Chapter 1

Essentials in Accident and Emergency Medicine Radiation Injury: Response and Treatment

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http://dx.doi.org/10.5772/intechopen.76863

Abstract

The discovery of radiation has enabled great healthcare advances as well as catastrophic injury. This paper reviews major historical incidents of public radiation exposure and the evolution of standards affecting today's public and health care workers. Current patient care and response assessment to radiation exposure are reviewed. The strengths of modern radiation therapy and the need for continuous process improvements to ensure optimal patient care and secure safe environments are identified. The discovery of radiation has brought significant scientific achievements as well as catastrophic injury.

Keywords: radiation, exposure, injury, therapy, safety

1. Introduction

Despite safety precautions and application of modern standards of radiation protection, injury from radiation can be generated from both intentional and unintentional situations

and events. Injury can be catastrophic, immediately life-threatening, and survivors of exposure remain with a lifetime risk of secondary events including chronic health changes and malignancies. Even with the development of radiation protection standards and oversite organizations, accidents and misadministration of radiation deviant from intent continue to haunt daily application of radiation therapy. There is no antidote to radiation exposure and the fingerprints of injury remain for a lifetime. In this chapter we will review major incidents of public radiation exposure and accidents in history including cause and effect. We will review the application and evolution of standards and how this affects both the public and healthcare worker in modern care. We will review modern patient care and response assessment to radiation exposure including agents that may protect or mitigate radiation damage from radiation exposure. We will identify strengths of modern radiation therapy and the need for continuous process improvements to ensure optimal application of X-ray in a safe environment.

2. History

X-rays were discovered in 1895 by William Roentgen. In part due to the century old use of electricity in medicine, X-rays were rapidly assimilated into the medical armamentarium portfolio as beneficial applications of X-ray treatment were identified by early radiologists. Due to protracted exposure times and minimal knowledge of risk, early practitioners of the application of X-rays to treatment situations became victims themselves. Friedrich Otto Walkoff took the first dental radiograph in 1895 by placing a photographic plate between his teeth and tongue. He was able to generate an image with a 30-minute exposure time. He applied similar techniques to patients and reported epilation and skin blistering. Walkoff developed the first dental imaging laboratory in 1896 with Fritz Geisel. Geisel died in 1927 of metastatic carcinoma caused by heavy exposure of radiation to his hands. In 1896, a child was accidently shot in the head and was brought to a laboratory at Vanderbilt University (Nashville, TN). Investigators sought the location of the bullet by X-ray and a plate holder was tied to the head of the patient. The X-ray tube was placed at the patient's head. The exposure was 1 hour. About 21 days after exposure there was epilation at the site of X-ray application. In 1896, HD Hawkes gave a demonstration of an X-ray unit in New York City. He had to discontinue work after 4 days due to injury to the skin of his hand and chest. Within 2 weeks he had significant skin injuries, his fingernails deteriorated, and he exhibited systemic signs of radiation injury. In the same year, William Levy sought out to localize a bullet that had been lodged in his skull for 10 years. He was warned about the potential of injury; however, chose to move forward. Images were created over a 14-hour period from three static positions at his forehead, his open mouth, and behind his right ear. Within 24 hours, the dermal surfaces of his head were blistered and within days his mouth and lips had sores and epilation occurred within 3 weeks. The bullet was found within an inch of the occipital protuberance. In this circumstance, the absorbed dose by the victim was at least 15 Gray (Gy). Clarence Dally worked at the Edison laboratory and had the role of being a glassblower for Thomas Edison. He is thought to be the first individual to die from chronic radiation workplace exposure in 1904 from metastatic carcinoma at the age of 39. It is thought that his exposure was at least 30 Gy. Numerous deaths were reported in X-ray manufacturers and workers with noted deaths of Nobel Laureates Marie Curie and her daughter

Joliot Curie from radiation-associated diseases during the discovery of radium in 1898 and the near immediate application of radium to treat cancer.

While the benefits of the application of radium and X-rays were moving forward, the risk of injury was continually recognized at an international level. At the second international congress of radiology in 1928 held in Stockholm, Sweden, participating countries developed standards for radiation protection. These were centered on recommendations from the United Kingdom as guidelines for radiation protection had been employed for the previous decade. The congress established the International X-Ray and Radium Protection Committee which was remodeled after World War II (WWII) into two commissions that are active today. These are the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU). In the United States today, the Environmental Protection Agency (EPA) is charged with the responsibility for providing guidance to federal agencies. The Nuclear Regulatory Commission (NRC) formulates rules for application of product materials and the Department of Energy is responsible for radiation safety regulations through the NRC. Multiple international agencies participate in radiation safety activities and help shape policy including health applications and strategy for nuclear energy [1–4].

3. Intentional injury

As the benefits and power of X-rays and radium matured, the use of nuclear tools for weapons of mass destruction came to power. During WWII, efforts for harnessing nuclear power for destruction reached application on August 6, 1945 with the use of a 9000-pound uranium-235 bomb known a "Little Boy" over the manufacturing city of Hiroshima, Japan. The bomb was dropped with a parachute and detonated 2000 feet above the city with blast equal to 15 kilotons About 2–3 days later, a plutonium-239 bomb known as "Fat Man" was dropped over the city of Nagasaki. The primary target was Kokura; however, clouds shrouded the primary target area. The plutonium bomb was more powerful than the bomb used on Hiroshima. The bomb weighed 10,000 pounds and produced a 22-kilotons blast. The topography of Nagasaki limited the radius of impact as the city is in a narrow valley between mountains. Initial destruction and death was due to heat and fire as well as associated trauma related to building damage and other structural/public health-related matters; however, those not at the epicenter of the blast were exposed to radiation as a function of distance from the epicenter. Early impact resulted in microcephaly and mental retardation in the most vulnerable unborn and young population with lifelong health risks including chronic health issues in multiple organ systems and cancer risks affecting all survivors. We have earned much about studying the population of survivors and have been able to apply this knowledge to risk assessment for the general population, healthcare workers, and pregnant/potentially pregnant patients [5–7].

4. Unintentional injury: nuclear power

After WWII, there was a significant interest in accelerating the production of nuclear weapons as well as promoting the use of nuclear energy in lieu of fossil fuels and other sources

of non-renewable energy reserves. While we knew individual risk of the indiscriminate use of radiation, despite the application of nuclear weapons, little was known about the impact of risk upon the general population about accidents in the application of nuclear power and the secondary development of nuclear weapons.

The International Atomic Energy Agency (IAEA) maintains as website reporting nuclear accidents. As of 2014, there have been more than 100 serious accidents associated with the use of nuclear power. It is worrisome that more than 50% of the accidents have occurred since the accident at Chernobyl (1986) and that more than 60% of the accidents reported have occurred in the United States. These accidents have occurred over time due to many circumstances including poor design of the reactor and human judgment error in the attempt to prevent and mitigate the problem. Many of the most serious events will be described as follows [5–7].

4.1. Louis Slotin

In 1946, Canadian investigators evaluating nuclear weapons brought two hemispheres of neutron-reflective beryllium around a plutonium core. The hemispheres were only separated by a screwdriver which was against policy. The screwdriver slipped which set off a chain reaction filling the room with radiation validated by the presence of blue light. Louis Slotin (physicist) rapidly separated the hemispheres preventing further exposure to co-workers; however, he died of radiation exposure 9 days later [5].

4.2. Kyshtym

This event was a radioactive decontamination accident in 1957. The accident occurred at Mayak which was a plutonium production site in the eastern Ural Mountains in the Soviet Union. The actual site was not marked on topographical maps, therefore the accident is named after a nearby town.

Because the Soviet Union was behind the US in the development of uranium and plutonium nuclear weapons, the facility was constructed over a short period of time between 1945 and 1948. Initially, high levels of radioactive material were dumped into a nearby river which flowed into the Arctic Sea. The reactors (six) were located on a lake which was used for the cooling cycle. The primary lake was Lake Kyzyltash which became quickly contaminated and a secondary lake, Lake Karachay, also quickly became contaminated. A storage facility for liquid waste was built in 1953. It was a simple design with steel tanks mounted in concrete base 27 feet underground. Because the nuclear waste generated heat, a cooling system was built around each tank. Facilities for monitoring the operation were primitive.

On the day of the event, the cooling system failed in one of the tanks containing 80 tons of liquid radioactive waste. The liquid evaporated, and an explosion ensued estimated at 1 kiloton. A 160-ton concrete lid was thrown into the air and an estimated 20 Millicuries (mCi) of radioactivity was released. Although most of the contamination was near the explosion, there was a plume of radionucleotides that spread over hundreds of miles through the air. The long-term contamination area is estimated to be more than 7000 square miles including cesium 137 and strontium 90. It is estimated that 22 villages were affected, and more than 10,000 people were evacuated from the site over a 2-year period. Due to secrecy surrounding the incident

and limitations in obtaining documentation, estimates of health damage, cancer, and current conditions can only be estimated. It is known that the East Ural region remains contaminated to this day and there were scores of documented cases of chronic radiation syndrome with an elevated cancer rate including a high rate of death due to malignancy.

In this situation, limited knowledge of reactor safety coupled with poor risk assessment resulted in an accident of significant magnitude, third only to the accidents at Fukashima and Chernobyl [5, 6, 8].

4.3. Windscale

In a similar manner, the British government initiated a nuclear weapons program after WWII using a plutonium-based platform. British physicists were involved in the Manhattan project and two reactors were built near the village of Seascale, UK, a few hundred feet apart from each other. The core of the reactors consisted of a large block of graphite with channels built for transport of uranium cartridges which would be pushed posteriorly into the back channel for cooling in a water filled channel. This was different from previous designs which had a constant supply of water that poured through the channels housed in the graphite. The first design was chosen because of fear of malfunction of the need for the constant water source. Filters were placed in situ in case one of the cartridges broke entering the water. Without water in the channels, cartridges did break and despite filters, radioactivity was documented around the site but not indicated to staff. One of the reactors was prone to heating and this was believed to be related to the graphite. It was known that neutrons created small fractures in the graphite which in turn could be annealed with increasing the heat of the system. This was known as the Wigner effect, named after physicist Eugene Wigner.

There was considerable political pressure for quickly producing a weapon and the decision was made to generate Tritium which required augmented heating in the reactor. To produce Tritium, the cooling fins on the plutonium cannisters decreased in size to increase heat exchange. Windscale was modified by adding enriched uranium and lithium-magnesium to the fuel rods making the situation more vulnerable to combustion.

On October 7, 1957, one of the reactors was heating more than norm and an additional Wigner annealing release was performed. This had the anticipated result except for one channel. A second Wigner release was performed which appeared to stabilize the situation. On October 10, 1957, a radiation detector in the chimney indicated a release of radiation. It was assumed that a rod had fractured. What was not recognized was the presence of a fire in the same channel likely started on October 7. To provide cooling, fans were augmented which unintentionally made the situation worse. Carbon dioxide and water did not extinguish the fire. It was estimated that 11 tons of uranium was ablaze. Leaders ordered evacuation and shut off all ventilation entering the reactor. This was successful and water flowing through the reactor was cold within 24 hours.

Radioactive material including Iodine 131 (740 Terabecquerel (TBq)), Cesium 137 (22 TBq), and Xenon 133 (12,000 TBq) was released. The presence of scrubbers and filters in the chimney proved to be important and likely limited damage. Both reactors were deemed unsafe for continued use and fuel was removed in 2012 [5, 6].

4.4. Stationary low-power reactor number 1 (SL-1)

SL-1 was a US Army nuclear power reactor located at the national reactor testing station 40 miles west of Idaho Falls, Idaho. The reactor became operational in 1958. The reactor used enriched uranium fuel and was cooled by water flowing through plates of uranium/aluminum alloy. The design relied on a primary central fuel rod. The reactor was closed for maintenance on January 3, 1961 and was being prepared to restart after the 11-day shutdown. Procedures that required the central rod be withdrawn to connect to the central drive mechanism. The rod was withdrawn too far, and the reactor instantly became critical. Within 4 milliseconds, the heat generated by the power excursion caused water to vaporize and explode. Radioactive water became a pressure wave striking the ceiling and a loose metal pin impaled one of the workers to the ceiling structure. It was determined on review that the 26,000-pound internal vessel had moved more than 9 feet in the superior direction and the control rod mechanisms struck the ceiling. There were three workers on site who each died quickly of their injuries. Their radiation exposure would also have been lethal, if they survived physical trauma. Review of the incident suggested that the central rod may have become fixed in position and one of the workers was able to free it; however, in the process the rod moved too far which generated the reaction.

Even without a containment structure, the reactor contained most of the radioactivity. In late 1961, the cleanup process began and all core and building materials were buried approximately 1600 feet from the site of the reactor. One of the conclusions was that design focus on a single central structure created untoward risk that could not be easily mitigated. First responders may have received significant compounded radiation dose due to increased radiation dose in the environment and during removal of the waste and remains of those who died. Those involved in the response were awarded certificates for heroism [5, 6].

4.5. Three Mile Island, Pennsylvania

During the evening of March 27, 1979, one reactor at Three Mile Island nuclear station was running at near full capacity, while a second reactor was shut down for re-fueling. The root cause of the accident occurred 11 hours prior to the declaration of the emergency, when the cooling system filters were cleaned with air compression and cooling water. A valve that was thought to be shut was open and water entered an instrument airline which caused a turbine trip. Three auxiliary pumps should have been activated when heat and pressure increased due to lack of cooling; however, these pumps were closed due to re-fueling. This was not NRC policy. A third valve opened to relive pressure; however, did not close when pressure was released, therefore coolant escaped and became root cause in core disintegration. Human factors delayed recognition of the problem as a light indicated that the open valve was closed and secondary safety procedures were not followed. Even though there was persistent loss of coolant, water levels increased through the open valve creating bubbles of steam in the liquid. At 4:15 am on March 28, 1979, the pressurizer in the relief tank ruptured and radioactive coolant leaked into the containment structure. In a series of activated pumping mechanisms, the coolant was then pumped beyond the containment area. At 6 am on March 28, 1979, the temperature in a pilot valve was noted to be excessive by an employee beginning his work shift and a back valve was used to stop the flow of coolant. However, by that time 32,000 gallons of coolant had leaked,

and radiation levels were 300 times expected. The containment building was significantly damaged; however, the radioactive material remained in situ as it did not extend beyond the reactor vessel despite that approximately half of the core uranium melted during the incident.

The incident became an example of managing authority and responsibility in the nuclear industry. Lines of authority between private plant ownership, state authorities, and the NRC were not clear and accordingly in the early phase of the accident, it was difficult to obtain accurate information for risk assessment. This resulted in delayed evacuation. Clean up was not completed for more than a decade and long-term risks remain not well defined. Most of radioactive gas release was xenon, which was not considered significant; however, radioactive iodine was also released and the impact of increase in thyroid cancers remains uncertain [5, 6].

4.6. Chernobyl

The Chernobyl accident is one of the two most significant nuclear events in the history of unintentional radiation injury. The incident occurred on April 26, 1986. The irony of the event is that it occurred during a safety procedure evaluation and safety systems were intentionally disabled as part of the intended procedure. The reactor was brought to minimal activity with the expectation that cooling systems would manage the heat generated by thermal decay. The systems onsite unfortunately required more than 1 minute to activate and running the reactor at minimal power (below safety standard) resulted in the crisis. A series of events triggered by flaws in reactor design and poor decisions made by onsite personnel created situation where reactor cooling was inefficient and two steam explosions generated from thermal decay exposed the graphite core to air, which fueled the massive explosion. Exposure to oxygen fueled the explosion. The fires were extraordinary and sent radioactive elements and gas into the air for a week. Plumes of radioactive gas extended well into Western Europe for an extended period of time. Casualties were significant including first responders attempting to put out the fires as those involved were exposed to lethal levels of radiation. Scores of people were affected by radiation syndrome and estimates include thousands who will develop secondary cancers due to exposure. Cleanup continued for decades. It is estimated that more than 350,000 people relocated as part of a series of evacuations. Unfortunately, many evacuated during the initial phase of the accident were exposed to medically significant radiation as the exit road was directly under the parallax of the radioactive plume from the reactor fires. Reactor fires were eventually attenuated by helicopter droppings of cement, clay, sand, and boron to absorb neutron activity. The government decided to place a cover over the remains of the reactor and today this is referred to as a sarcophagus. Full understanding of risk and damage remains elusive due to limited access to information and lack of full disclosure for years by government sources [5, 6].

4.7. Fukashima

The nuclear power plant at Fukashima sustained damage from a massive Tsunami 50 minutes after the Tohoku earthquake in 2014. At the time of the earthquake, a mandatory shutdown of the reactor took place; however, decay heat, despite the elimination of the fission component of the reactor energy generation, needed to be managed and cooled with backup generators

and power. The secondary backup cooling systems were damaged in three of the reactors and consequently, heat generated explosions contaminated the environment with radioactive particles and gas. Unlike Chernobyl, three had no direct deaths associated with the explosions and radiation exposure; however, issues with the cleanup continue until today. In the construction of Fukashima, more advanced backup systems existed in modern construction sites and these withstood the injury. The affected reactor had an older cooling design. Deaths occurred as part of the evacuation process, due in part to damage to facilities and inability to move rescue supplies into the region. This also compromised restoring the cooling mechanisms to the backup systems as batteries and generators that may have been helpful could not be transported to the site. The damage to the environment continues to today. Fukashima and Chernobyl are considered as two most powerful nuclear accidents in our history [5, 6].

4.8. Aftermath

The experiences listed depict the extraordinary damage created by nuclear accidents to people and the environment. Reactor design, poor secondary cooling backup systems for failure, poor response by onsite providers with decisions made in panic, and natural disasters with poor preparation have created an uncertain future for the safety and durability of nuclear power. Injuries for onsite providers are related to explosions, thermal and high dose radiation. The incidents can occur in fractions of seconds and the injuries and environmental impact can last generations. It is sobering to see the radiation injuries sustained by first responders and those who attempted to mitigate the disasters. Information for these people arriving onsite for disaster management was not clear and in retrospect was inaccurate. Their brave and self-sacrificing response could not overcome the power and danger imposed by the situation. The impact on the nearby population and environment will not be resolved for decades and the disaster at early accidents continues to haunt the environment. The impact on the lives of the victims has no clear limit or statute of limitations. We need improved safety, infallible design, and protective strategies moving forward. In the upcoming sections, we will describe what information is currently available for those involved in the triage of radiation injury for both acute and long-term injuries [5–11].

5. Unintentional injury: nuclear submarines

With the interest in nuclear power, efforts were developed to use nuclear power for transportation. Submarine technology for nuclear power was developed as it limited the need to refuel and missions could be extended for a significant period. However, as such issues and safety within the nuclear power community, safeguards, and measures of protection could not be provided with security. In the Soviet submarine fleet, many accidents occurred which limited the safety and security of the power source. In 1961, similar to a nuclear power plant, the cooling system failed on the K-19 Soviet nuclear submarine and the temperature rapidly rose as a result of decay heat. The captain ordered a secondary cooling built and sailors/engineers in the process of building a cooling system were exposed to lethal doses (LDs) of radiation in the process of building the system. More than 20 died of radiation injury. In 1968, nine sailors died during an explosion that released radioactive gas. In 1985, 10 died in an explosion caused by malfunction of a lid designed to keep fuel rods in position and 49 people were exposed to

significant radiation, many of whom were first responders to the explosion and subsequent fire. These events demonstrated that safety precautions including well understood policy and procedure were and remain essential to mission if nuclear energy sources were being used [5].

5.1. Unintended injury from the application of radiation therapy and use of diagnostic X-ray equipment

In this section, we will describe a series of events that imposed injury to people and the environment from applications of therapeutic radiology and unintended overuse of imaging equipment. These events have significant consequence to unintended victims of equipment, safety measures, and human error.

5.2. Radiation accident in Morocco

In 1984, an Irridium-192 radioactive source became dislodged from the safety container. A worker unintentionally took the source back to his residence which exposed himself, his family, and visitors to high doses of radiation with three people sent to the Curie institute for treatment. It is believed that eight deaths were caused by the accident and there is a report that some deaths were due to pulmonary hemorrhage. Similar injuries have been reported in patients with myeloma undergoing total body radiation therapy as part of preparation for bone marrow transplant noted at doses of less than 10 Gy [5, 11].

5.3. Goiania, Brazil

In 1985, a Cesium-137 source was inadvertently left behind when a private radiation oncology clinic moved to a new facility. The source was found 2 years later by two people who brought the source and source carriage home and eventually ruptured the capsule of the source. During this time, hundreds of people were exposed and at least four died of radiation-related injuries. Cleanup processes took 6 months and at least 300 people were identified as having exposure to Cesium [5].

5.4. Zaragoza, Spain

On December 7, 1990, maintenance was performed on a linear accelerator at the radiation therapy clinic at Zaragoza, Spain and it returned to patient care service on December 10. What was not known was the accelerator (14 years in service) was incorrectly repaired and there was a breakdown in the internal control mechanism, therefore not detecting that patients were receiving much higher doses than specified with a higher beam energy. Initially, after 10 days of treatment, patients were identified as having accelerated dermal injuries. The first death associated with radiation injury was in February 1991. In total, 25 patients died in the first year after the event and 11 were attributed to injuries imposed by the incident [5].

5.5. San Salvador, El Salvador

In 1989, an accident occurred in a facility using a Co-60 source to sterilize medical products. The device became frozen in the on position. The worker by-passed safety measures and

entered the room with two other workers to try and free the equipment. The exposure was so high that one worker died within 6 months of exposure and the two other workers sustained injuries requiring amputation [6, 7, 9].

6. Modern accelerator safety issues

The modern linear accelerator has a vast array of safety features including computer override systems which prevent improper application of therapy and internal monitoring diodes which monitor dose application. Safe operation of linear accelerators is a challenging task and users of modern equipment have to assume greater responsibilities for safe execution of patient care. Complex treatment plans and delivery system require thorough hands on understanding of machine operations and safety systems. Continuous process monitoring ensuring safe delivery of care is essential to mission to prevent abhorrent behavior of equipment. This includes well trained staff who can detect potential issues and report concerns to appropriate individuals for next step action to mitigate potential problems. Nevertheless, significant errors have occurred which continue to haunt patient care delivery. Advancement in therapy application often require tools that are developed by different companies and the tools must be harmonized through hardware and software adjustments to provide appropriate patient care. This has led to serious and life-threatening injuries when not applied appropriately. The most common errors in computer override situations are software flaws that indicate that a situation is safe when it is unsafe. Examples of software flaws include unintentionally reporting that multileaf jaws are moving appropriately during treatment when they are not and assuring the individual delivering therapy that system delivery is compliant to plan and calculation when the situation may be less secure. Treatments now require thousands of dynamic motions of individual leaves hidden in the gantry of the machine. Linear accelerators and radiation therapy treatment planning have become exceptionally complex. Treatment delivery capability has become exceptionally precise in its capability to deliver very high doses of treatment to small areas with submillimeter precision. The power of the new equipment is extraordinary; however, the power is often used as a marketing tool and does not recognize that new systems including training of personnel have not been appropriately vetted. This represents both the strength and weakness of modern care. The instrument is powerful; however, if not applied appropriately can cause significant harm. If not calibrated and executed properly, life-threatening injuries occur. In recent reporting through the New York Times, Walter Bogdanich accurately reported on misadministration of radiation therapy to multiple patients in several separate situations causing severe injury and death including injuries to tissues that could not be repaired. These are the innocent victims of our technology and their injuries are a sobering reminder that we must maintain a culture of safety [12].

Although software matters can be addressed, we must improve on right patient and right treatment. Human error remains too frequent in treatment delivery. Technology cannot resolve all causes of error and department processes including double identification and time out must be documented and validated to ensure patient safety. More sophisticated digital identification processes may be implemented into clinical operation including iris and fingerprint strategies

for identification, similar to modern computer identification technologies. Written policies and validation that processes have been followed are crucial to successful clinical operation. Recent review of adverse events of radiation oncology devices from 1991 to 2015 revealed that adverse events increased over time and peaked in 2011. During this period of time, there was significant change in practice strategies including enterprise application of intensity modulation and the application of image guidance into daily therapy. About 50.8% of adverse events involved external therapy, 24.9% of events involved brachytherapy, 20.9% were mechanical, and 20.4% involved user error. While a department will perform 100 times more teletherapy treatments than brachytherapy applications, it was interesting to note that brachytherapy adverse events were only half of those reported for teletherapy, therefore potentially more prone to misadministration. Brachytherapy is done less often, and accordingly departmental processes may not be repeated frequently enough for flawless reproducibility and execution of care. Our department is responsible for more than 50,000 external treatments every year and each individual treatment and brachytherapy application must be correct. Injuries can be imposed by diagnostic X-ray equipment especially in situations requiring interventional radiology and the use of fluoroscopy. The radiation dose cannot be extracted once delivered and the injuries imposed often have no cure [6, 7, 9, 13, 14].

7. Impact of radiation therapy on normal tissues

7.1. Accidents and weapons: unintended exposure

In these circumstances, injuries imposed are related to strength of the radiation source and distance to the source of radiation. Thermal and mechanical injuries are immediately life-threatening. Within 15 minutes of exposure, victims exposed to high dose radiation can experience symptoms associated with the event. These symptoms are manifest with high exposure by neuromuscular changes and gastrointestinal effects. At very low-level exposure, the victim may appear well; however, gastrointestinal and bone marrow symptoms may become more visible in the upcoming month post exposure. Intermediate dose exposure results in upper abdominal symptoms and lassitude seen within hours of the exposure. High dose exposure results in more extreme symptoms including rapid fluid loss and hypotension associated with more pronounced neuromuscular symptoms. Often normal tissue sequelae associated with exposure can be divided into acute injury, sub-acute injury, and chronic injury. Unintentional exposure requires evaluation by a trained group of experts who can assess both injury to the victim and risk to others with continued exposure of radioactive sources either on or inhaled/ingested by the victim. The initial screening of victims requires evaluation by trained radiation safety officers and members of emergency services who can begin to apply best supportive care. In the initial phase of the evaluation, it is important to ascertain as accurate assessment of dose exposure as possible. Lymphocyte counts due to intermitotic death and chromosomal damage assessment can be qualitative surrogates for exposure in the early phase of response assessment. Healthcare workers will likely be monitored for exposure; however, the general public will not be monitored, therefore involving experts in radiation exposure early in response assessment is essential to mission in order to appropriately define the extent of the damage and risk of injury [7, 9, 15].

Acute injury occurs within 90 days of exposure, sub-acute injury occurs from 90 days to 2 years after exposure, and chronic injury occurs 2 years after exposure. All organ systems are affected by radiation exposure. At very high exposures of 10 Gy, death will occur within 24–48 hours due to unrelenting swelling within the central nervous system which compromises all neural processes. At exposure of 5–10 Gy, death will occur within 1–2 weeks due to de-population of gastrointestinal stem cells and bone marrow progenitors. Profound and uncontrollable fluid losses compounded by infection are the cause of death. Victims have survived exposures to this level if they can afford maximal supportive care with fluid replacement and bone marrow support. The term LD 50/30 is a term initially used in pharmacology to determine lethal dose (LD) in 50% of the population within 30 days. Historically, the LD 50/30 for radiation exposure was believed to be 2 Gy; however, with modern support services it is believed that this can be increased to 5 Gy.

If the exposure is determined to be at or below 5 Gy, most experts recommend no immediate intervention other than best supportive care and symptom management. The victim will need to be carefully monitored for manifestations of acute and sub-acute injury as well as chronic events that can appear at any point in later life including the development of malignancy. If the exposure is determined to be greater than 5 Gy, then death by hematopoietic syndrome including loss of bone marrow progenitors becomes a visible concern. Intervention with barrier nursing and appropriate blood product support is needed to move the victim through this phase into recovery. Recent nuclear accidents have suggested that infection control and vigorous supportive care may help victims survive an exposure dose of up to 7 Gy. The role of bone marrow transplantation in this effort remains to be established. It is likely of benefit in selected patients [15–17].

7.2. Response applications

Since the development of nuclear weapons and need for response metrics to injury, there is been a scientific interest in identifying compounds that can protect normal tissue from the effects of radiation exposure. Protectors are given either prior to or immediately thereafter exposure. Mitigators are compounds given after exposure to influence and diminish the impact of the exposure to normal tissue. Therapeutic compounds are applied when the event has occurred. After WWII, it has been known that sulfhydryl groups can function as radiation protectors with the simplest compound being cysteine which contains a natural amino acid. Sulfhydryl groups are toxic which can be decreased by the addition of a phosphate group. Once the compound enters the cell, the phosphate group is released, and the sulfhydryl group becomes a free radical scavenger. Sulfhydryl groups have been shown to protect mice from lethal doses of total body radiation. The only compound approved by the US Food and Drug Administration is amifostine (WR-2721). It is sold as ethyol and has been used to prevent xerostomia in patients treated with radiation therapy for head and neck malignancies. In clinical trials, the use of the compound has been shown to improve quality of life scores for patients undergoing radiation therapy. It has also been used to protect other mucosal surfaces (rectum) and pulmonary parenchyma in patients undergoing total body radiation therapy in preparation for bone marrow transplant. To date, there has been no defined tumor protective effect

assigned to amifostine. There are complexities to outpatient clinical application which can be manifested as hypotension and nausea, therefore patients need to be carefully monitored both before and after administration. It is unusual in clinical practice for patients to receive every assigned dose each day. The success is well documented; however, with improvements in radiation dose delivery across salivary tissue, amifostine is not as commonly used in clinical practice as it was a decade earlier. Citron and colleagues have identified nitroxides as agents for protection. These function as well through a free radical scavenger mechanism. Superoxide dismutase (SOD) compounds with gene therapy applications have also been explored. The gene therapy vector has been used in animal models to enhance intracellular accumulation of SOD with SOD functioning as a free radical scavenger [18–21].

Mitigators are compounds that potentially limit damage of radiation exposure once the event has occurred without clinical manifestation of injury. These compounds influence the metabolic cascade of events that occur post exposure. These compounds include those that can stimulate bone marrow and dermal progenitors. These include granulocyte stimulating growth factor (G-CSF) and keratinocyte growth factor (KGF). KGF also appears to influence the recovery of mucosal surfaces as well as improve dermal integrity. Mitigators of late toxicity center around limiting fibrosis and the primary target is transforming growth factor beta (TGF beta) and interruption of the signaling pathway that promotes expression. Investigators at the University of Massachusetts have evaluated the use of interleukin 1 alpha to limit neutrophil infiltration into the site of radiation injury to limit the extent of injury in damaged dermal tissue. Knockout mice deficient in IL-1 alpha demonstrated both decreased dermal injury to radiation and more rapid time to repair injury. In another series of experiments, investigators at the University of Massachusetts studied optical imaging as a tool to evaluate radiation injury and determine if changes in metrics associated with oxygenation and deoxygenation can be related to dose. Optical imaging demonstrated that changes in dermal tissue associated with radiation within 12 hours of exposure and imaging defined consistent metrics for acute and chronic injury. In a separate patient breast cancer treatment protocol optical imaging successfully defined radiation dose and dose asymmetry (hot spots) in patients undergoing serial imaging during breast cancer radiation therapy. Chronic changes were likewise well defined on images obtained post treatment [18, 22, 23].

With increased risk of nuclear weapons and exposure to radiation through accident and future air/space travel, it is of increasing importance that emergency services become more familiar with the management of radiation exposure and injury. Radiation experts and safety officers likewise need to be aware and available to support colleagues in emergency services to optimize care for those affected by unintended exposure in time of crisis. There have been numerous incidents of unintended radiation exposure with victims exposed to both partial and total body X-ray. The Medical Science Division of the Oak Ridge Institute for Science and Education operates a Radiation Emergency Assistance Center for the US Department of Energy. The center is a 24-hour consultation service with both medical and health physics support for issues associated with radiation and X-ray exposure. The resources are comprehensive and include expertise for dose assessment, computation of dose from radionucleotides, and laboratory support. The 24-hour emergency telephone is 865 576 3131 and the website is http://www.orau.gov/reacts [9, 13–16, 24, 25].

7.3. Injury with diagnostic and therapeutic X-rays

There is an increasing number of cancer survivors. It is estimated that in each primary care practice by 2025 that 20% of the panel of patients in every primary care practice will be a cancer survivor. This creates a challenge for both the primary care and oncology community as management of the normal tissue imprint of therapy on the survivor does not have clear definition as providers differ in their perceived responsibilities and expertise. Historically, the focus of cancer management was driven to tumor control as a sole endpoint. Today, success brings new challenges. With survivorship improving, more patients now live in symbiosis with the known and unknown sequelae of management. Accordingly, cancer survivorship is beginning to mature as a sub-specialty service defined in oncology and executed through primary care. Gaps in both anticipation of injury and responsibility of management often are initially recognized in crisis by emergency services and often are not easily recognized as sequela of management. Unfortunately, electronic medical records are often insufficient in providing necessary information to facilitate problem solving and management. Most radiation therapy equipment and radiation therapy planning volumetric archives reside in proprietary software systems that are used to operate and validate daily treatment operations. Commercial electronic record systems do not have access to this information as the information in radiation oncology resides in proprietary systems. Although interfaces can be built to facilitate note transfer and medical billing documentation, in evaluation of a patient, the volumetric imaging, and radiation dose information is an essential aspect of problem solving in the emergency environment. For example, in the cancer survivor being evaluated for new onset chest pain, it is essential that dose/volume relationships to cardiac subsegments be available for review for analysis of risk assessment. The evolving field of oncocardiology requires an accurate record of radiation dose volume analysis to specific subsegments including pericardium, vessels, myocardium, cardiac valves, and the electrical conducting system. Each area can be affected by specific dose volume review and this information becomes essential for evaluation of the modern patient. Radiation is not a drug and has specific residual fingerprints on the area treated. Modern management of the cancer survivor requires comprehensive understanding of the impact of treatment on normal tissue by those who evaluate the patient after treatment is completed. The imposition of therapy on normal tissue lasts for the lifetime of the patient, therefore information on treatment needs to be available and in an easily retrievable format for all providers. In the next section, we will evaluate injury to tissue that is both acute and chronic. Acute effects of radiation exposure affect cells of rapid self-renewal potential such as skin, bone marrow, and gastrointestinal progenitors. Every organ system can manifest a late effect from radiation exposure [9, 13, 14, 24–26].

7.4. Skin

Skin is the visible site of acute reactions to X-ray and harbors chronic changes from therapy. Dermal stem cells reside at the basement membrane of the epidermis and the self-renewal process for the epidermis is 3 weeks in tissues that are uninjured. Prior to the use of linear accelerators for patient care, diagnostic X-ray equipment was used to treat patients for malignancies. This resulted in a much higher dose to superficial tissues including skin. Both acute and late effects of radiation therapy are influenced by daily dose and fractionation. In this circumstance, the skin would receive significantly high dose to skin surfaces relative to target. This has importance because fluoroscopy used in interventional radiology and cardiology can deliver

exceptionally high doses to skin surfaces, especially in procedures that are highly complicated. Patients would unintentionally receive higher daily dose and accordingly, dermal sequela of management was and still can be highly visible and a significant problem. Modern linear accelerator equipment delivers dose below the skin surface, therefore skin sequelae with traditional treatment fractionation models are less visible in the modern world. However, from an emergency services perspective, radiation beams resonate on dermal surfaces in skin folds and intertriginous regions. These include skin folds in the breast and regional lymph node regions and inguinal/gluteal regions of patients treated for pelvic and anal malignancies. Dose to these areas is higher daily, therefore may have desquamation, both moist and dry, as a consequence of management. Uninformed providers refer to this issue as a "burn". This is inaccurate. Daily treatment limits the self-renewal capacity of stem cells and injury to the basement membrane exposes the dermis to air with resultant moist changes. Although this can be a future site of infection, conservative treatment measures uniformly outpace any barrier application applied in thermal injury, therefore symptom management is often the best approach in this situation. With interest in compressed fractionation schedules for selected patients, the degree of injury during the acute management phase may be more pronounced, therefore from an emergency services perspective, it is important to ask what for the daily dose, not just whether the patient has been treated. The skin is often hyperpigmented during this phase of treatment. Chronic changes appear as hypopigmentation and thinning of dermal tissue associated with fragments of visible surface blood vessels known as telangiectasia. In the chronic phase, the skin is functional; however, if injured, repair may be more protracted. Modern intensity modulation techniques can limit both the extent and volume of radiation dose asymmetry, thus ameliorating the extent of acute and chronic dermal injury for modern patients. It is also to recognize recall of injury by many medications including antibiotics. Modern targeted therapies including epidermal growth factor receptor (EGFR), B-Raf Proto-Oncogene (BRAF), and mechanistic target of rapamycin (mTor) therapies also result in dermal injury and the integrated use of radiation therapy may augment the reaction, even in areas not irradiated. Radiation oncology is evaluating the use of more compressed treatment strategies for outpatient care including stereotactic therapy. There are reports of dermal injury to patients due to equipment augmenting dose to skin. Treatment planning needs to limit this risk [19, 21–23, 27–33].

7.5. Bone marrow

Acute effects of radiation therapy affect marrow elements with rapid self-renewal potential. Lymphocytes die an intermitotic death, therefore can be used as a highly qualitative biomarker for radiation dose during exposure. Neutrophils self-renew on a near daily basis, therefore are highly sensitive to X-ray exposure like platelets. Red cells do not have nucleus, therefore decreased red cell count requires further evaluation to rule out a source of cell loss or limitation in production. It is interesting that the use of intensity-modulated radiation therapy (IMRT) for patients with pelvic malignancies is demonstrating an increase in issues associated with blood counts in patients treated with standard chemotherapy for gynecologic and rectal malignancies. This is due to the fact that most radiation oncologists have applied tighter bowel constraints for attenuation of small and large bowel sequelae of management. This brings dose further into pelvic marrow elements and away from bowel. Radiation oncologists must be conscientious on these points. Modern investigators are using advanced technology MRI and metabolic imaging tools to distinguish between red and yellow marrow elements

and use IMRT for conformal avoidance to address this point. Prior to the use of modern tools for image guidance, radiation oncologists used more generous planning target volumes, and this likewise contributed to the problem. Pancytopenia and bone marrow aplasia and dysfunction are becoming a common consequence of therapy including secondary liquid malignancies. Often, these are first identified in the acute care setting. Bone marrow deficiencies can often take years and decades to develop as a consequence of therapy, therefore vigilance remains important in this area as part of patient management moving forward [19–21, 33].

7.6. Gastrointestinal tract

The cells that line the gastrointestinal tract have a rapid self-renewal potential with gastric lining undergoing renewal every day and the small bowel every 3 days. The mucosa is dynamic and is responsible for absorption of nutrition and water. Without mucosal lining, body fluid is readily lost and with intermediate level total body exposure, repopulation of mucosa cannot keep pace with fluid loss, hence the genesis of gastrointestinal death from exposure. Infection is also an issue as the barrier is denuded and intestinal flora autoinfect the victim. Therefore, barrier nursing, blood and fluid support are essential to survival in victims who have received an intermediate dose of X-ray. Investigators have demonstrated that bone marrow progenitors may repopulate and differentiate in the gastrointestinal system, indicating a potential benefit to bone marrow transplantation in victims of radiological exposure.

Therapeutic X-ray impact on the gastrointestinal tract is influenced by several factors including co-morbidities and previous surgery. Sequelae can be seen in patients who receive intermediate therapeutic dose to large segments of bowel as well as those who receive high dose to small bowel segments. Strictures are not thought to be a direct effect from treatment; however, if a bowel segment is fixed in position by adhesions, if irradiated, this segment of the GI tract can be further injured and may require surgical removal if symptoms become too demanding and life-threatening. Late effects from management include every tissue component of the gastrointestinal tract. Atrophy of mucosa exposures underlying submucosal tissues to external injury can lead to chronic infection and malabsorption with pain as nerve roots become exposed in the unprotected internal environment. Insufficiency syndromes including the exocrine pancreas are now being observed [19–21, 33].

7.7. Liver

With the marked increase in viral- and diet-induced liver disease, there is a significant increase in primary hepatic malignancies. Coupled with the improved efficacy of radiation therapy for metastatic disease to the liver, hepatic and diaphragmatic injury from radiation treatment is now well described. Although hepatic parenchyma does not have a rapid self-renewal component, injury to the hepatic reticulum results in disorderly repair limiting blood flow to parenchyma. This limits filtration of both nutrients and toxins. With increased vascular stasis due to disorganized repair, veno-occlusive disease (VOD) becomes an insidious issue and serves to complicate the delivery of care. Metrics for the degree of pre-existing VOD influence the radiation therapy approach to radiosurgery for both primary and metastatic patients. This is important in assessing hepatic disease in the acute care setting. One of the more challenging issues for emergency room providers and primary healthcare delivery teams is the fact that radiation

therapy volumetric objects do not reside in a standard electronic medical record (EMR). This makes communication to the patient/family as well as disease assessment problematic including the delivery of intravascular therapy. In a chaotic vascular system, one can never be certain that dose intent is dose delivered. Efforts are made with external radiation therapy to limit mean liver dose and in an otherwise healthy liver to 30 Gy to 30% volume [19–21, 33–35].

7.8. Renal

Similar to the liver, the kidney is a sensitive late responding critical organ. Radiation doses greater than 20 Gy in 2 Gy fractions can result in renal damage with downstream consequence of anemia and hypertension. Although not validated through clinical trials, the tolerance dose is lower is patients who have also received chemotherapy. With advanced treatment technologies, modern radiation oncologists can optimize dose to the kidney using intensity modulation; however, even modern technologies leave a footprint which can limit future function. In comparison with siblings, cancer survivors have a higher likelihood of renal failure. We need to be aware of the tolerance dose as we design care plans with imaging [19, 21, 33].

7.9. Lung

Similar to the liver and kidney, the lung is a sensitive intermediate to late responding organ. In extreme situations, radiation injury to the lung is life-threatening. The period of active inflammation generally occurs 2–6 months post completion of therapy. Fibrosis can occur years after therapy and this can create distortions in pulmonary anatomy relative for the region treated and dose delivered. During the active inflammatory period, changes consistent with inflammation are visible on thoracic imaging. Interestingly, changes on imaging are often more frequent than symptoms, nevertheless, when symptoms occur at times management is challenging. Injury outside the radiation treatment field is often ascribed to radiation therapy and often we dismiss this as an event without merit. Recent investigations have demonstrated that nitric oxide gas is produced as a by-product of treatment which may explain, in part, why changes in untreated lung can be seen. It is important for radiation therapy treatment objects be available for acute care providers. Although the most recognized metric for pulmonary injury is the volume of parenchyma receiving 20 Gy, in selected situations, the volume of parenchyma receiving 10 and 5 Gy may be of equal importance in determining root cause of pulmonary dysfunction. Oncology treatment records are important for review as chemotherapy agent, targeted therapies and immunotherapy can significantly contribute to pulmonary toxicity. Cancer survivors have a higher risk of chronic pulmonary disease compared to siblings; therefore need to be vigilant to their long-term pulmonary health [21, 33, 36].

7.10. Cardiovascular

Although historically, the heart and large vessels were thought to be a late responding tissue to injury, modern cardiovascular evaluation and imaging have demonstrated that radiation therapy has an impact on all cardiac structures including coronary arteries, valves, myocardium, and the electrical conduction system. Although efforts in planning radiation therapy now focus on cardiac avoidance and compartment dose volume analysis, there are multiple

generations of patients treated with traditional technologies that may remain at higher risk for cardiovascular injury. Chemotherapy agents also contribute to this risk and targeted therapies may unintentionally add to risk. For example, breast cancer patients are often treated with Adriamycin on an adjuvant basis. This agent has an established history of cardiotoxicity. After administration of Adriamycin, the recovering myocardium expresses Her 2 Neu. Her 2 Neu positive breast cancer patients will receive Herceptin after initial chemotherapy, therefore these patients are at higher risk for cardiac injury without radiation therapy. Modern radiation technologies including optical tracking of position, breath hold, and intensity modulation contribute to decreasing mean heart dose and limit radiation dose to specific cardiac volumes including the left ventricle which is an issue for left breast patients. The field of oncocardiology is an important field of study. Cancer survivors have a higher risk of cardiovascular disease compared to siblings and introducing cardiac-oriented survivorship plans as patients complete their primary therapy needs to become the standard of care. Long-term radiation injury is noted to the microvasculature in all organ systems; however, large vessels were thought to be less susceptible to injury. However, as we move to treatments that include non-traditional fractionation protocols and overlap of previous areas of radiation therapy, evaluation of large vessels with surveillance imaging including the carotid vessels for patients treated for head and neck cancer. With more patients being retreated for secondary events, conformal avoidance to cardiovascular structures as part of primary management and avoidance of radiation dose asymmetry will be important to optimize outcome moving forward [37–43].

7.11. Central nervous system

The brain has multiple cell systems susceptible to injury uniformly viewed as late responding tissues. Necrosis can occur after radiation therapy, especially in circumstances of compressed fractionation and stereotactic radiosurgery and radiotherapy. Although highly unusual, demyelinating syndromes can occur both in the brain and spinal cord associated with both radiation dose and volume treated. Toxicity is also increased with chemotherapy agents including but not limited to Ara-C and Methotrexate, both used in multiple disease settings due to penetrance beyond the blood-brain barrier. There are injuries noted to tissues with end arterial vascular systems. The optic chiasm is susceptible to injury with radiation therapy due to the unique arterial system at doses of 54 Gy. The cochlea is susceptible to injury especially when cis-platinum is used as part of the care plan. Brachial plexus injury was described in breast cancer patients at doses of 54 Gy; however, this is an issue which identification of this dose may be inaccurate. At the time of description of the injury, radiation therapy techniques unintentionally created overlap with anterior and posterior fields under the lateral third of the clavicle where the entire nerve plexus enters the upper extremity. It is rare to see plexopathy in head and neck patients, therefore the experience with the breast cancer population and regional treatment may have related to technique rather than radiation dose. This again point to the importance of increasing the knowledge of radiation therapy in the general medical community and acute care providers [33, 44].

7.12. Endocrine

Hypothyroidism is exceptionally common in patients treated with both surgery and radiation therapy to the upper thorax and neck. This can have significant health issues and is often overlooked and underappreciated in the acute care environment. The thyroid is also highly

vulnerable to injury with unintended exposure and a source of secondary malignancies due to exposure. Gonadal exposure leads to both fertility issues and endocrine dysfunction, which can affect every organ system including growth and development in children. Atrophy and dysfunction of multiple organ systems is identified in patients where limitations in estrogen and testosterone function are not identified. Pituitary dysfunction is well described in multiple disease systems especially in patients treated with high retropharyngeal adenopathy or primary disease in the nasopharynx. Modern survivorship plans need to include strategies for endocrine malfunction [33, 26].

7.13. Pediatrics

Children are a highly vulnerable population. Although treated at a young age, late effects often become more visible when these cancer survivors transfer their long-term care into adult medicine. At radiation doses of 20 Gy, limitations in musculo-skeletal development are seen and at dose of 55 Gy bone necrosis can occur, especially in patients treated with chemotherapy. Exit dose from cranio-spinal radiotherapy can impose changes in cardiovascular and pulmonary health and development. Treatment for Wilms tumor makes children vulnerable to renal health problems as adults. Because these children are treated as infants and young children, even low dose therapy affects gonadal function and other gastrointestinal injuries including maldevelopment of bowel segments. With advanced imaging techniques, structures once thought immune to radiation effects now are known to be more vulnerable to injuries. Sacral insufficiency fractures are now visible at radiation doses of 50 Gy. Stereotactic body radiosurgery is now associated with injuries once thought historical in nature including rib fractures from pulmonary therapy. Often childhood patients do not have survivorship plans that can detail what is needed when they become adult patients and adult physicians need to detail a plan when caring for these patients as they become adults to provide a comprehensive survivorship plan.

Intentional and unintentional radiation exposure can have significant impact on normal tissue, both immediate and late. In assessing acute exposure, it is essential to determine exposure and dose. Optical imaging may be a tool moving forward which can validate computational extrapolation of dose as injury can be seen within 12 hours of exposure. Appropriate support needs to be applied to victims of acute exposure and intentional therapy needs to be mitigated by strategic planning and application of therapy. Survivorship plans for those exposed to radiation including those with unintentional exposure need to be developed. An understanding of these effects is essential for modern healthcare providers in the acute care setting [19–21, 26, 33, 45].

8. Conclusions

It has been more than 100 years since the discovery of X-rays and radium. The power of radiation is significant and appropriate application of radiation has saved lives and become an extraordinary source of energy. The devastating side of radiation is equally visible. Both intentional and unintentional injury remains at significant risk in spite of a century worth of knowledge concerning radiation safety and application of safety measures. Radiation therapy and diagnostic imaging remain tools that are essential to mission for patient care, nevertheless we must remain vigilant and apply continuous process improvements in practice to ensure

optimal patient care and secure safe environment. Enhanced knowledge of the impact of radiation on normal tissue is important for emergency care workers.

Conflict of interest

The authors certify that there is no conflict of interest in relation to this manuscript.

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