**RESEARCH ARTICLE**

# Survivorship Programs for the Cancer Survivor: Next steps for the Modern Cancer Patient

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**Abstract:**
Cancer remains a significant medical challenge for modern health care. Therapies have improved. Chemotherapy can now be applied and targeted to specific expression products and biomarkers. Radiation therapy is directed to specific targets with applied image guidance including less normal tissue in the treatment fields. Surgery has improved with robotics and improvements in rehabilitation and recovery. More patients are surviving their primary challenge from malignancy. As such, more patients now have the imprint of therapy upon their normal tissues. It is important for all practitioners, including primary care physicians and medical subspecialists, to participate in the aftercare of these patients with a comprehensive strategic manner to both prevent normal tissue injury and ameliorate injury if/when it occurs.

## Introduction:

The care of the modern cancer patient has significantly changed over the past several decades. While clinical trials of the past placed primary emphasis on patient survival and disease-free survival as objectives, modern clinical trials incorporate normal tissue endpoints including non-inferiority coefficients into studies to evaluate the impact of therapy on normal tissue. This has become an important aspect of patient care. Historically process improvements in cancer care were exclusively evaluated by survival for outcome analysis. Today, it is recognized by all professionals that as care has improved, so have expectations of management. Precision and personalized therapies are intended to eliminate tumor with minimal to no impact on normal tissue function. While a laudable objective, therapy uniformly has a price and leaves indelible marks on normal tissue architecture and physiology.

In this situation, patients are often caught in a dilemma. Oncologists continue to place emphasis on new patients and process improvements in their field of interest and primary care physicians remain less informed about expectations of risk of management. Accordingly, the potential impact of therapy on normal tissue outcome is not incorporated into the past medical history of the patient. This often remains unrecognized until an event occurs. At this point, often it is assumed that the event is driven by whole organ risk and preventative strategies are not implemented and only mitigation strategies can be implemented for care.

This has become particularly visible in the pediatric population as this group matures into adulthood. Adult practitioners including primary care and subspecialty specialists, are largely less familiar with therapy risk assessment, including risk of secondary malignant events, for this population as both the pediatric disease and intensification of therapy are not part of the adult practitioner lexicon for daily practice. More emphasis and education is required to provide an improved level of service for this vulnerable population.

In this manuscript, we will outline potential strategies for incorporating subspecialists into the post therapy care of the cancer survivor to develop reproducible plans for both preventing normal tissue events and mitigating events when they occur to minimize the degree of injury when it occurs (1,2). Effective application of preventative strategies will provide cost effective care for the cancer survivor in multiple normal tissue systems.

## Central Nervous System

This is an important area for patient and family support. Brain tumors have an impact of near equal incidence per decade and 25% of pediatric malignancies are brain tumors. Very few diseases have as profound an impact on the quality of life of the patient as tumors in the central nervous system. The impact of disease can be profound and the imprint of therapy can have life-long impact on the patient. The specific site of limitation is driven by target location; however, the impact can be profound including lifelong neurocognitive, endocrine, balance, neuro-muscular, and behavioral issues. As such, multiple providers from educators, speech/hearing therapists, physical therapists and behavioralists are needed to coordinate care for these patients and the care needs to be choreographed by an individual with skill in both oncology management and neurologic sequelae of management. Often neuro-oncology can play this role, however often the neuro-oncologist must place focus on oncology management and not the sequelae of management. In this situation, a highly skilled physician extender can help work in parallel with neurology-based colleagues to help define problems and provide support for the development of a

 

strategic plan to mitigate damage anticipated by both the disease and treatment. The plan would place focus on the site of primary disease and the impact of therapy.

Oncologists, specifically radiation oncologists, can provide support for the patient and outcome providers by both optimizing targets and accentuating radiation dose gradients along structures not requiring primary therapy. Radiation oncologists can also make this information more readily available to support teams to help assess both the clinical and therapy risks and develop a plan in parallel to this information. Currently, electronic medical records do not house this information in a meaningful manner because there are no specific radiation oncology modules imbedded into electronic records. Radiation oncologists would need to move these objects into the medical record for disseminated use by all providers. It is an important step, and this confirms what was treated and reinforces that therapy does not place uniform risk upon all components of the end organ (figure 1).

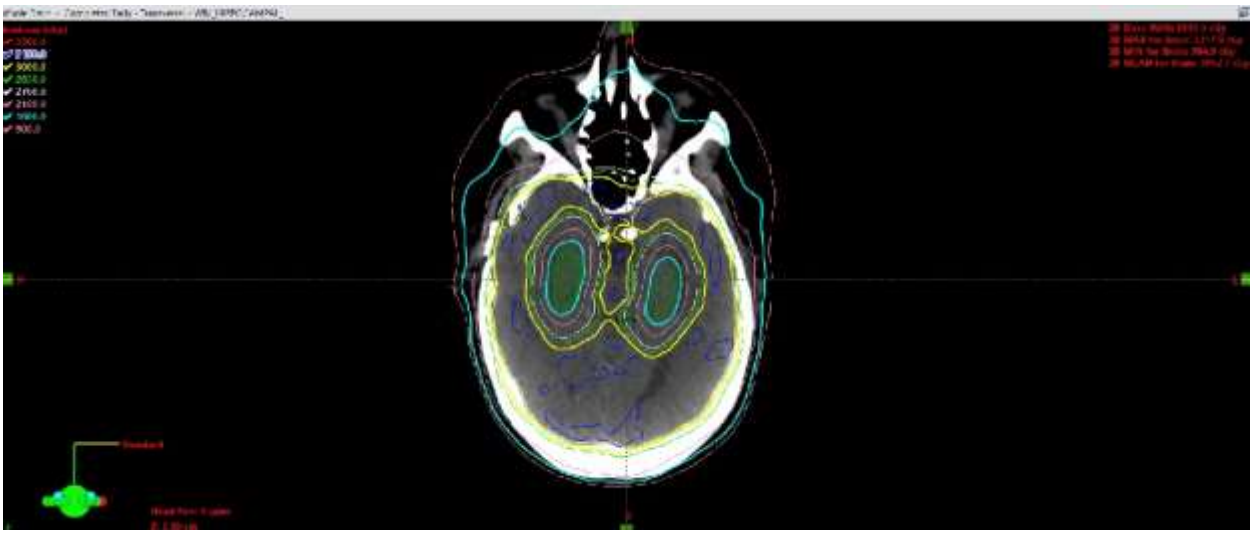

**Figure 1.** is an example of whole brain radiation therapy with dose gradients placed through the hippocampus. This is an example of improvements in technology that permit more normal tissue sparing with now proven benefit to outcome relative to neurocognition. Telehealth will now provide an opportunity to assess status and adjust care for these patients in a timelier manner as often these patients have limitations in travel and are fully dependent on family/friends for support (1-4).

## Head/Neck

Patients with head/neck cancer are an especially vulnerable population of patients with specific care needs before, during, and post therapy. Their needs cross multiple modalities independent of therapy and include nutritional support, speech/swallowing support, physical therapy, and dental support. Often these patients have multiple needs pre-therapy which require near immediate attention to support the initiation of therapy. Navigating the course of therapy can be problematic as these patients can experience significant mucosal discomfort and require significant nutritional, emotional, and social support. After completion of therapy, follow up is often only provided by otolaryngology and radiation oncology with focus on tumor control. Modern care requires a more comprehensive approach including access to

 

providers of care including speech/swallowing, physical/massage therapy, nutritional therapy, and dental support. This approach requires coordination with emphasis on medical support. Physician extenders can insure that a plan can be completed, however the plan requires direction and leadership including coordination of care between multiple departments and allied health providers. In many NCI designated cancer centers, medical oncology assumes responsibility for the medical aftercare for each patient with surgical and radiation oncology providers assuming responsibility for physical examination and image interpretation. These patients require support and attention to detail during follow up and careful data management can provide an infrastructure for translational science including biomarker analysis and therapeutic personalization including therapeutic titration when appropriate.

While historically providing care of patients during therapy was considered the gold standard of management, today expectations for care have changed. As can be seen in Figure 2, many normal tissues including the parotid glands and mandible receive less dose than more traditional three-dimensional radiation therapy. Patient expectations for outcome have increased with patients anticipating outcome to be near identical to their pre-morbid status with respect to speech/swallowing and dental health. Managing expectations is now an important aspect of follow up care which now requires comprehensive support from all physician and allied health members of the treatment team[1] (1-3, 5,6).

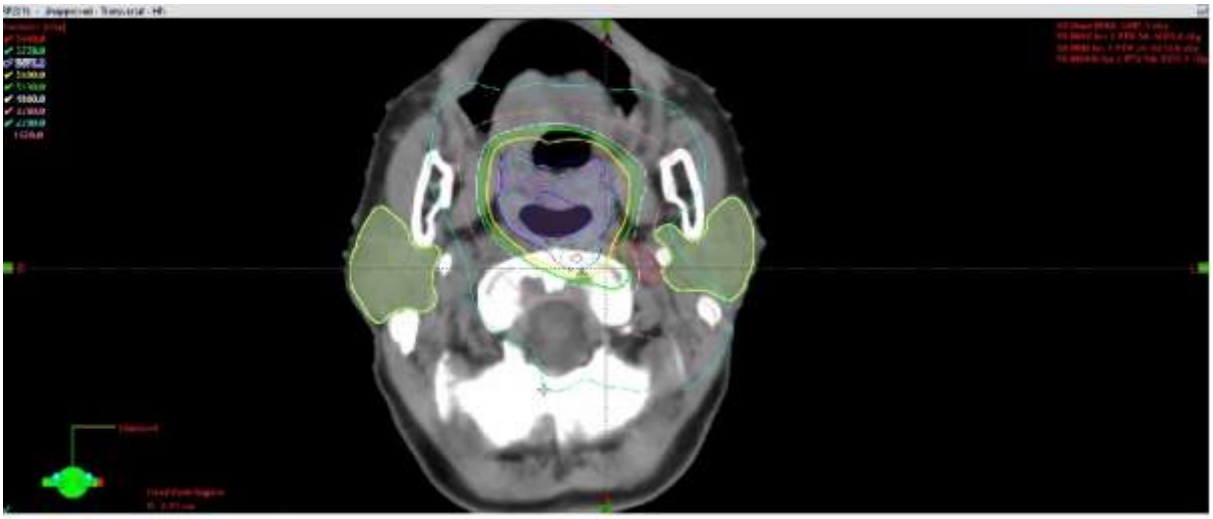

**Figure 2.** The figure shows an example of sparing of parotid tissue during head and neck management.

## Cardiovascular/Respiratory

This is an important aspect of post management care as the lung can be both an intentional and unintentional normal tissue target and the cardiac structures including major/minor blood vessels are uniformly an unintentional target volume for treatment. Both structures are critical for function and therapy associated compromise of function is detrimental and serves to limit quality of life.

Cardiology and pulmonary medical subspecialists will play an increasingly important role in outcome and therapy evaluation for patients treated for both breast

 

and thoracic malignancies. Modern radiation oncology permits more conformal avoidance of normal tissue structures than the past, nevertheless countless patients treated with two- and three-dimensional radiation therapy remain at risk for injury due in part to historical limitations in both radiation therapy technology and delivery systems. As can be seen in Figures 3 and 4, modern therapy permits exclusion of more cardiac and pulmonary structures than the past, however for the next several decades patients treated without volume titration and image guidance will remain more vulnerable to events both anticipated and unanticipated.

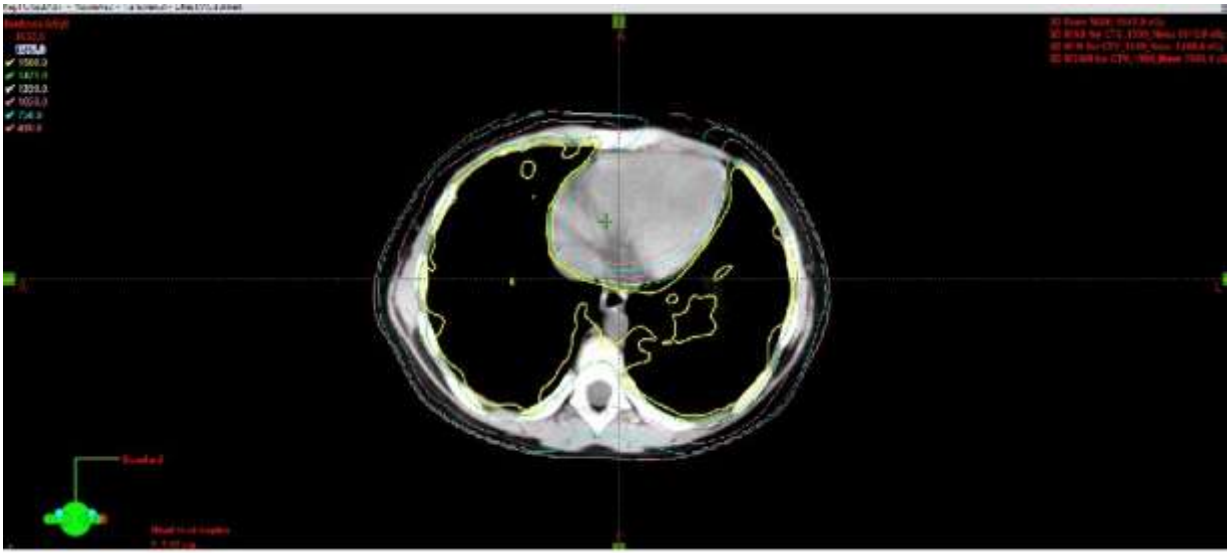

**Figure 3.** The figure demonstrates cardiac avoidance during whole lung radiation therapy

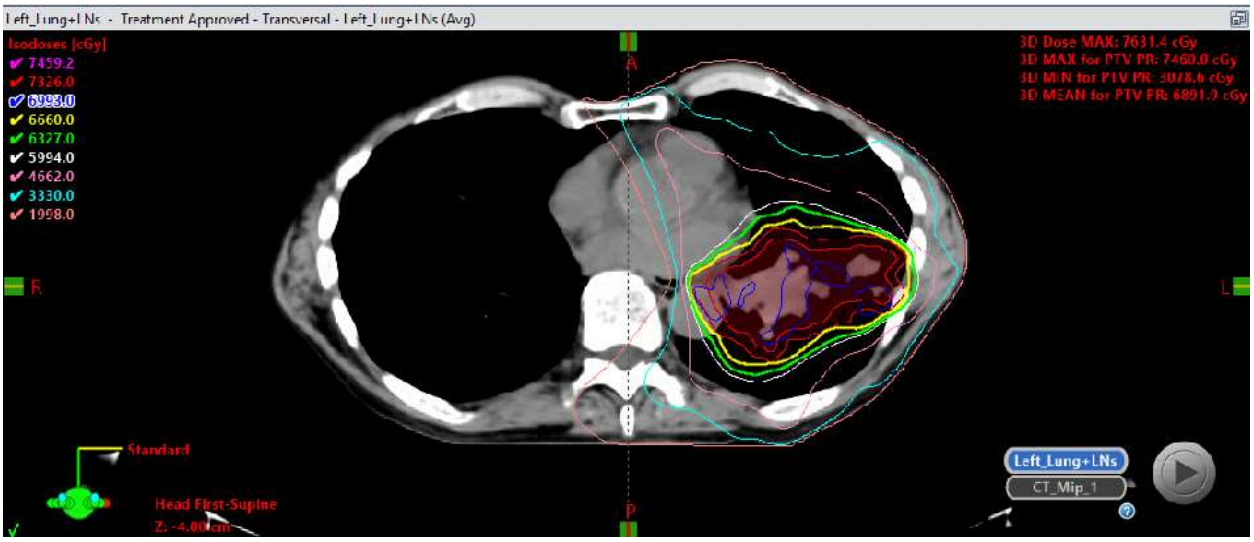


**Figure 4.** The figure demonstrates cardiac avoidance in a patient with a primary lung cancer in a retrocardiac location

 

Modern radiation oncology permits dose volume analysis to help optimize patient care and meet guidelines thought to be associated with injury. These include but are not limited to mean lung dose, volume of parenchyma receiving 5, 10, and 20 Gy, and individual dose to specific cardiac substructures including myocardium, electrical conduction system, cardiac valves, and coronary arteries. Tumor anatomy is inconvenient and often abuts structures desired for conformal avoidance. Lower esophageal lesions can abut the left atrium and extend in a lateral plane towards pulmonary parenchyma in a location that occupies more pulmonary volume than the upper lobes. These targets can unintentionally include hepatic and renal volumes to treat nodal volumes at risk in the celiac region. Radiation oncologists must provide a balance of constraints between all structures and make certain that the tumor target including motion is receiving the intended dose to the correct volume. Although tissues remain at risk for injury, modern therapy provides an opportunity for volume exclusion for these structures to decrease the risk of a long term event that will limit the quality of life for the patient.

The volumetric materials are of significant value to cardiology and pulmonary colleagues. This provides the optimal platform for risk assessment and both clinical and imaging strategies can be applied by medical subspecialty colleagues for decreasing the risk of an event and optimally mitigate an event if it occurs (1,2, 5-14).

## Liver

This is an area of increasing importance. As chemotherapy, surgery, interventional radiology, and radiation oncology has improved, outcomes with patients with both primary and metastatic disease to the liver have improved. Although hepatic parenchyma can regenerate post intervention, disorderly regeneration coupled with veno-occlusive disease can limit therapeutic strategies moving forward. This is an important area for imaging as MR can help determine the presence and volume of veno-occlusive change which can determine both the volumes of treatment and potential dose for radiosurgery. The liver can be a site for unintentional therapy for tumors of the thorax and abdomen and measurable volumes of hepatic parenchyma can be included in fields of treatment for both pancreatic malignancies and cholangiocarcinoma.

The collaboration between imaging, interventionalists, and medical experts in management of liver disease will be of increasing importance moving forward. Radiofrequency techniques do not often deliver uniform tumoricidal therapy and areas of residual disease will need attention. Conversely, radiation oncologists can apply uniform dose to the target, however they must apply a coefficient for motion and targeting with daily treatment validation can be challenging with densities seen on cone beam computer tomography (figure 1). Co-existing hepatic injury will influence target definition and the ability to apply therapy to the target without risk. Interactions between providers both in pre and post therapy evaluation is essential for process improvements in the care of these patients as the therapies overlap and can compete without provider harmonization.

 

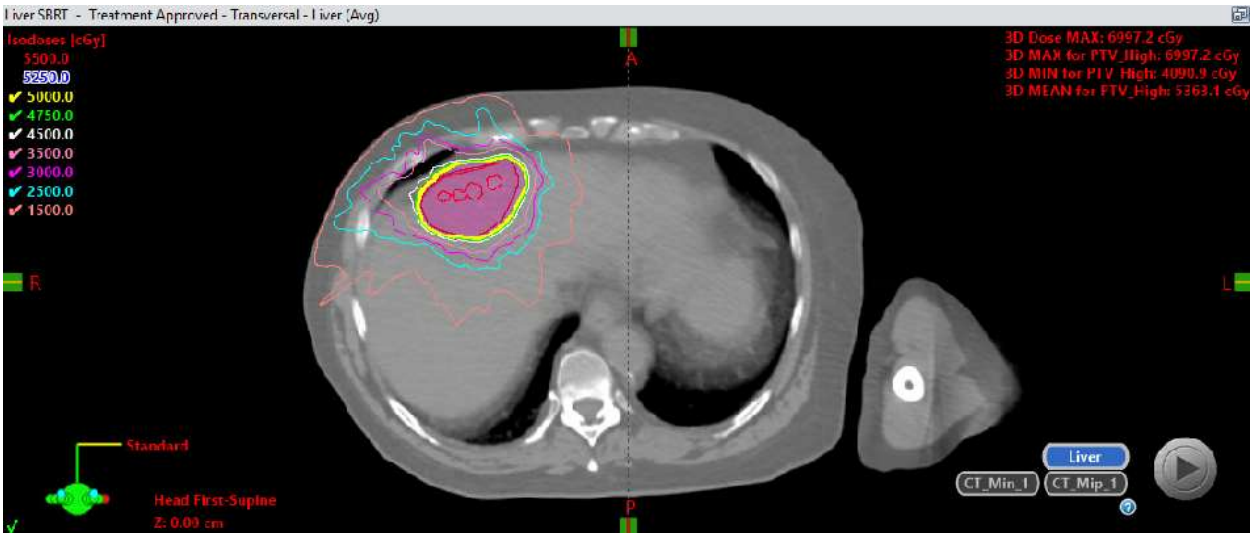


**Figure 5** is an example of hepatic radiosurgery with dose volume histogram. Note the proximity to the heart including the need for motion management which often can include the need for abdominal compression and breath hold techniques when applicable (15,16).

## Renal

Life expectancy has increased. As patients age, medical comorbidities influence management decisions and often genito-urinary patients are not candidates for surgical management. This includes all areas of genito-urinary care including renal, renal pelvis, bladder, and ureteral malignancies. Radiation therapy is used frequently for primary management of these malignancies when surgical options are not available or medically advised. Today, radiation physicians and renal medical subspecialists often collaborate on renal transplant patients with secondary malignancies due to protracted immune suppression, however further collaborations will be needed as radiation oncologists provide more intervention for partial volume therapy for renal malignancies and other genito-urinary directed therapies which have impact on renal function. Optimizing function of residual renal parenchyma will be a collaborative effort as radiation oncologists titrate volume of therapy to target and renal subspecialists provide a strategy to maximize renal health. Figure 6 is an example of modern radiosurgery delivered to a target in the renal pelvis and liver on a simultaneous basis (17).

 

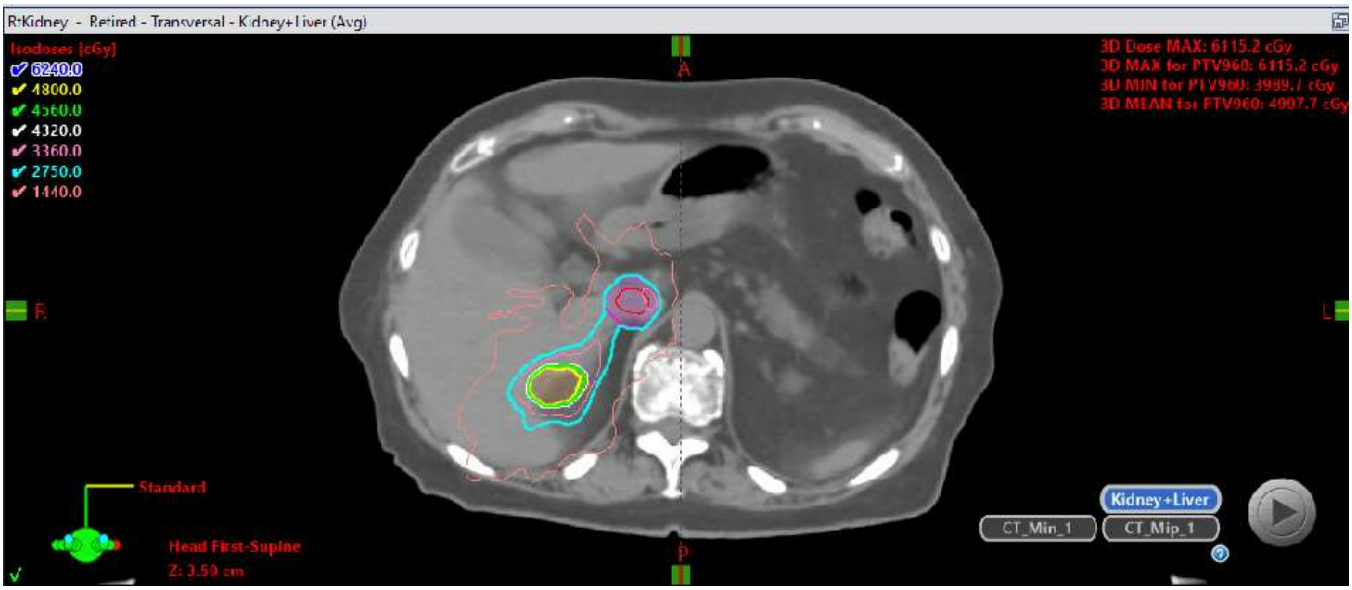


**Figure 6.** The figure reveals simultaneous treatment of a renal calyx primary lesion and a liver metastasis with the same plan

## Musculo-skeletal

It was originally thought that threshold for musculo-skeletal injury was associated only with high dose due to the limited self-renewal capacity of both bone and muscle, however advanced technology imaging is demonstrating injuries including insufficiency fractures to both weight and not weight bearing areas that have received radiation therapy to lower doses. This includes changes in the sacrum and other pelvis bone regions for patients treated for malignancies of the pelvis. In patients treated for gynecologic malignancies, radiation oncologists often treat lymph node regions in the pre-sacral region. Although modern image guidance has permitted dose gradients to be placed across the sacrum potentially limiting the risk of injury, more generous planning target volumes will place full dose across the structure. Figure 7 demonstrates an example of placing a dose gradient across the sacrum using a limited planning target volume compatible for modern image guidance.

 

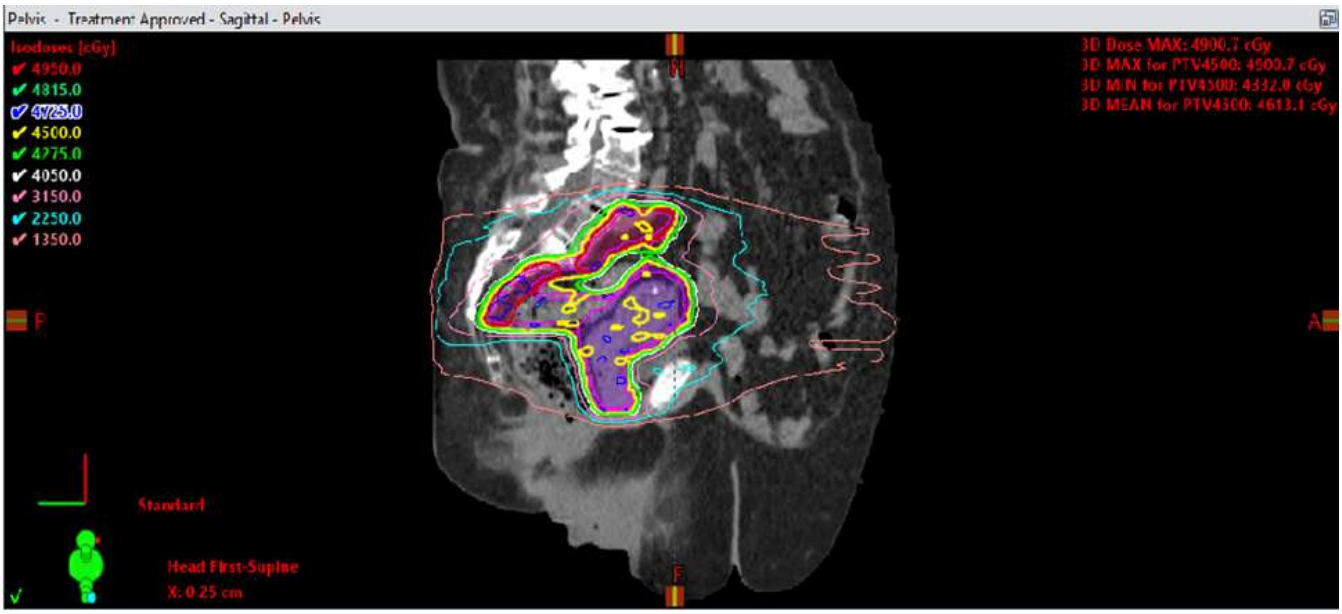


**Figure 7.** The figure demonstrates placement of radiation dose gradients across bone in pelvis treatment to limit risk of insufficiency fractures.

The pediatric population is especially vulnerable for effects to muscle and bone and this is an important element for late effects. This is a challenging issue for adult providers as often areas of therapy and strategies for risk prevention are conspicuous by absence. It will be the responsibility of the treating radiation oncologist to make this information available and visible in the electronic medical record for review. This is challenging as radiation oncology does not have a place identified at this time in most, if not all, electronic medical records. Creative problem solving will be required to correct this issue moving forward (18,19).

## Endocrine

This is an important and often overlooked aspect of patient care as symptoms can be non-specific and associated with alternate disease processes independent of their primary malignancy and therapy. Brain tumor patients can have deficiencies in pituitary function which can have impact in multiple important body function. The pituitary is a small structure, therefore often difficult to place a meaningful dose gradient across the structure, therefore often best approached by conformal avoidance techniques with modern therapy in a similar manner applied to the optic chiasm when appropriate. The thyroid gland is vulnerable to deficiency secondary to surgery and radiotherapy. Treatment of pelvic malignancies can influence ovarian and testicular function with replacement therapies applied when appropriate. Currently multiple providers apply segments of care for replacement therapies as deficiencies can be identified in nearly all organ systems if left unattended. Identifying areas at risk will help providers anticipate these issues and provide support before symptoms occur. These can be made available to practitioners with volumetric tools and dose volume histograms (2).

## Summary:

There are an increasing number of cancer survivors. It is estimated that more than 20% of a primary care physician panel by the year

 

2030 will be composed of cancer survivors, therefore providers must plan for this issue and prepare a wellness strategy for the cancer survivor. This should be coordinated with the providers of oncology care for risk assessment and colleagues in medical subspecialty practices to mitigate risk. This will require effort on the part of all practitioners to make this goal a reality. Patients currently feel a gap between their primary provider and medical oncologist for their post therapy care. There is an educational gap for the primary care physician and medical subspecialty physicians which can only be closed by oncologists for patient centered aftercare post therapy. To date, oncologists have placed practice emphasis on oncology management but need to recognize responsibility in generating a strategy for aftercare and be available for consultation as needed for advice and direction. Treatment leaves fingerprints of injury which may be initially subtle but become meaningful in later life. Addressing these points as part of a formal survivorship plan will optimize patient care, limit the medical and potentially legal risk of therapeutic injury, and compromised normal tissue function. The more the potential of injury can be anticipated, the less one will have to react if/when an injury occurs.

 

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