeMarco, 2007).

Although tailoring the cardiovascular CT imaging protocol to the clinical indication and the patient is critical for the optimization of both image quality and dose, the rapid development of scanner hardware and software as well as manufacturer differences in scanner design have largely prevented standardization of protocols. This is reflected in recent studies (Hausleiter, 2009) demonstrating large variations in coronary CTA protocols, resulting in a wide range of radiation doses at different centers as well as recent, highly-publicized egregious errors in noncardiovascular CT imaging that have resulted in dramatic patient overexposure. Clearly, a coordinated effort is needed to standardize and regulate radiation exposure during cardiovascular CT, including regular monitoring of the radiation burden (Abbara et al., 2009), formation of imaging groups with collective experience of various imaging modalities (multimodality imaging). In such groups, dedicated protocols are designed in collaboration by radiologists, cardiologists, physicists, and technologists. Based on individualized review of the clinical indication, the patient is directed toward the most appropriate diagnostic test or strategy. Choosing the right test for one individual gives possibilities to reduce the burden of cumulative dose, using radiation as the last option. Adopting an approach based on appropriateness can lead to spare radiation use at the level of population, increasing the overall health benefits (figure 3). Differences in estimated cancer risks have a noticeable weights translating inappropriate clinical decision-making from individual health care to these of a sub-group of population (table 1).

Table 1. Appropriateness in medical practice can modify the final cancer risk at population level.

Differences in cancer risks	***Sample 100000 persons*** ***Age 40-50*** ***Males 50 %*** ***Females 50%***	
Scintigrafy Sestamibi Tc-99m	**Scintigrafy Tallium**	**TC-chest**
Incidence 58.1 (45,6-74,2) 1/1721 (1/2193 - 1/1348) **Mortality** 33,2 (26,0-41,0) 1/3012 (1/3846 - 1/2439	**Incidence** 264,9 (207,9-337,8) 1/378 (1/481-1/296) **Mortality** 151,5 (118,5-186,6) 1/662 (1/844 - 1/538)	**Incidence** 45.2 (35,5-57,7) 1/2212 (1/2817 - 1/1733) **Mortality** 25,9 (20,2-31,9) 1/3861 (1/4951 - 1/3135

In conclusion the emphasis falls on the justification of medical procedures and optimization of radiation protection as actions to be taken to reduce irradiated dose. In diagnostic and interventional procedures, justification of procedures (for a defined purpose and for an individual patient) and the management of patient dose, proportionate to medical purposes, are the appropriate mechanisms to avoid unnecessary exposure to radiation or unproductive. The use of equipment to facilitate the management of patient dose and diagnostic reference levels derived in relation to the appropriate national, regional or local level are probably the most effective methods.

In particular, a few preliminary observational data in IFC highlight the potential for dose irradiation reduction coming from: adequate increase in knowledge of imaging techniques users; up-to-date knowledge of the radiological dose (and corresponding cancer risk) of commonly prescribed imaging examinations, both from practitioners and prescribers; risk-benefit analysis in health technology assessment, including long-term risks and downstream costs due to cancer; communication of radiological risk to patient undergoing an exam (SUIT-Project, 2008).

A few political strategies, other then those developed in the health-care sector, are cross linked to the radioprotection issues and to the final health outcomes; including passenger safety in air travels, management of radioactive hazardous waste, disposal of contaminated equipment, occupational safety, cost-benefit analysis for new health technologies, industrial sector convenience, medico-legal issues. Policy actions in these sectors may indirectly affect proximal determinants in the causation chain described and the overall exposure model (Figure 3).

Same actions has been taken from different private and institutional organizations to re-address common understanding about the risks from medical devices using IR. The Medical Imaging Technology Alliance, a group of medical imaging equipment manufacturers, innovators, and product developers, has endorsed measures to promote the responsible use of ionizing radiation-based diagnostic imaging procedures. Other proposed initiatives include promoting patient awareness of medical radiation, expanding appropriateness criteria into clinical decision making, incorporating safeguards into scanner designs, developing radiation dose reference values for specific procedures, incorporating radiation dose values into the electronic medical record, creating a national dose registry, establishing minimum standards for training and education of imaging personnel, and expanding mandatory accreditation for advanced imaging facilities (Neumann & Bluemke, 2010).

Risk factors

A great deal of data on cancer risk from ionizing radiation technology are at the present available (BEIR VII, 2006; President's Cancer Panel 2010). Existing estimation of years of life lost for attributable cancer poses an alarm for public health policies reinforcement towards an adequate use of modern health imaging technologies.

Main risk factors, related to induced cancers from IR are: working in the health care sector-staff of the interventional cardiology, the sharp rise in the number of diagnosis with IR (number of prescriptions can be used in policy as risk factor indicator), the health care strategies (i.e. extensive replacement of the classic technologies for diagnosis with new technological devices), disease in the range of cardio vascular pathologies, patient stratification by clinical risks, other social factors (i.e. patient expectation to be assisted, underestimation of risks by practitioners and physicians).

Risk factors (especially environmental), act in different settings as showed in table 2. The radiation sources may be both natural and artificial. The medical sources of radiation have accounted for about one fifth that of natural radiations (that first come from radon and after from cosmic rays and terrestrial radiation) in 1987, close to half in 1993, 100% in 1997, and now 150% that of natural radiation in most affluent countries. The medical sources of radiation in industrialized countries are therefore now greater than natural sources. Among the exposures associated with sources artificially formed, the main contribution to population exposure is related to the use of radioactive substances in medicine for diagnostic and therapeutic. Medical imaging is the largest controllable source of radiation exposure in the population of industrialized countries – totalling around 150 chest x-rays per head per year. Of these exposures, two-thirds come from cardiovascular testing (cardio-CT, nuclear cardiology and interventional cardiology) (Bedetti, 2008). Interventional cardiologists are today the most exposed among health professionals (Venneri et al. 2009).

The present report does not describe natural contamination sources, as they are not relevant to the policy implementation for reduction of exposure from diagnostic use of ionizing radiations. Other man-made sources of exposure are activities which involve the possession, use, handling of radioactive materials, products and equipment containing these materials in general, including treatment, storage and possible disposal of waste. Numerous artificial sources are listed in current regulation, between those we focus on the use of radiation in medical practice and exposure coming from computed tomography for cardiovascular testing. The principal risk factor addressed is related to this specific exposure.

Table 2. Risk factors acting in different settings

Settings / Risk factors	*Home environment*	*Workplace environment*	*Community environment*
Natural sources (environmental and food matrices) [a]	fallout, DMOS, milk, beef, etc.		fallout, DMOS

Artificial sources (activities with use of ionizing radiation sources) [1]		use of radioactive substances mainly in medicine for diagnostic and therapeutic, dismantling of contaminated equipment	safety in international flights, management of radioactive hazardous waste, radiation exposure from medical imaging

The concerns about the increase in medical exposures to the population and the potential for misuse of the available technologies have prompted both the National Institutes of Health (Neumann & Bluemke, 2010) and the Food and Drug Administration to announce initiatives to reduce unnecessary exposure from medical imaging examinations. The Medical Imaging Technology Alliance, a group of medical imaging equipment manufacturers, innovators, and product developers, has also endorsed measures to promote the responsible use of ionizing radiation-based diagnostic imaging procedures. Proposed initiatives include promoting patient awareness of medical radiation, expanding appropriateness criteria into clinical decision making, incorporating safeguards into scanner designs, developing radiation dose reference values for specific procedures, incorporating radiation dose values into the electronic medical record, creating a national dose registry, establishing minimum standards for training and education of imaging personnel, and expanding mandatory accreditation for advanced imaging facilities.

Pediatric population and medical staff

Rapid growth in the use of CT and other sources of ionizing radiation for diagnostic and other imaging in children is of special concern. Children are inherently more sensitive to radiation than adults. They are three to five times more vulnerable (American College of Radiology, 2009) to the damaging effects of radiation because of their rapid development.

In 2007, CTs on children numbered in the range of 3.5–7 million (5–10 percent of all CTs); of these, 750,000–1.5 million were scans of children under 5 years of age (Brenner, 2009).

The potential for radiation-induced lifetime cancer risk increases the younger the child is at the time the dose is received, even when the dose is the same. According to one estimate, a 1-year-old is 10–15 times more likely than a 50-year-old to develop a malignancy from the same dose of radiation (McCormack et al., 1998). Thus, avoiding unnecessary radiation risks in this sensitive population is crucial (Sadetzki & Mandelzweig, 2009). As many as one-third of CTs currently performed in children may be unnecessary (Slovis, 2002).

Scans of children are often done without adjusting dose to weight, resulting in up to 50% of the dose being unnecessary (Ron, 2002). A small individual risk is multiplied by millions of examinations a year worldwide, becoming an important population risk (Ron, 2002).

[1] Plants, factories, institutes, departments, surgeries, laboratories, engaged in activities' which involve the possession, use, handling of radioactive materials, products and equipment containing these materials in general, treatment, storage and possible disposal of waste into the environment as well as' the use of devices generating ionizing radiation (Source: DLgs 17 march 1995, n. 230).

The Society for Pediatric Radiology and the National Cancer Institute (NCI) collaborated to develop and circulate a pamphlet (National Cancer Institute, 2008) for health care providers on pediatric CT and radiation risks.

Protecting radiation technologists and other medical staff from excessive radiation exposure has been a concern for many years, with dose limits and lifelong monitoring procedures established in most countries (Rehani, 2009). Only one-half percent of medical workers reach or exceed this dose limit (Rehani, 2009). The dose limit recommended by the International Commission on Radiological Protection (ICRP) and adopted by all but a few countries is 20 mSv annually, or 100 mSv over 5 years (Valentin editor, 2007).

Health outcomes

Ionizing radiation is known to cause harm. High radiation doses tend to kill cells, while low doses (i.e., < 100 mSv) tend to damage or alter the genetic code (DNA) of irradiated cells. The biological effects of ionizing radiation are divided into two categories: deterministic and stochastic effects. Deterministic effects, such as erythema or cataract, have a threshold dose below which the biological response is not observed (BEIR V, 1990; UNSCEAR Report, 2001; Hall, 2000). Some cardiological interventional procedures with long screening times and multiple image acquisition (e.g. percutaneous coronary intervention, radio-frequency ablation, etc) may give rise to deterministic effects in both staff and patients (ICRP, Publication 59, 1991; Vano et al., 2005; Vano et al., 2008). A stochastic effect is a probabilistic event and there is no known threshold dose. The likelihood of inducing the effect, but not the severity, increases in relation to dose and may differ among individuals. In fact, the effect of low doses of radiation - less than 50 mSv - do not cause an immediate problem to any body organ, but spread out over long periods of time after exposure. Damage are at DNA level and is considered to be the main initiating event by which radiation damage to cells results in development of cancer and hereditary disease in the future children of exposed parents (Hall, 2000; BEIR VII, 2006). In fact, ionizing radiation exposure produces long-term health effect through, both directly or indirectly (free radical interaction), damage to cellular DNA, producing oxidized bases, bulky DNA adducts, and DNA strands breaks.

The cell has repair mechanisms against damage induced by radiation as well as by chemical carcinogens. Consequently, biological effects of low dose radiation on living cells may result in three outcomes: (1) injured or damaged cells repair themselves, resulting in no residual damage; (2) cells die; or (3) cells incorrectly repair themselves resulting in a biological change.

However, the effects of low-level exposure remain uncertain (Brenner et al., 2003). The associations between radiation exposure and the development of cancer are mostly based on populations exposed to relatively high levels of ionizing radiation (e.g., Japanese atomic bomb survivors).

A linear, no-threshold dose response relationship is used by the IRCP in order to describe the relationship between radiation dose and the occurrence of cancer (NCRP, Rep. 136, 2001). This dose-response model suggests that any increase in dose, no matter how small, results in an incremental increase in risk. Genetic effects are the result of a mutation produced in the reproductive cells of an exposed individual that are passed on to their offspring. These effects may show up as birth defects or other conditions in the future children of the exposed individual and succeeding generation. Indeed, studies with laboratory animals have provided a large body of data on radiation-induced genetic effects (Dubrova, 2003; Foffa et al., 2009)

Different health outcomes from radiologic exposure in cardiovascular imaging testing are shown below.

Table 3. Biological effects of ionizing radiation. (Redrawn and modified from Foffa et al., 2009).

	Deterministic effects	Stochastic effects
Dose	Medium-High	Low
Occurrence time	Short	Long
Threshold dose	Yes	No
Cell biology	Cell Death	DNA damage
Clinical effects	Skin lesions, erythema, ulcers, epilation, cataracts, permanent sterility	Cancer, genetic effects

Attributable total cancer risk (fatal cancer + non-fatal cancer) is herein chosen as health outcome. It is statistically calculated combining evidence of dose estimates and cancer risk estimates.

Pilot application

Two operational phases have been performed with the aim of testing the full chain model (figure 1) referred to the radioprotection policy in Tuscany. An extensive review of present evidence and an experts consultation, have allowed the identification of factors responsible for modifying exposures to ionizing radiation in the wide context, and specifically in the healthcare environment. Inner bibliographic resources, stored at the Institute of Clinical Physiology (located at the National Research Council, Pisa, Italy), as well as real data gained from the Institute clinical activity, have been arranged to perform the risks estimates, focusing on the attributable long-term cancer risk. The two phases are briefly described.

Phase 1. Literature review and experts consultation

The work undertaken in Rapid Italian case study, in particular the causal chain building, was strongly informed by the completion of state-of-the-art reviews of key areas of research, including determinants of health, risk factors, health effects. Table 4 summarizes the results of these reviews based on papers published on scientific journals with high impact factor and scientific association guidelines and recommendations, focused to medical imaging and/or computed tomography use. Selected references are primary study or most updated reviews, published from 2003 to 2010. They totally sum to n. 69.

Reviews have been completed early in the project allowing to refine a checklist for the experts consultation (table 5). It includes factors that have been pointed out to determine the final health effects.

Table 4. Summary of results of state-of-the-art reviews used to inform the Rapid case study method.

Chain level	Issue	Bibliographical Entries
Policy	Policy on Radioprotection 2008-2010	Regione Toscana, 2008
	National Guidelines	ICRP, 2007, 2008; ECRP, 2008;
Health determinants	Present medical practice	Hall & Brenner, 2008; Brenner & Hall, 2007; Huda & Vance, 2007; Picano et al., 2007; Bedetti et al., 2008; Winslow et al.,2008; ICRP, 2007, 2008; Sodickson, 2009; Griffey & Sodickson, 2009; Fazel et al., 2009; Foffa et al., 2009; Tsapaki et al., 2010; Halliburton & Schoenhagen, 2010;
	Technological updating	Einstein et al., 2007; Gaztanaga & Garcia, 2009;
	Training strategies	Jacob et al., 2004; Lee et al., 2004; Correia et al., 2005; Arslanoğlu et al., 2007; Brenner & Hall, 2007; Bruner et al., 2009; Tsapaki et al., 2010
	Patient/operator awareness	Correia et al., 2005; Brenner & Hall, 2007; Karsli et al., 2009; Bruner et al., 2009;
	Workplace environment	Vañó, 2003; Delichas et al., 2003; Andreassi, 2004; Venneri et al., 2009; Ciraj-Bjelac et al., 2010;
	Community environment	Gerber & Gibbons, 2010
	Commercial/Economic reasons	Picano, 2004; Hall & Brenner, 2008; Street et al., 2009; Hausleiter et al., 2009; Halliburton & Schoenhagen, 2010;
Risk factors		
Pediatric population	Age	Brenner et al., 2001; Brenner & Hall, 2007; Harrison & Day, 2008; Thomas & Wang, 2008; Berrington de Gonzalez et al., 2009; BEIR VII; Gerber & Gibbons, 2010;
	Gender	Berrington de Gonzalez et al., 2009; Harrison & Day, 2008; BEIR VII;
	Diagnosis	Huda & Vance, 2007;
Adult population	Age	Brenner et al., 2001; Brenner & Hall, 2007; Berrington de Gonzalez et al., 2009; Harrison & Day, 2008; BEIR VII;
	Gender	Berrington de Gonzalez et al., 2009; Harrison & Day, 2008; BEIR VII; Gerber & Gibbons, 2010;
	Diagnosis	
Health outcomes	Fatal cancer	Picano, 2004; Picano et al., 2007; Einstein et al., 2007; Brenner & Hall, 2007; BEIR VII; Mettler et al., 2008; Little et al., 2009; Sodickson, 2009; Berrington de Gonzalez et al., 2009; Little et al., 2010; Tsapaki et al. 2010, Halliburton & Schoenhagen, 2010;
	Non-fatal cancer	Yoshinaga et al., 2004;
	Skin and eye lesions (medical staff)	Renaud, 1992; McKetty, 1996; Vañó et al., 1998; Finkelstein, 1998; Yoshinaga et al., 2004; Andreassi, 2004; Vano et al., 2005; Vano et al., 2008; Foffa et al., 2009; Ciraj-Bjelac et al., 2010
	Teratogenic effects	Andreassi et al., 2005,2006a, 2006b; Foffa et al., 2009; Ait-Ali et al., 2010

The checklist is meant to provide a relatively simple approach that can highlight important information about the potential effect and relevance of listed factors, on final health impacts. In this desktop exercise, an expert decide whether a factor has, or has not an effect (or it should be considered uncertain) and assesses the importance of each factor by attributing a score (0 "low", 1 "intermediate" and 2 "a lot"). The total score, by factor, helps guide a decision about pursuing a focused policy action on highly relevant factors.

Table 5. Checklist used for the experts consultation.

Chain level		**no**	**uncertain**	**yes**
Policy	Commercial/Financial Other health care policy			
Health determinants	Present medical practice Technological updating Training strategies Patient/operator awareness Workplace environment Community environment Other			
Risk factors				
Pediatric population	Age Gender Diagnosis Other			
Adult population	Age Gender Diagnosis Other			

Inner resources from IFC-CNR and collaborative consultants from University and Health care departments have been selected for the consultation. The multidisciplinary team was constituted as follow:

Cardiologist (Senior Researcher);
Radiologist (Technical Consultant);
Hemodynamist (Research Director);
Pulmonologist (Researcher);
Nuclear physicist (Principal Investigator);
Geneticist (Researcher);
GP (Generic Physician);
Manager and Scientific Coordinator, Physical co-worker (Sanitary department).

Phase 2. Cancer risk estimates and diagnostic imaging exposure

The risk of cancer associated with diagnostic imaging has been quantified using a computational software (RADIORISK 1.3, Paterni et al., 2010) based on three main sub-components of exposure: natural, diagnostic, professional. The result is the amount of cumulative risk either for the patient or a subpopulation. The simulated risk is secondarily associated with current indications of appropriateness to inform the physician about the proper clinical decision to be taken. The software basic function is to estimate the cancer risk based on the personal history of exposure to ionizing radiation. Current guidelines, dose references and accepted evidence in BEIRVII are used to calculate risk (BOX 1).

BOX 1

Guidelines:

- Gerber TC et al: Ionizing Radiation in Cardiac Imaging. A Science Advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation 2009;119:1056-1065
- The Royal College of Radiologists (RCR): Making the best use of clinical radiology services (MBUR), 2007, 6th edition
- Budoff MJ, Achenbach S, et al: Assessment of Coronary Artery Disease by Cardiac Computed Tomography. A Scientific Statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114:1761-1791

Dose Reference:

- Reference European guideline (2001)
- Guidelines of Italian Minister of Health
- Peer reviewed journal
- Government Agency
- From each exam data file (if available)

Cancer Risk Estimation - BEIR VII,2006:

- The estimation is based on 100000 studies, including 87000 Hiroshima and 407000 nuclear workers
- 2 to 3 confidence intervals of attributable risks estimate
- X-rays and gamma-rays are a proven carcinogen (WHO's International Agency of Research of Cancer)
- Epidemiological evidence up to now above 50 mSv
- Re-affirm Linear No-Threshold hypothesis

Advanced software interfaces display either information on exposure levels by source (mSv unit), and annual and cumulative exposure by observational period, referred to RX equivalent.

Main results about risks are displayed as well and expressed as incidence cases and mortality attributed to the different sources of exposure. Medical imaging use extra risk on 100 person (or on a defined population) is than available, with a calculated range of uncertainty.

Uncertainties in estimated risks

The effective dose, expressed in units of millisieverts (mSv), is the dose quantity most commonly used to relate exposures from low doses of ionizing radiation to the probability of detrimental health effects. The effective dose represents the amount of whole body irradiation that yields a biological risk equivalent to the irradiation of only a portion of the body (as with cardiovascular CT). Although the effective dose quantity is thought to be the best quantity available for linking radiation dose and health risk, it must be recognized that the effective dose is associated with a level of uncertainty on the order of $\pm$40% when it is used to quantify dose for medical exposures (Martin, 2007).

Further, the effective dose is not intended to express absolute patient-specific risk (i.e., risk to specific persons of known age and sex) but rather risk to the general population. These limitations of the effective dose underlie the recommendation to use a different metric, the dose-length product, reported by the CT scanner in units of mGy X cm, to characterize the amount of radiation from a single CT examination in the patient report (Abbara et al., 2009; Raff et al., 2009; Hendel et al., 2009) and in research studies.

The calculation of numerical risk from the effective dose estimates is further limited. Cancer risk from the relatively low doses of ionizing radiation used during medical imaging is linearly extrapolated from the radiation risk data of atomic bomb survivors in Japan after World War II. The validity of this approach relies largely on the linear nonthreshold theory, which assumes a linear relationship between dose and cancer risk even at the smallest doses. However, the linear no-threshold theory is controversial and the subject of debate (Strzelczyk et al., 2007; Tubiana et al., 2009; Little et al., 2009). Therefore, estimations of risk from low doses of radiation delivered during medical imaging examinations must be interpreted with regard to the imprecision of the calculation.

Further, any potential risk of future stochastic events must be balanced with the risk of forgoing a medically necessary examination (Gerber et al., 2009).

Usual conventional analysis of risks in health technology assessment consider only acute direct costs. At present long term risks and downstream costs due to cancer are not included in risk-benefit analysis. As to radioprotection goal both individual risk calculation (per exam per patient) and the radiological cumulative risk (lifetime) are necessary to be performed.

However a debate is ongoing regarding the true incremental risk to subjects exposed to doses currently administered in cardiovascular procedures fails to take into account the uncertainty of the dose-response relationship in this lower range, as well as tissue-specific reparative responses, also manifest at lower levels of exposure (Warren et al., 2010). The leap from radiation exposure to the risk of stochastic effects such as cancer is controversial, particularly for individual patients, because of known uncertainties in dose estimates and risk models (Halliburton & Schoenhagen, 2010).

Results

Estimated risks for individuals or different sub-populations depend on the exposure model upstream in the chain of causation. Different approaches in medical practice are already known to modify individual and population exposure, as to reduce useless radiation and cumulative life burden of radiation (Figure 3). In particular the case study stresses the relevance of multi-factorial proximal determinants of health that, acting upon distal risk factors, can lead changes in the exposure model as well (Table 6). Therefore the wide range of health determinants and risk factors contributing to the overall exposure have been linked in a causal pathway from policy to the outcome (Figure 4). Such overall representations of factors which interact each other, has been duly supported from a few research sub-actions, performed in the IFC tertiary care referral centre, which have shown that:

- radiological awareness is very low even among practitioners and prescribers of exams with very high radiation exposure (Correia et al., 2005) with at least 40% of stress imaging testing being inappropriate (Picano et al., 2007).
- long-term risks should be included not only in the assessment of diagnostic appropriateness but also in cost-benefit analysis, with potential to completely overturn on current approaches to cost-benefit assessment (Bedetti et al., 2008).
- an alternative proposal of radiological informed consent form addresses the problem of the current limitations (Bedetti & Loré, 2007), being consistent with the requirements of transparency, clarity and legal sustainability proposed by the International Atomic Energy Agency in 2008.
- dose has to be translated into risk and dose reduction has to be translated into number of spared risks, calculating the cumulative risk for patients (Bedetti et al., 2008) and for invasive cardiologists, as well (Venneri et al., 2009).

Table 6. Ranking of health determinants and risk factors from experts consultation.

	Risk factors	Health determinants
Very relevant	Age - paediatric population	Training strategies
Relevant		Technological updating
Moderate	Gender - paediatric population Age - adult population	Present medical practice Patient/operator awareness
Slight effect	Gender - adult population Diagnosis - adult population Diagnosis - adult population	Workplace environment
Not relevant	Familiarity	Commercial/Financial policy Other health care policy Community environment

Conclusion

In view of an informed policy action a more inclusive web of causation has been delineated, merging together available information on risk factors with less usual information on indirect factors, inducing modification in medical practice. The adoption of an integrated approach, in which applied doses in medical imaging are considered together with other sources of exposure and modifiable individual behaviors, can be translated in a remarkable health and socio-economic benefit. The present case study takes a step in this direction allowing decision makers to identify an optimal strategy.

Recommendations from the 2007 White paper of the American College of Radiology, suggest "education of all stakeholders in the principles of radiation safety, the appropriate utilization of imaging to minimize any associated radiation risk, the standardization of radiation dose data for its ultimate use in benchmark good practice". This strategy of improving appropriateness through knowledge-based intervention may be a very cost-effective policy for primary prevention of cancer in industrialized countries, since 10% of all cancers may be attributable to the medical radiation. Better knowledge of risks will help to avoid small individual risks translating into substantial population risks.

Radiologically speaking the doctors (on average) do not know what they do: on one hand this leads to a colossal amount of waste and risk in our health system, and on the other hand it offers a unique opportunity to spare an enormous amount of resources (the useless examination and its linked direct and downstream costs). Reducing inappropriate testing will improve the quality of health care, shorten waiting lists inflated by useless examinations, and – most importantly - reduce long-term oncogenesis due to ionizing radiation. This situation is unavoidable in a system that pays according to volume and not appropriateness. The change in prescription pattern and reimbursement policy by necessity should by necessarily follow a systematic recognition of current practice in the "best" (high-tech, technology-oriented, research-driven) institutions.

The 2002 statement of the International Atomic Energy Agency (International Atomic Energy Agency, 2002) recognized that "Health professionals involved in the process of diagnosis and treatment are the critical link. Training them properly and ensuring intensive information exchange among them are, therefore, probably the most cost-effective ways of achieving patients' safety".

The SUIT-Heart project was promoted by IFC as an opportunity to reshape current clinical cardiological practice, with a paradigm shift based on expanding physician knowledge. Inside the SUIT-HEART research context the application of the delineated RAPID model is a wisdom way for enlarging the base of knowledge as to achieve the goal of reducing estimated cancer risk due to radiological examinations, stemming from the general policy on radioprotection.

A shift in the health concept, from a thigh view (limited to the consideration of outcome depending from the exposure to physical hazards) to a broader one (including the indirect actions of socioeconomic factors on the final presentation of the outcomes) is expected to build a more inclusive knowledge background and disseminate it to the stakeholders, physicians and practitioner involved.

The development of a set of indicator to highlight results from this basic "cultural intervention" would address the question of quantifying the effects induced on final outcomes in consideration of the modification of proximal determinants of health.

As to this specific investigation, an evaluation of post interventional actions would in future allow baseline comparison of diagnostic practice and highlights a different overall balance among risk and benefit; acting on proximal factors leading to maximizing health benefits and reduce the expected negative effects. Hence, the best practice on the use of computed tomography in cardiovascular disease could be comprehensively integrated with the considerations of socioeconomic determinants of health and institutional factors.

Main outcomes of such further investigation will keep the policy decisions informed reporting the overall results, research strategy, motivation for choices, subject involved in the consultations, and a minimum set of recommendation.

It is, therefore, proposed that future quantification of the overall effect upon final outcomes has to be approached by the model herein described, and characterized by the key features below described:

- Literature consultation
- Experts rating
- Risk estimates comparison
- Overall consideration for best practice
- Reinforcement of communication on risks.

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Figure 1. Top-down risk assessment model.

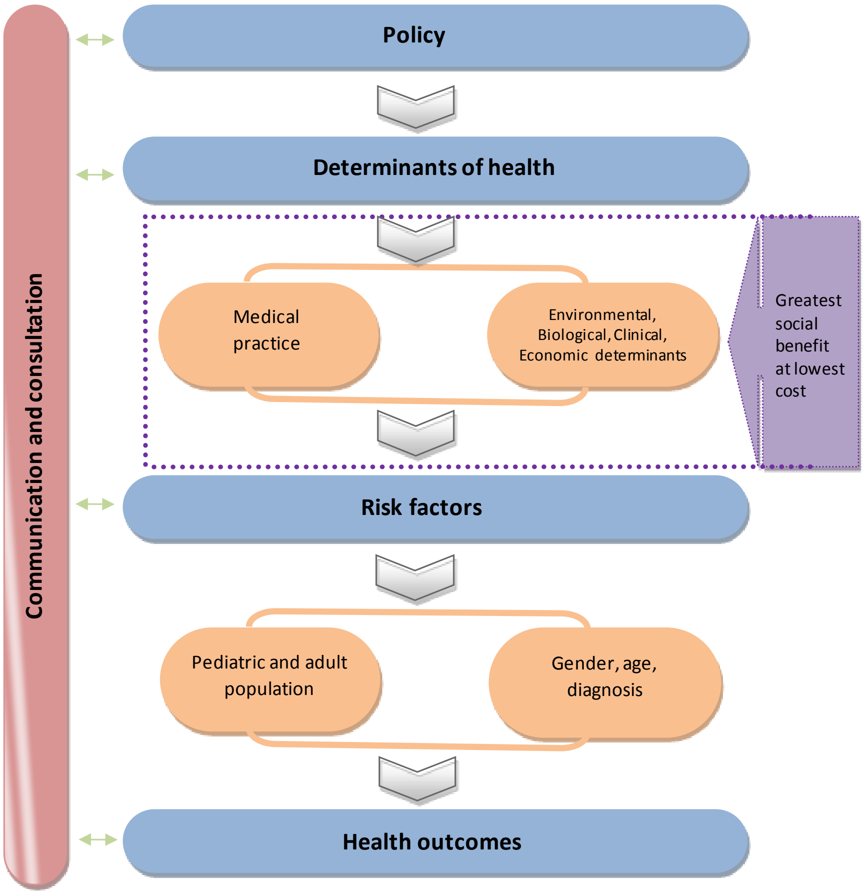

Figure 2. Top-down risk assessment model fed with current knowledge.

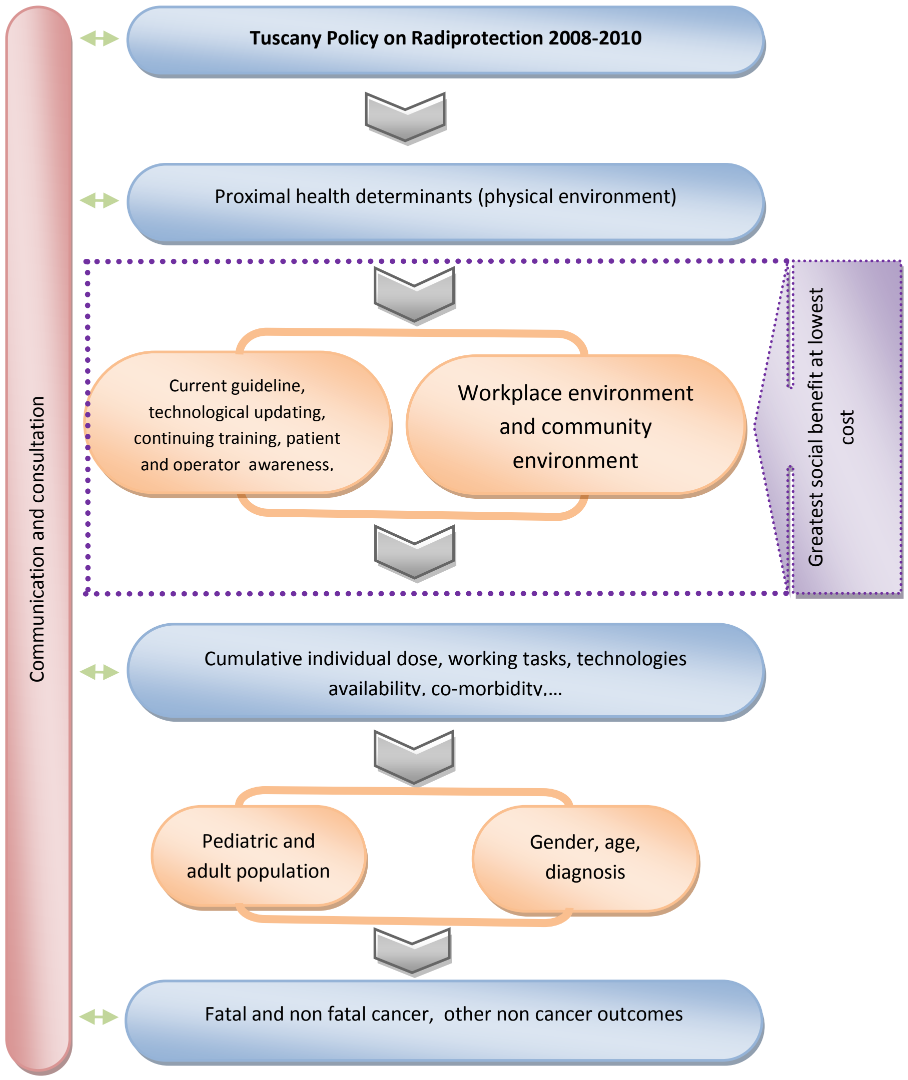

Figure 3. Decision-making in Clinical Practice

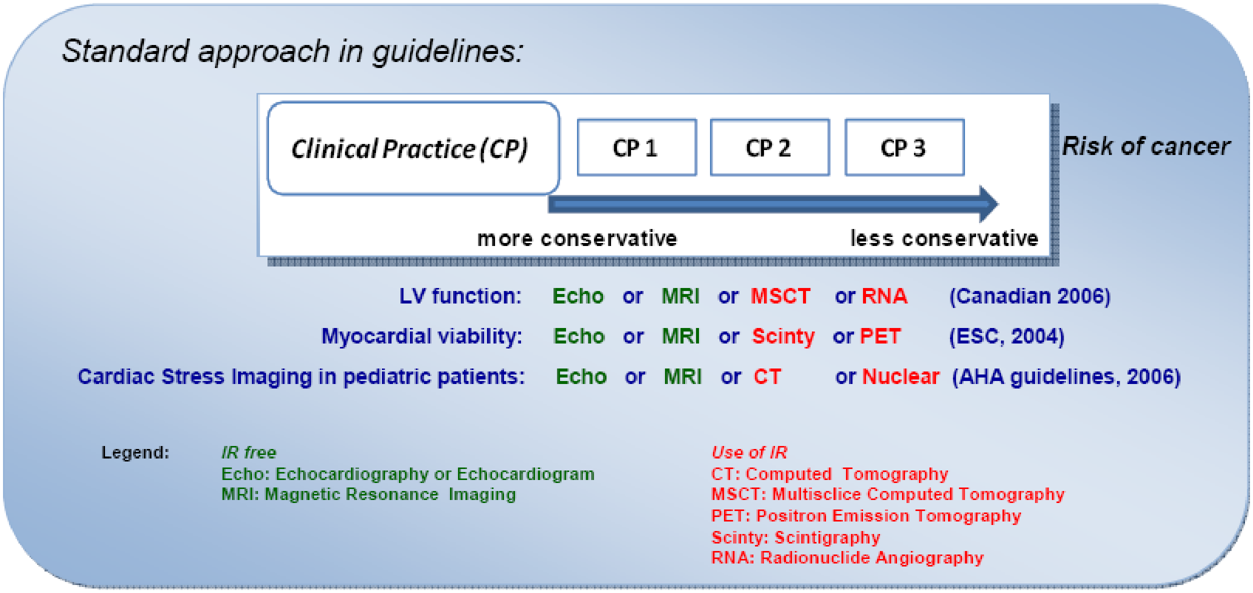

Figure 4. The RAPID framework applied to regional radioprotection policy and health.