REVIEW ARTICLE

Radiation Oncology: Modern Review of Treatment Toxicity

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Abstract:

Radiation therapy has undergone an extraordinary transformation in treatment technology. Daily patient care is vastly different today than the past with less normal tissue in the treatment field and fewer acute sequelae during and immediately post therapy. It is anticipated that modern therapy will decrease acute effects during treatment. Modern primary care physicians and internal medicine/emergency physicians will encounter more patients in their practice who are survivors of therapy. In this paper we review current expectations for clinical sequelae of management and strategies to both identify and manage treatment effects moving forward including what is needed in the medical record for evaluation of late effects.

Introduction

Traditional models for radiation therapy treated patients with two-dimensional treatment planning using fluoroscopy for defining the target volume of interest. It was difficult to estimate the volume of normal tissue in the radiation field with two-dimensional models (1,2). Although efforts were made to create radiation therapy planning systems that used normal tissue estimates as co-efficients for optimizing patient specific therapy plans, this effort was largely qualitative in nature. Internal medicine physicians assessing normal tissue damage of cancer survivors had to assume full organ exposure when confronted with injuries to normal tissue. This remains challenging for physicians, including providers managing adults who are survivors of therapy for pediatric malignancies, as effects of therapy are influenced by the type and duration of treatment as well as the age of the patient at the time of treatment (1-5).

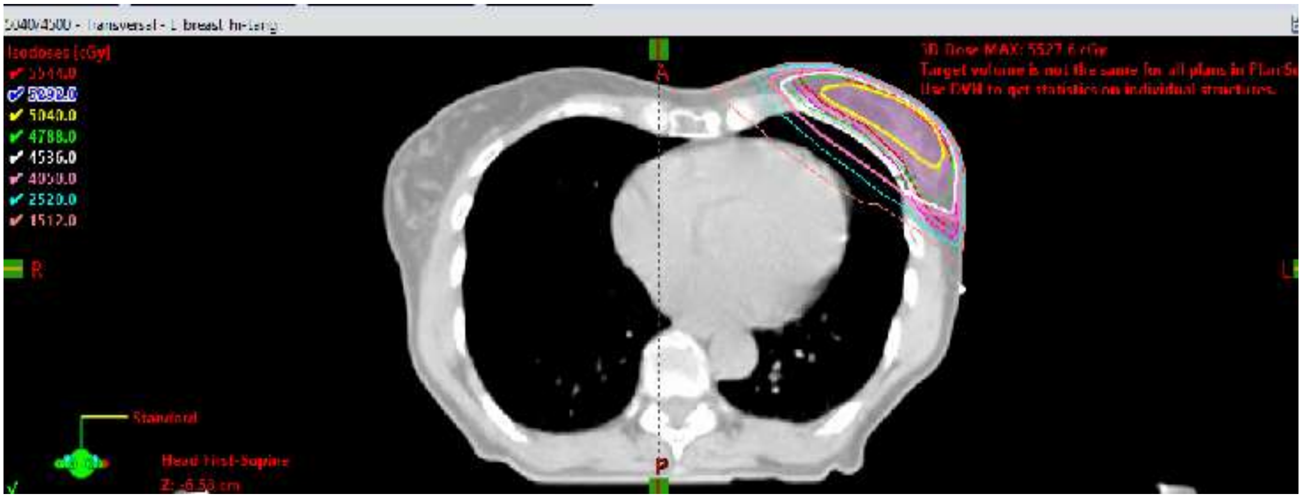
The paradigm of three-dimensional analysis shifted with volumetric radiation therapy treatment planning (4,5). With the increased use of computer tomography in radiology, radiation oncology replaced fluoroscopy simulation with simulator units using computer tomography. Planning systems now required radiation oncologists to draw target volumes of interest and radiation dose was defined to a volume and not a center of interest. This adjustment provided an opportunity to study subsegments of normal tissue volumes and assign areas of low and high dose to end organs as both intended and unintended targets. Further progress was made when the fluence patterns across the volume could alter the dose segments within the field and therefore the intensity of the beam could be modulated across the field. This advance was called intensity modulation which could be applied to tumor targets and normal tissue, thus avoiding areas of dose asymmetry across normal tissue and permitting radiation oncologists to assign limits to both normal tissue and the percent normal tissue receiving therapy. This improvement was validated with daily image guidance. Kilo voltage diagnostic imaging coupled with cone beam computer tomography were integrated into modern linear accelerators providing security that the intended target of therapy was treated on a daily basis per written directive. The imaging device could also measure dose confirming dose delivered to each sub-segment. These changes provided security that the intended dose was the actual dose treated to the correct volume. Optical tracking systems provide additional security that the patient maintains position during treatment, including breath hold techniques, which serve to exclude additional normal tissue from treatment. For breast cancer patients it is now routine to exclude the majority if not all the heart from treatment. Patients with Hodgkin lymphoma who require therapy to the mediastinum and pericardial tissue can be treated with significant cardiac structure exclusion with further limitation of pulmonary parenchyma in the therapy field. Patients treated to whole lung therapy can now be treated with four-dimensional planning and cardiac exclusion (6).

These technology changes will improve outcome for the modern patient, however millions of cancer survivors under evaluation today were treated at the time of two-dimensional radiation therapy, therefore modern internal medicine physicians and subspecialty providers must work through these issues for each specific patient with the help and support of their radiation oncology colleagues. A more comprehensive understanding of volumetric therapy will help providers anticipate the development of sequelae and provide a survivorship strategy to mitigate and limit the impact of these issues for the cancer survivor’s quality of life.

Modern radiation therapy planning

Modern patients are planned for radiation therapy using detailed and complete volumetric planning in all disease areas including four-dimensional applied techniques when appropriate. Often four-dimensional planning is essential to mission both when the lung and liver are intentional and unintentional targets including tumors in the thorax and upper abdomen. Patients are imaged in the four-dimensional simulator which includes computer tomography and camera imaging of patients in all 10 phases of the breathing cycle. Images are collected and collated and targets are drawn on the computer tomography simulation average study as this defines target location in all phases of the breathing cycle. Strategies can then be applied for breath hold technique which often limits lung volume in the treatment field for thoracic patients and cardiac volume potentially exposed to treatment in left sided breast patients (four-dimensional planning/breath hold). Tumor targets defined as high risk (gross tumor), intermediate risk (tissue abutting gross tumor/at risk volumes) and low risk (potential areas of microscopic disease) are defined and contoured as well as normal tissue targets in the radiation therapy treatment field. The radiation oncologist and planning team draw the targets and the radiation oncologist defines constraints to both the tumor and normal tissue to support the planning team. This defines the parameters and ceiling that will be permitted to normal tissue based on radiation dose and volume of normal tissue within the therapy field.

Figure 1 is an example of standard normal tissue constraints applied to breast cancer patients. Most plans applied to patients treated for curative intent are generated using intensity modulation where radiation fluence profiles are altered across the field using dynamic motion of multi-leaf collimators. This further serves to titrate areas of radiation dose asymmetry and optimize dose to normal tissue to meet constraints assigned by the radiation oncologist. This generates dose volume histograms for tumor and each normal tissue requested by the radiation oncologist (figure 2).



3D Dose MAX: 5527.6 cGy
Target volume is not the same for all plans in PlanSe
Use DVH to get statistics on individual structures.

Figure 1. Breast cancer contour designed to limit dose cardiac dose

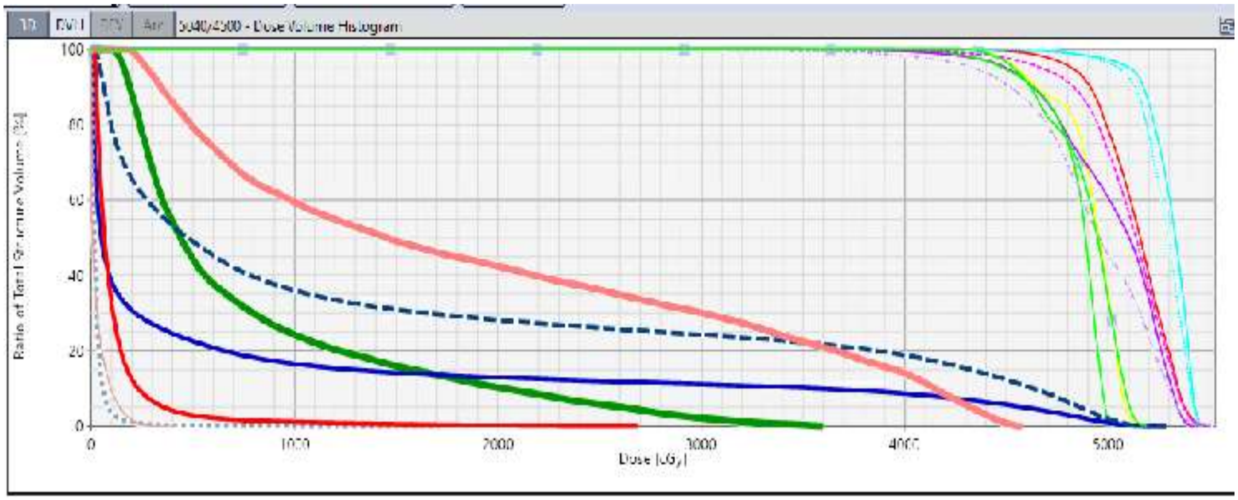


Figure 2 represents a dose volume histogram for tumor and normal tissue for a standard breast cancer patient. This provides a frame of reference to compare plans and achieve objectives for consistency between individual plans assuming contours are defined in a consistent manner.

A typical plan for a patient with esophageal cancer is displayed in Figure 3. As can be seen in Figure 3, constraints need to be applied to normal tissue both above and below the diaphragm including pulmonary tissue, cardiac tissues, liver, and kidney. The plan provides balance to each structure by applying a circular distribution of dose to the tubular target and limit dose to each structure and not apply more dose than desired to each structure. Currently, radiation therapy software identifies dose to targets drawn by the planning team. Organs are now generally drawn manually with validation and this is a time-consuming process. Artificial intelligence will help define dose volume analysis to individual subsegments as the computer models mature and become more predictable and reproducible. For the heart, individual dose to each valve, cardiac compartment, electrical conduction system, and coronary vessels can be specified for each patient. For this esophageal patient, the left atrium abuts the target and dose to the target and electrical conduction system will be routinely provided once computer models mature for this analysis. This is important because most primary physicians and physician subspecialists currently associate radiation to an organ as a uniform distribution to target. It will be incumbent on the radiation oncology community to make segmental dose to target known to define at risk populations for late effects of treatment and help primary care and medical subspecialty physicians prepare for the next generation of patients treated with radiation therapy.

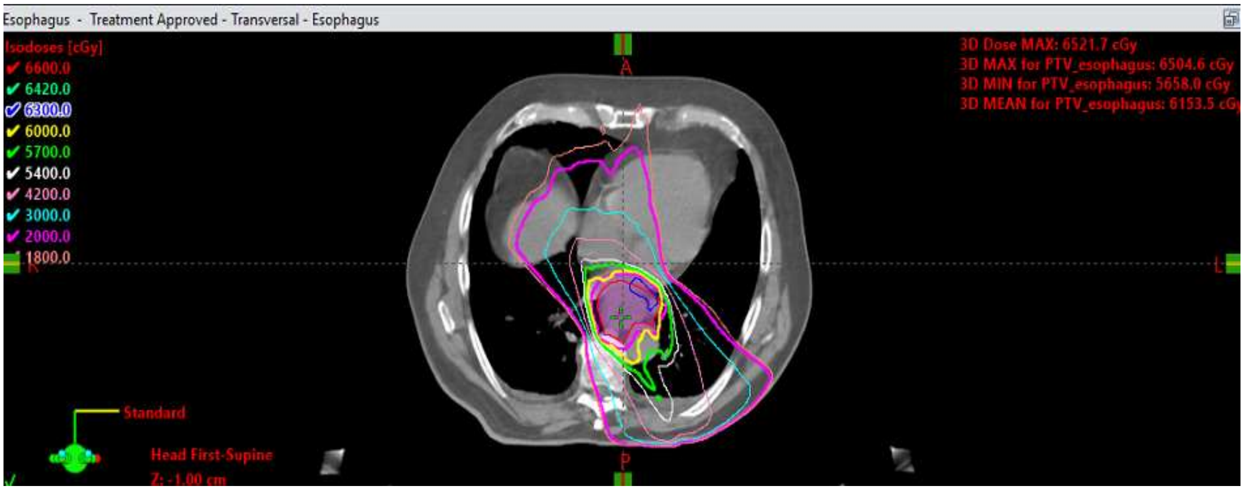


Figure 3: Esophageal cancer treatment plan designed to provide cardiac avoidance

Central Nervous System:

Although often difficult to define the effect from therapy from the effect from disease, it is important to optimize care for these patients as effects of treatment have ramifications that can extend over the lifespan of the patient. Twenty-five percent of pediatric malignancies are primary brain tumors and disease subtypes including medulloblastoma and germ cell malignancies require extended volume therapy that often includes the entire central nervous system. Efforts to titrate dose and volume of tissue treated for these diseases have only been met with partial success, therefore long-term ramifications of treatment will need to be managed for the lifespan of the patient. For children, these issues can include learning/cognitive development, endocrine heath relative to pituitary function, hearing, vision, and neuromuscular function. Limitations in any of these functions can lead to challenges in both acquired and de novo neuro-psychiatric health. Age at the time of treatment plays a fundamental told in outcome as even modest expanded targets can unintentionally include more normal tissue than desired for optimal outcome (7). Titration of volume and segmental dose volume analysis of critical structure dose can improve outcome (7). Modern image guidance provides security that smaller expanded targets in select populations can be applied to improve outcome (figure 4).

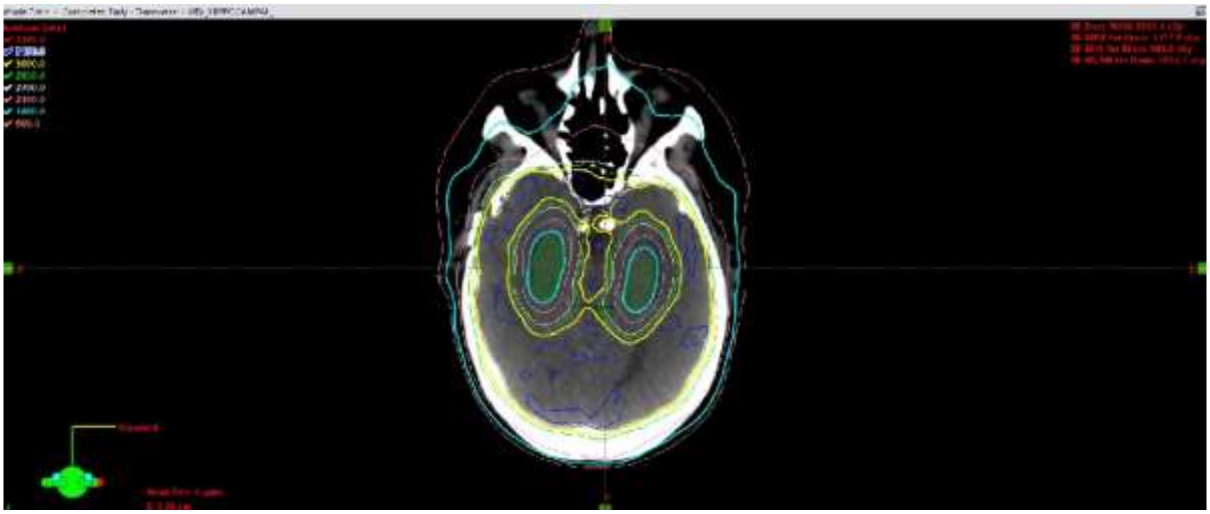


Figure 4 shows hippocampal sparing technique when applying whole brain radiation therapy designed to improve functional outcome (hippocampal sparing). Understanding what was treated to dose with the specific fractionation scheme will help internists of the future manage late effects (8,9).

Head and Neck

This is an important area as the human papilloma virus has altered the landscape of head and neck cancer. Although more work needs to be done to help optimize patients at risk and adjust therapy titration to potentially favorable situations, until vaccines can prove effective, there will be an increasing number of these patients requiring management of both their primary malignancy and effects of management. Planning with radiation therapy has become exceptional. Modern imaging is potentially defining the extent of disease and modern protocols are evaluating both dose and volume titration to improve outcome relative to late effects. Immobilization devices and image guidance has provided security in daily treatment reproducibility. Optical tracking further provides confidence in daily positioning. Evidence is clear that the quality of treatment matters, and radiation therapy plans well designed and executed from the initiation of therapy provide the best quality of care for each patient (10). Nevertheless, optimal outcomes relative to tumor control and normal tissue tolerance in management of these patients requires significant attention to detail. Radiation oncologists have optimized planning to secure radiation doses under 50 Gy to the spinal cord, therefore minimizing the risk of long-term injury to this structure. Retropharyngeal lymph nodes require treatment in nearly all circumstances of therapy for head/neck malignancies including patients with level 2 and 3 disease in the neck, placing salivary tissue and swallowing at measured risk for compromise. This is important for dental colleagues and the oral cavity can maintain an acidic environment altering the health of local tissue including mucosa and gums. Secondary effects are seen on teeth in adults and tooth development in children. Management of these patients requires diligence and attention to detail to prevent minor issues from becoming significant management problems. Frequent cleaning and use of toothpaste/mouthwash with basic pH will help stabilize the oral cavity environment. It is important to limit the dose to mandible to promote dental health and stability for future repairs. For these patients treated to the head and neck, internists must be cognizant of dose to the carotid vessels as a late effect and thyroid function must be periodically monitored, especially for patients who have had neck surgery and radiation therapy to the thyroid. It will be incumbent on the radiation oncologist moving forward to provide information relative to the dose and structure of each of these targets to prepare providers for management of the cancer survivor. While the acute effects of management relative to tissues with a rapid self-renewal potential, including skin and mucosa, remain the responsibility of the radiation oncology provider, often late effects require management by providers who may be less familiar with the patient during their treatment and unfamiliar with tissue both treated and avoided. Information such as this is often not visible in electronic medical records and often needs to be provided by radiation oncology for evaluation. This is especially true for patients who are being re-treated with radiation for a secondary tumor after completing therapy for their initial disease. There are multiple normal tissue structures within the radiation therapy treatment field in the neck including but not limited to the carotid arteries, therefore rapid availability of treatment objects is essential to modern patient care (11).

Cardiovascular

This is an increasingly important aspect of cancer survivorship with lifelong ramifications for the oncology patient. Although there are few acute effects from radiation management to the heart and vessels during management, late effects can have a significant impact on the quality of life of each patient treated to the thorax/breast.

For breast cancer patients, tangential therapy to the breast can unintentionally include the left ventricle and intentional therapy of the internal mammary nodes can include more volume to this structure than anticipated with field images. This would also include distal cardiac vessels promoting vascular defects to myocardium residing in close approximation to the chest wall (figure 5).

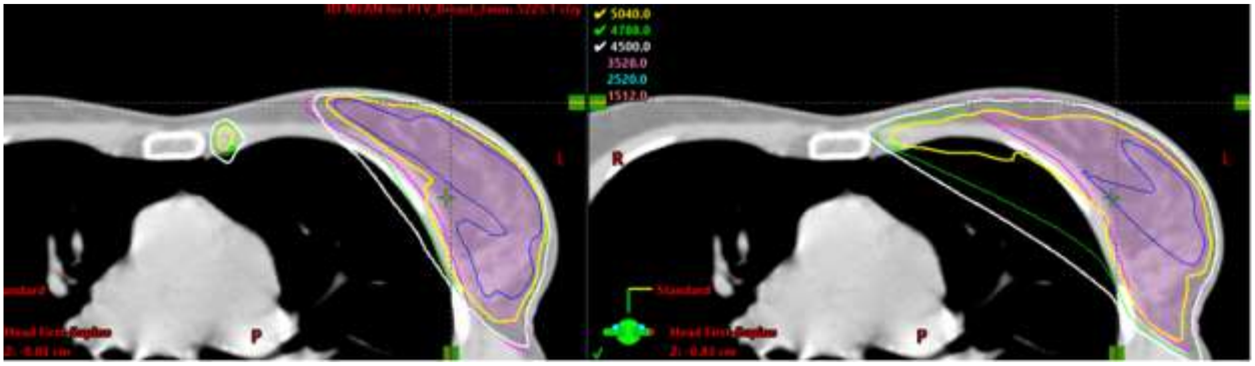


Figure 5. An example of unmodulated three-dimensional therapy.

Intensity modulation can significantly limit cardiac dose. Further improvements can be seen with breath hold techniques which can be validated by optical tracking. These technologies are essential to mission moving forward as they can serve to significantly limit dose to structure as well as mean heart dose.

One primary problem in current radiation therapy treatment planning is we uniformly define the heart as a single end organ structure and have not yet, even in clinical trials, asked investigators to sub-segment areas of the heart that would be deemed "at risk" given the nature of the underlying malignancy and its relationship to cardiac anatomy. Likewise, we do incorporate pre-existing cardiac disease as a coefficient into our radiation therapy planning portfolio in a uniform manner. We have much to accomplish to optimize personalization of therapy, however our tools are improving, and we will be able to provide this information colleagues in near real time to improve patient care and provide predictive indices to potentially mitigate significant cardiac events in the future (11,12).

Pulmonary

This is an important area for optimization of radiation planning to provide as much opportunity as possible for optimal patient outcome. Lung cancer has evolved over the past 40 years. While many providers traditionally saw patients with squamous cell carcinoma associated with environmental factors, the modern lung cancer patient often has adenocarcinoma originating in a peripheral location with a small but increasing incidence of small cell cancer. Lung cancers are now associated with biomarkers and are often treated with targeted therapies based on biomarker analysis and mutation status. Of equal importance is that patients at the time of diagnosis often have compromise in lung function which requires evaluation for radiation therapy. Often it is challenging to determine how much pulmonary function is compromised secondary to disease or background injury. Likewise, it is challenging to ascertain what can be reversable or irreversible as part of a therapy plan when disease and therapy are superimposed on a background of pre-existing injury. It is important for providers to understand the process of modern radiation therapy treatment planning and the efforts made to limit the application of therapy to functional parenchyma. Patients are imaged in four dimensions and techniques are utilized to fully cover gross tumor targets and areas considered at risk for disease including contours accommodating for motion. Because of modern daily image guidance and optical tracking, planning target volumes that accommodate for daily patient set up variability can be titrated relative to target size and need to limit parenchyma receiving 5 and 20 Gy. The expanded target can often be limited to a few millimeters or the limits of motion in cases where sparing lung parenchyma are a near equal priority to tumor control. Often these patients have compromise in function due to both disease and background injury. For those with limited restrictive changes, breath hold can be used to spare additional parenchyma. Often this technique can be applied when the lung parenchyma is an unintentional target including patients with thoracic lymphoma and esophageal cancer.

In treating patients with thoracic malignancies, radiation oncologists generate dose volume histograms of the target treated and normal tissues in the therapy field. A key objective is to insure the volume of normal tissue is titrated without compromise of tumor target coverage. Efforts are made to limit dose to critical structures including retrocardiac therapy to exclude cardiac structures from therapy as well as other tissue of limited self-renewal capability including but not limited to rib, chest wall, esophagus, and brachial plexus. In this capacity, the information serves as an archive to provide a reference to late effects if/when they occur. An example of contours of a lung cancer case and dose volume structures is seen in Figure 6.

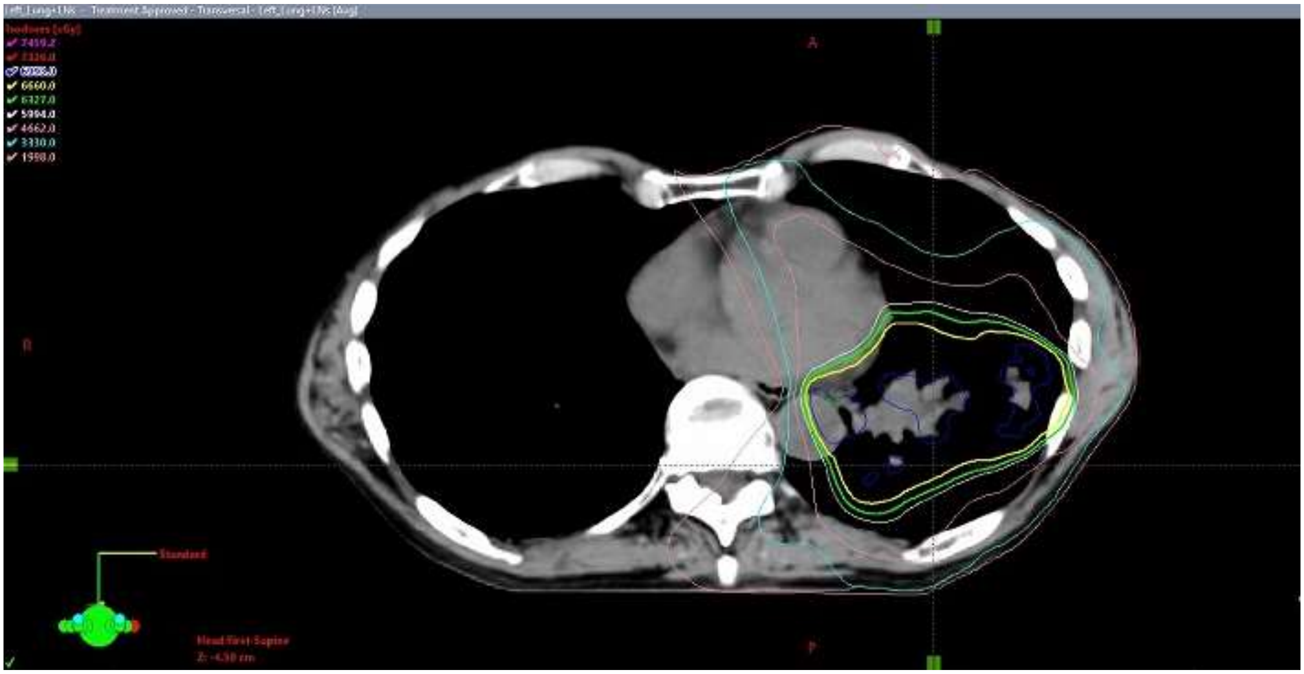


Figure 6. A dose volume histogram showing contours of a lung cancer case and dose volume structures

Although the tools of radiation therapy treatment planning have evolved in a dynamic manner, we need progress in multiple essential areas to optimize the planning design. To date, radiation oncologists have applied anatomical constraints assuming lung function is uniform in nature. As we know, function is variable and to date functional coefficients have yet to be used at an enterprise level for radiation planning purposes. These would be patient specific and require functional imaging strategies to be developed and fused into traditional planning images. A modified precursor of this approach would be to evaluate areas of limited function (blebs) and see is therapy can be directed through that structure to further promote sparing of functional parenchyma. There is evidence that even low dose radiation (V5-volume receiving 5 Gy) can negatively influence pulmonary function, therefore optimizing planning to drive dose through non-functional segments may serve to mitigate this issue (13-17).

Liver

Radiation therapy to the liver is becoming more prominent both using radiosurgery teletherapy techniques and radioisotope therapy. Both provide therapy to limited hepatic volumes directed to tumor specific regions of the liver. Response to radioisotope therapy be inversely correlated to dose migration seen on serial (daily) SPECT studies (single positron emission computer tomography) and radiosurgery is influenced both by motion and ability to define targets of daily treatment validation with cone beam computer tomography. These patients likewise have multiple therapies including surgery and radiofrequency ablation, therefore radiation therapy is superimposed on a background of previous therapies which in turn impose injuries in the regenerating liver. Therefore, outcome with radiation therapy to the liver is largely driven by pre-therapy function. This is an area where current magnetic resonance (MR) imaging may have a role as radiomic signature for veno-occlusive changes and pre-existing areas of hepatic vulnerability to therapy applications.

These signatures may help provide a predictive model for injury moving forward and help influence how therapy can be applied moving forward. This creates an irony that treatment of tumor in regions of pre-existing hepatic injury may be treated with less radiation dose and that larger volumes may also receive less dose, nevertheless this provides a strategy for care in finding balance between tumor kill and normal tissue protection (figure 7).

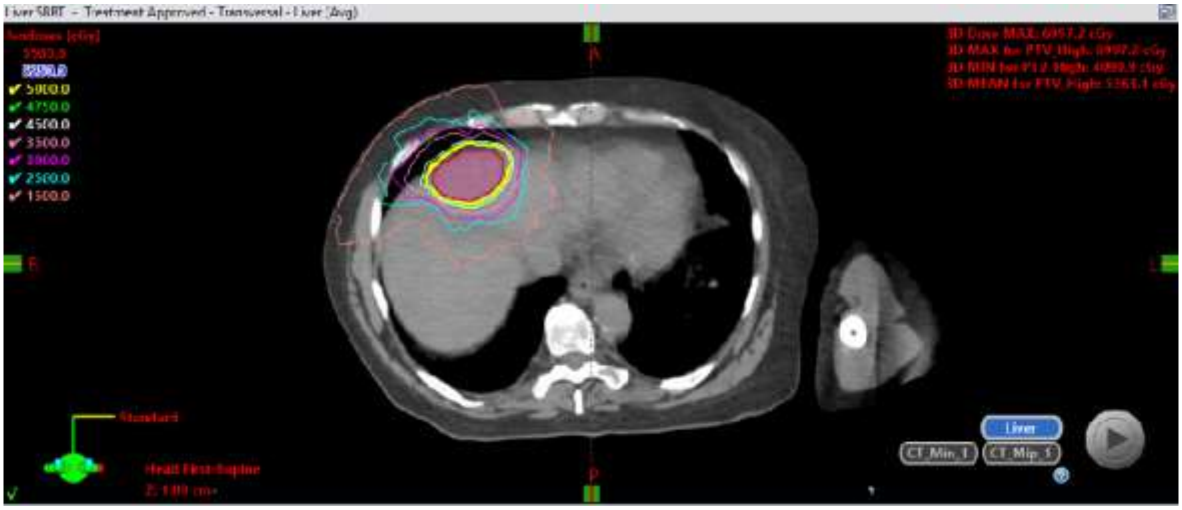


Figure 7 is an example of hepatic stereotactic radiosurgery (18,19).

Genito-urinary Radiation Therapy:

This is an area of increasing importance in patient care. As we age as a society, renal therapy and sub-total renal volume treatment is becoming essential for patient care including care for the patient with bladder cancer. Patients are not uniformly capable of undergoing renal surgery and renal volumes must be titrated to target to protect normal tissues. This includes additional GU structures including the renal pelvis and ureter. Stereotactic therapy to renal, renal pelvis, and ureteral volumes can be done on patients, including those medically compromised, with few sequelae as the retroperitoneum provides a convenient location for normal tissue exclusion. It is important to plan patients with four-dimensional techniques and it is optimal to treat them with optical tracking to insure target location and treatment reproducibility. This provides an important tool for treatment of these patients who often do not have surgical options due to age and medical co-morbidities (20).

Musculoskeletal

Although once thought to less susceptible to injury from radiation therapy due in large part to limitations in self-renewal capacity, modern imaging is demonstrating subtle and more obvious changes in bone at lower radiation doses than previously identified. Historical thinking suggested that radiation therapy doses of 6,000-7,000 cGy were acceptable for therapy with traditional fractionation, however selected MR sequences are demonstrating structural changes and insufficiency fractures at doses of 5,000-6,000 cGy. This is now becoming an important issue for the cancer survivor, especially in an aging population where bone related changes are becoming more visible and part of health maintenance.

Chemotherapy and hormone therapy also play an additive role in this area as well.

Radiation oncologists can mitigate this point with strategic application of expanded objects, especially in pelvic geometries. As can be seen in Figure 8, using an expanded volume for patient set up variability of 5 mm can place full dose through the sacrum. With modern image guidance and strategies to improve patient flexibility and pliability as done by Baima and Moni, compressed expanded targets can be applied to place dose gradients through bone to potentially limit late effects from management (21). The same plan with compressed planning target volumes is seen in Figure 8 as one can see dose gradients across the sacrum which should decrease the risk of late effects (21,22).

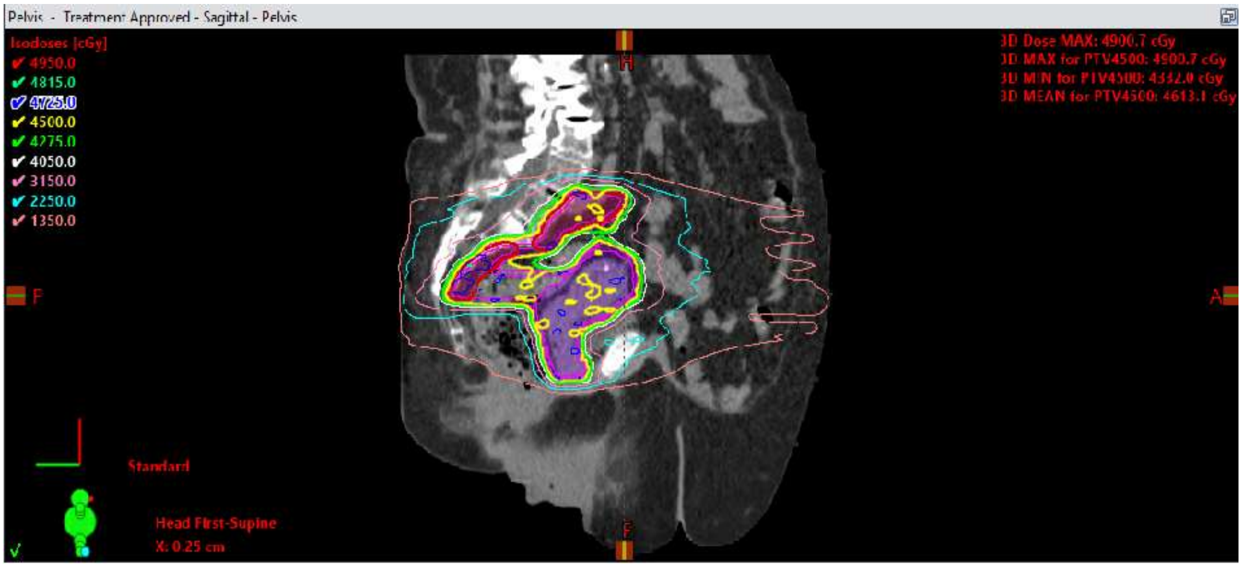


Figure 8. Gynecologic pelvis treatment designed to place dose gradient across the sacrum to decrease risk of insufficient fracture.

Pediatrics:

The survivor of childhood cancer is exceptionally vulnerable to the effects of treatment in all body systems. This issue is compounded as the child transitions to adult providers of care who are not familiar with pediatric oncology and the methods of treatment. Adult subspecialty providers likewise have no immediate working knowledge of pediatric therapy as records from therapy become obscure and vulnerable to loss. This includes radiation therapy treatment records which may not be kept on file and the documentation of volume and dose may not be available for review and the analysis of injury may be qualitative and ultimately superficial. For analysis of both late effects and risk of developing late effects, it is important to house radiation therapy volumetric dose volume records in the medical record. Most current electronic medical records do have a utility for incorporating radiation therapy records into the record made available to internal medicine providers and experts in emergency medicine. Fifty percent of pediatric malignancies are leukemia and 25% are brain tumors. The remaining disease areas include tumors which can involve all organ systems including Ewing sarcoma, rhabdomyosarcoma, soft tissue sarcoma, lymphoma, Wilms tumor, osteogenic sarcoma, rhabdomyosarcoma, and retinoblastoma. Sites of origin can be in all body areas and treatment can be directed to all body regions affecting growth/development and long-term health. Compared to siblings, pediatric cancer survivors have a decreased life expectancy and quality of life with increased of illness in all body regions best thought of as a sequela of management. The quality of care received by the cancer survivor needs to be different in all body areas including but not limited to cardio-respiratory health, dental health, and mental health (1-5).

Future Directions and Conclusions:

We are fortunate that survival has significantly improved for the cancer patient over the past several decades. This also brings responsibility to all providers of care as we all share the responsibility of documenting the past medical history. For cancer management, the past medical history is highly meaningful as therapies leave fingerprints of management. It is important moving forward that the therapy community provide meaningful information concerning patient management to both the patient and the medical record and likewise, it is important to make additional information available to providers when more detailed questions are required for injury assessment. It will be important to know what dose was directed to each specific cardiac segment as part of cardiovascular management. It will be important to know what dose was delivered to each functional pulmonary segment. Each organ system requires attention to detail as defined in multiple figures presented in the manuscript. Information such as this is crucial to outcome and important to detail for injury assessment and repair. Qualitative descriptions to organ segments will become less useful overtime and may not accurately depict areas at risk for injury. Likewise, without attention to detail, the oncology community will be less capable of validating metrics needed to provide risk assessment to patients moving forward.

We are in a new era of cancer management as the modern patient not only expects disease cure, but amelioration of risk of injury from therapy. The imprint of therapy, both chemotherapy and radiation therapy, will live with the patient for a lifetime and it will be the responsibility of all medical providers to optimize our collective understanding of the impact of therapy upon normal tissue outcome and adjust the linear strategy for care to both prevent injury and limit the extent of injury if/when it occurs. Volumetric data will optimize this assessment of risk and serve to support providers when injury occurs. It is the responsibility of the radiation oncology community to provide as much educational support to our colleagues as possible to close the gap in support of our patients moving forward.

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