RESEARCH ARTICLE

Advanced Technology Radiation Therapy with Dose Painting: Opportunities for Outcome Improvement for Management of Lymphoma

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Abstract:

Radiation therapy remains important in the modern management of both Hodgkin and non-Hodgkin lymphoma. Radiation is applied as both consolidation therapy post chemotherapy and primary therapy for selected limited volume clinically favorable histology. Application of modern therapy techniques permits more sparing of normal tissue in all anatomical locations. Modern image guidance permits both security in daily patient treatment set up and permits strategic titration of the planning target volume to further spare normal tissue. Four-dimensional planning makes certain targets are fully treated in all phases of the breathing cycle. Dose painting with altered fractionation permits identification of low, intermediate, and high-risk areas of concern and treat each in a single plan with multiple fractionation schemes saving both time of treatment and cost of therapy. In this paper we present multiple examples of the application of modern therapy techniques in lymphoma management and demonstrate advantages of modern radiation in several anatomical regions.

Keywords: Radiation therapy, lymphoma, dose painting

Introduction:

Management of the modern lymphoma patient has become increasingly complex. Clinical biomarkers and expression products coupled with modern and targeted choices for systemic management have created new clinical pathways for patient care in all disease subtypes for Hodgkin and non-Hodgkin patients. This has led to the modern dilemma of revisiting how traditional therapies continue to be applied in these disease groups for the next generation of patients treated for this disease.

Radiation therapy has been an important cornerstone to the care of patients with lymphoma and continues to be a valued asset in the care of patients. Studies have shown that excluding radiation therapy in selected management situations can have a negative impact on tumor control. The balance in this discussion is the impact of therapy on normal tissue tolerance. As successful application of systemic treatments matured, the role of radiation therapy both as primary management and consolidation therapy is evolving. Recent studies have evaluated the impact of using response driven imaging to identify patients who might benefit from radiation therapy. However, some patients with good response on anatomical and metabolic imaging may not have a durable response when therapy is titrated.

It is important in the general oncology and the radiation oncology communities to demonstrate continuous process improvements in the care of patients. As more lymphoma patients survive their primary malignancy, outcomes will be measured both by tumor control and normal tissue function. Therefore, to maintain a pivotal central role in the care of patients, the radiation therapy community needs to continue to educate colleagues on modern radiation therapy including radiation therapy planning strategies and security in daily treatment execution with modern image guidance.

In this manuscript we describe multiple examples of complex management issues in patients with lymphoma and the application of modern radiation therapy to address the potential clinical challenges to patient care. The goal of modern radiation therapy is to secure the initial response to therapy, offer definitive therapy to appropriate patients, and provide safe and effective care to minimize risk of acute and long-term sequelae of management. In this manuscript we provide examples of how modern therapy can be safely applied and integrated with systemic management for clinical care (1-12). The goal of this paper is to demonstrate the process improvements in normal tissue sparing with modern radiation therapy to further promote the use of radiation therapy in the management of patients with lymphoma.

Methods and Materials:

The medical and radiation therapy records of selected patients were reviewed and presented. All patients remain well. The radiation therapy plans were each designed with advanced technology therapy including volume modulated arc intensity modulated therapy. Each case was re-planned with more traditional volumetric therapy in three dimensions and the primary normal tissue dose was compared between the plans to demonstrate process improvements modern therapy provides. Dose painting was applied in each case to targets of varied risk of failure in order to both limit dose to normal tissue and apply maximal dose as needed to tumor targets. Statistical comparison between the volume of normal tissue included in the therapy fields between historical traditional plans and advanced technology plans was conducted with a t-test.

Patient 1:

The patient was a 17-year-old female at the time of radiation therapy. At the age of 13, she developed Stage 2A supradiaphragmatic Hodgkin lymphoma with significant bulk. The patient received 2 cycles of chemotherapy with a good metabolic response to chemotherapy. She completed chemotherapy for definitive care. She was not referred for radiation therapy due in part to consideration of late effects. Four years later she relapsed with disease in original sites of bulk tumor. She had a modest response to second line chemotherapy and the decision was made to move forward with autologous bone marrow transplant. Residual mass was identified post-transplant that was metabolically negative. The patient was referred for radiation therapy. Figure 1 is the tumor burden at the time of initial failure in 2019.

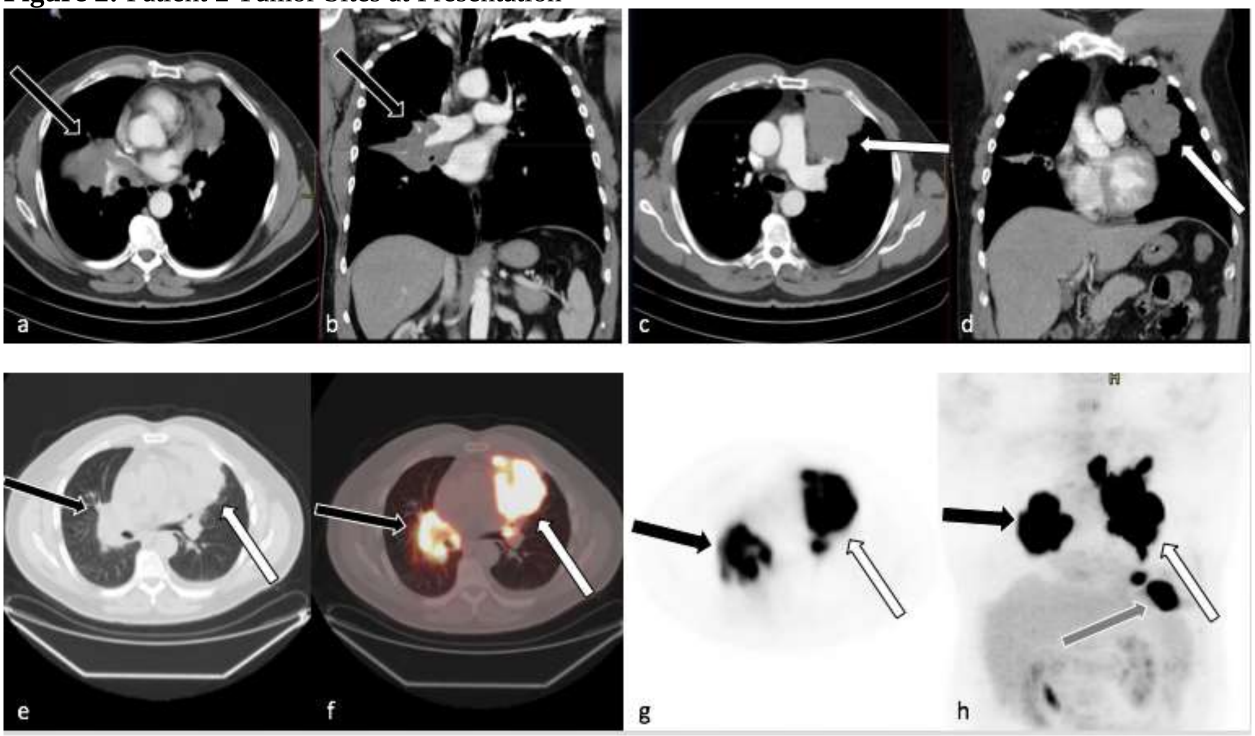
Figure 1: Patient 1 Tumor Sites at Malignancy Relapse

Coronal fusion (a) and maximum intensity projection (MIP) (b) from FDG PET/CT demonstrate a moderately to intensely FDG-avid mediastinal mass (white arrows) and right supraclavicular lymph nodes (black arrows).

Patient 2:

The patient was a 61-year-old male at the time of radiation therapy. He presented to providers with progressive shortness of breath and prominent mediastinal mass with a pericardial effusion. Disease involved the pericardium at presentation. Biopsy established a diagnosis of large cell B cell non-Hodgkin lymphoma, Stage 2 with bulk including pericardial and pleural effusions. He completed 6 cycles of chemotherapy and was referred for radiation therapy. Figure 2 is the tumor burden at the time of presentation.

Figure 2: Patient 2 Tumor Sites at Presentation

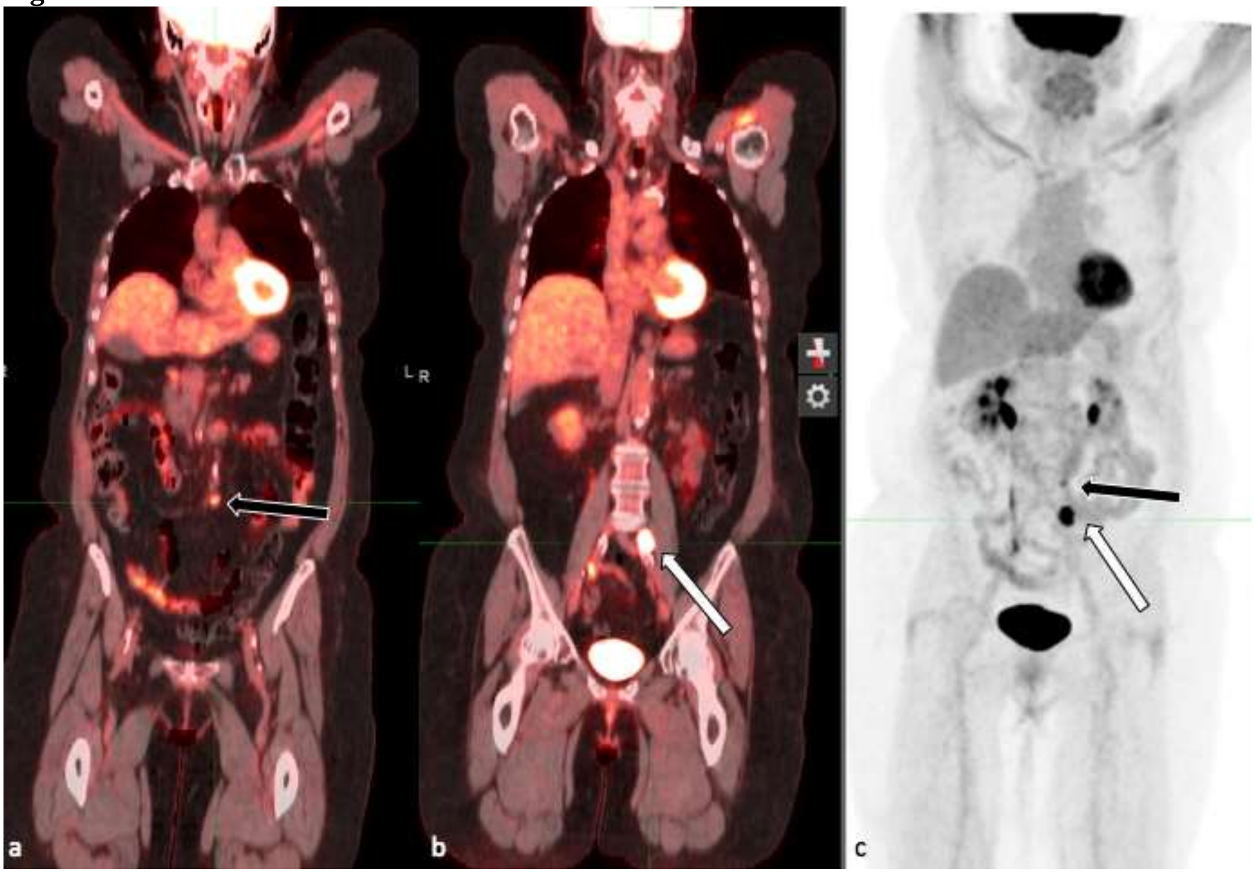


Axial (a, c, e) and coronal (b and d) contrast enhanced CT images demonstrate a mediastinal mass narrowing the right pulmonary artery (black arrows) which are FDG avid on axial fusion (f), axial PET (g), and MIP (h) images. A left upper lobe mass (white arrows) invades the pericardium with resultant pericardial effusion. Epiphrenic lymphadenopathy is also seen (gray arrow).

Patient 3:

The patient was a 76-year-old female at the time of radiation therapy. During an evaluation for an abdominal aortic aneurysm she was identified with limited volume para-aortic and common iliac adenopathy. Computer tomography biopsy with a limited tissue sample revealed a B cell malignant process best characterized as Hodgkin lymphoma. The patient had multiple medical co-morbidities precluding chemotherapy and the patient was referred for radiation therapy as primary management. Figure 3 is the tumor sites at the time of presentation.

Figure 3: Patient 3 Tumor Sites at Presentation

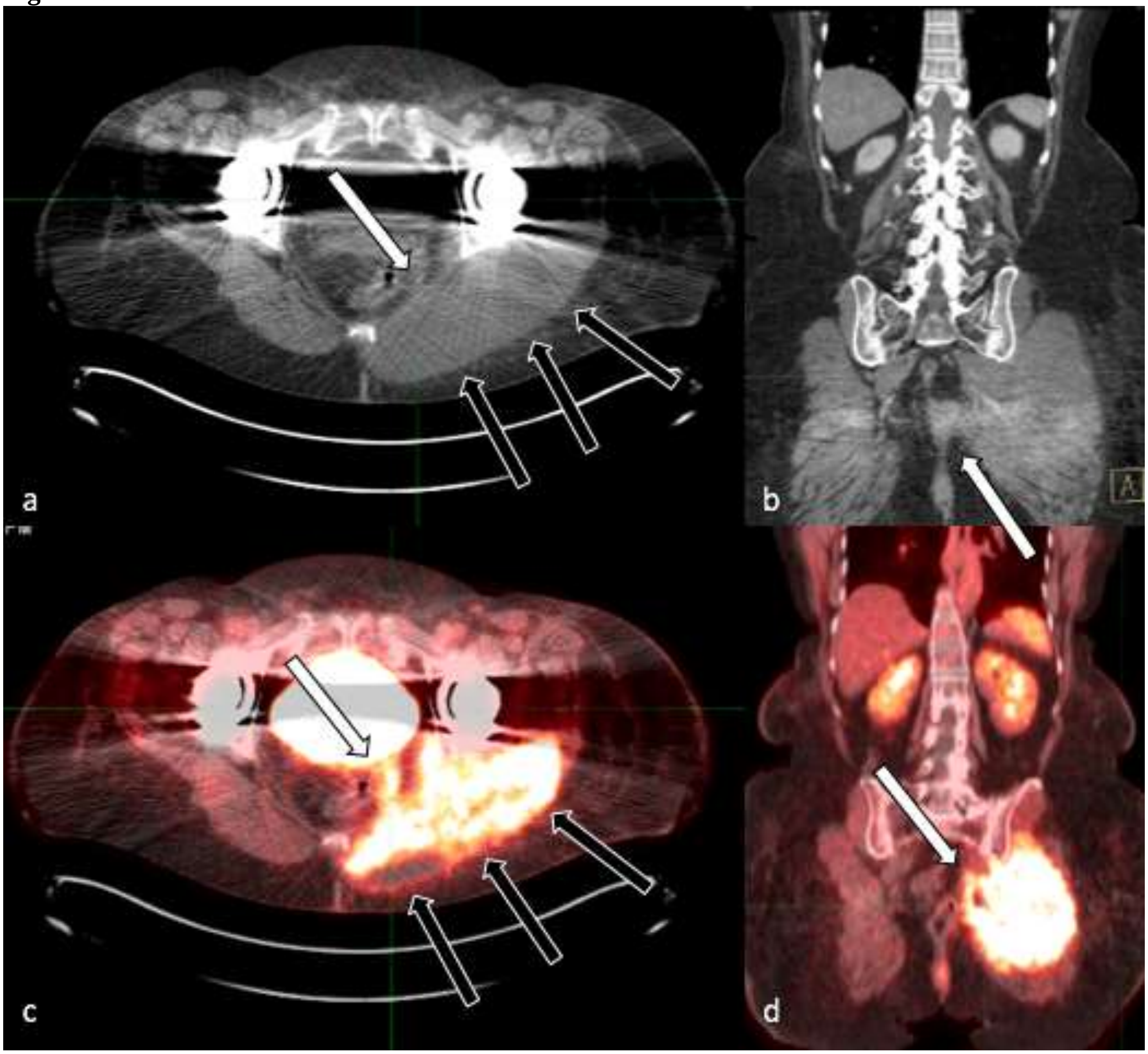


Coronal fusion (a and b) and MIP (c) demonstrate FDG-avid para-aortic (black arrows) and left common iliac (white arrows) lymphadenopathy.

Patient 4:

The patient was a 65-year-old female at the time of radiation therapy. The patient had bilateral hip replacement procedures. She had progressive pain in the left hemi-pelvis/gluteal region thought initially related to the left hip procedure, however imaging revealed a prominent mass occupying the majority of the left gluteus maximus region extending through soft tissue into the left hemi-pelvis abutting the rectum and involving tissues in the peri-rectal fat plane. Biopsy revealed large cell B cell lymphoma, double expressor. The patient had a good response to R-EPOCH chemotherapy and was referred for radiation therapy after stem cell collection pre-transplant. Figure 4 is the tumor burden at presentation.

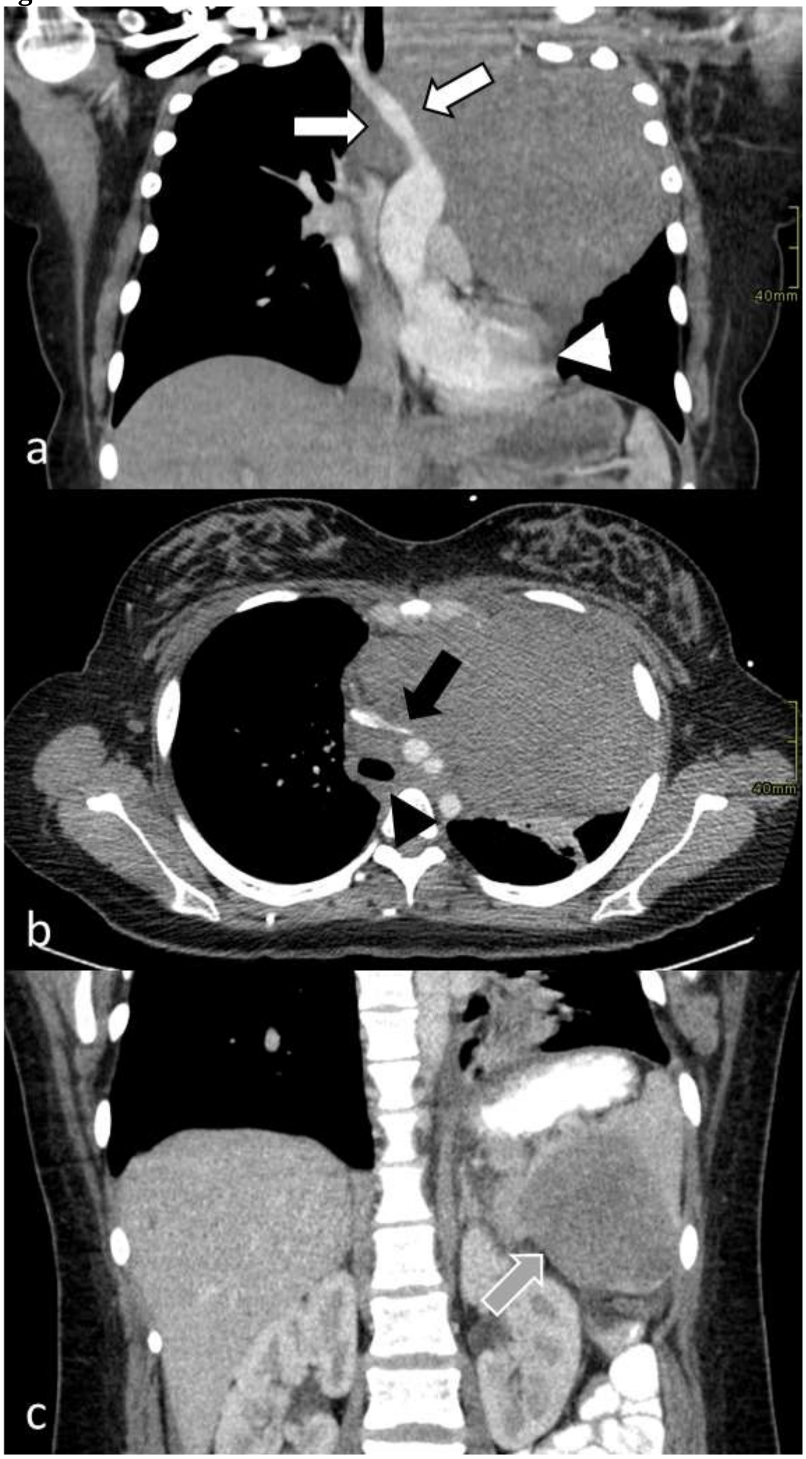
Figure 4: Patient 4 Tumor Sites at Presentation



Axial (a) and coronal (b) CT and fusion (c and d) images demonstrate intensely FDG-avid infiltrative left gluteals mass which extends into the left hemipelvis (black arrows), abutting the rectum and approaching the mesorectal fat plane (white arrows).

<u>Patient 5</u>:
The patient presented to emergency evaluation 30 weeks into her first pregnancy with a large left neck mass and significant mediastinal/paracardial adenopathy with a pericardial effusion. Her trachea was significantly deviated to the right. The infant was delivered via cesarian section and biopsy of the left neck mass confirmed Hodgkin lymphoma. The patient was transferred as an inpatient to the oncology service for initiation of chemotherapy. Figure 5 depicts the tumor burden at presentation.

Figure 5: Patient 5 Tumor Sites at Presentation



Coronal (a) and axial (b) images from contrast-enhanced chest CT demonstrate a large anterior mediastinal soft tissue mass measuring up to 20 cm which insinuates around the great vessels (white arrows) with resultant mass effect on the mediastinal structures including the heart (white arrowhead) and trachea (black arrowhead). The mass compresses and obliterates the left brachiocephalic vein (black arrow). Coronal image from contrast-enhanced abdominopelvic CT (c) also show a hypoenhancing lesion in the spleen (grey arrow), representing an additional site of lymphomatous involvement.

Results:

Patient 1:

The patient was referred to radiation oncology post-transplant. The modern challenge for relapse patients being treated with curative intent is to select a target volume of interest that accommodates the clinical situation. In this situation, disease since the time of primary diagnosis was located above the diaphragm however including all sites of original disease without strategic application of radiation therapy would result in significant compromise of cardiac and pulmonary tissue. Decision was made to include all original sites of disease but segment and augment both daily and total dose to the areas identified on metabolic imaging as positive at the time of failure and further augment dose to residual areas of concern post-transplant. This required three separate volumes of therapy in a single radiation therapy plan. Dose painting with volume modulated arc therapy was applied to each site with increasing fractionation to sites requiring higher dose as part of a single plan of therapy. This enabled decreased dose to critical normal tissue structures with treatment delivered in minutes using four-dimensional planning validated by optical tracking. The plan and application of dose is demonstrated in figure 6 and the difference in dose delivered to the heart and lung is shown in table 1 with P value <0.05.

Table 1: Organ Mean Dose in % of Rx

Plan Type	Heart	Lungs
AP/PA	37.1	40.1
VMAT	24.9	25.6

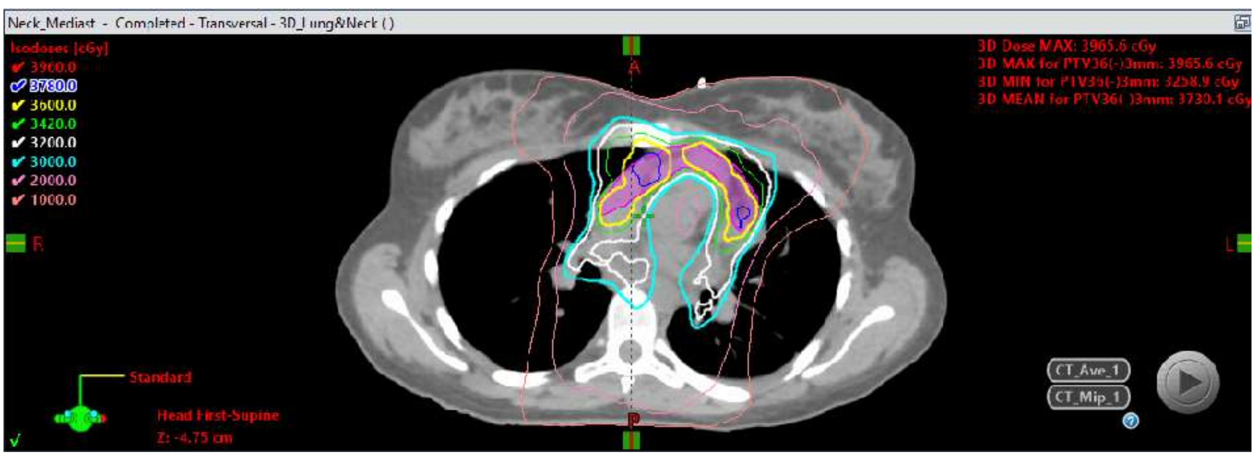


Figure 6: Radiation plan for cardiac avoidance patient 1

Patient 2:

The patient was referred to radiation oncology after completing 6 cycles of R-EPOCH chemotherapy with resolution of metabolic disease. There was residual mass in the mediastinum seen on anatomical imaging. The challenge in targeting was to treat areas of original metabolic tumor involvement including the residual mass seen on anatomic imaging with appropriate dose constraints applied to cardio-pulmonary tissue. In this circumstance, three dose platforms were applied to the target volumes with lower daily and total dose delivered to pericardium and augmented dose to areas of original disease in the mediastinum and residual mass in the thorax. The dose plan is depicted in figure 7 and table 2 represents the volume of heart lung treated in both the executed plan and a traditional anterior-posterior plan with P value <0.05.

Table 2: Organ Mean Dose in % of Rx

Plan Type	Heart	Lungs
AP/PA	78.0	49.9
VMAT	39.1	27.5

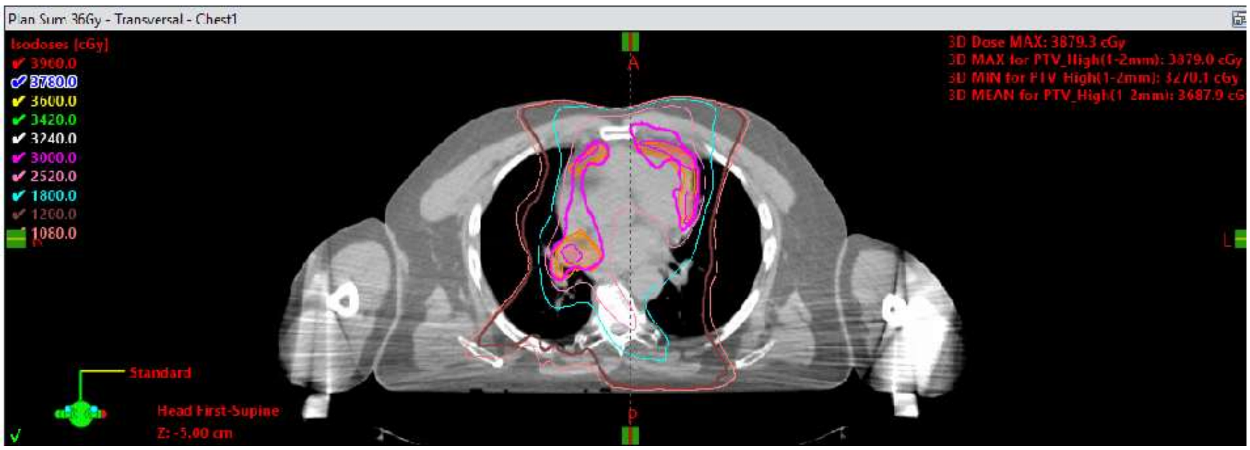


Figure 7: Radiation plan for cardiac avoidance patient 2

<u>Patient 3</u>:

The patient was referred to radiation oncology for definitive care due to medical co-morbidities. As radiation would be her only therapy modality, decision was made to treat with two target volumes of intermediate and high risk in a single radiation therapy treatment plan using two different daily and total doses to the targets. The plan is shown in figure 8 and table 3 depicts the difference in dose and volume to small bowel with traditional an anterior-posterior plan and the plan with VMAT, P value < 0.05

Table 3: Organ Mean Dose in % of Rx

Plan Type	Bladder	Bowel
AP/PA	13.9	47.6
VMAT	7.4	34.5

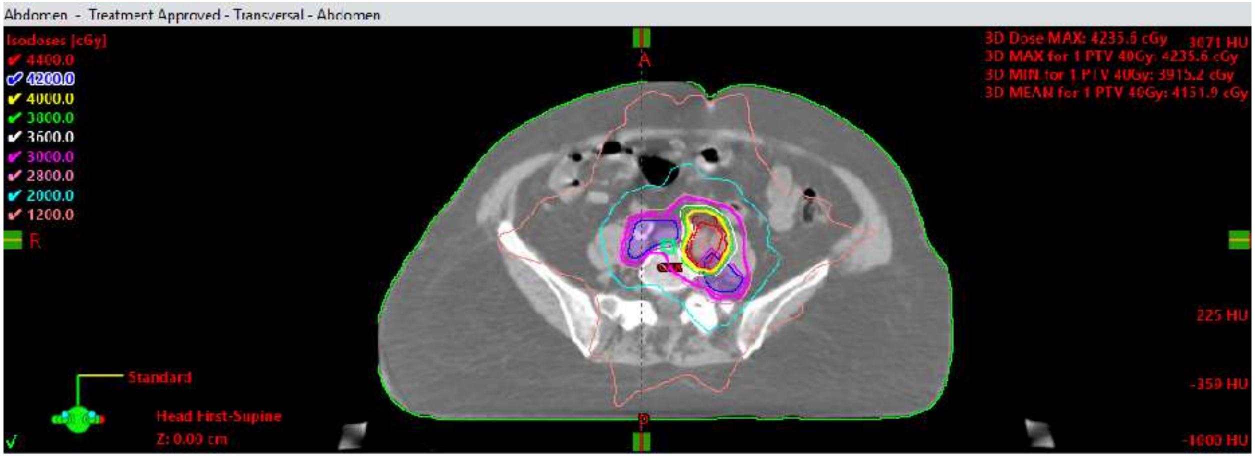


Figure 8: Radiation plan for patient 3 for bowel/bladder avoidance

<u>Patient 4</u>:

The patient presented for radiation therapy after completing chemotherapy for double expressor (BCL-2/C-myc). Tumor involved the gluteus maximus with extension into the left hemi-pelvis. A single plan was designed to treat a high dose volume to the region of residual mass seen on anatomical imaging metabolically negative, an intermediate volume of disease at presentation, and an area considered low risk in the left inguinal femoral region metabolically equivocal at presentation and of indeterminate significance. The plan is presents in figure 9 and table 4 depicts the volume of small bowel, bladder and rectum that would be include in a traditional anterior-posterior plan and a VMAT plan, P value for each normal tissue volume is < 0.05.

Table 4: Organ Mean Dose in % of Rx

Plan Type	Bladder	Rectum	Bowel
AP/PA	100.4	100.2	59.0
VMAT	54.5	65.2	32.3

Figure 9: Radiation plan for bowel avoidance patient

Patient 5:
After completion of chemotherapy, the patient had residual mediastinal mass and given the volume of her initial disease, consolidation radiation therapy was delivered. Areas of low, intermediate, and high risk were identified and contoured. The plan is depicted in figure 10 and table 5 represents the difference in normal tissue dose between traditional AP-PA plan and dose painting with P value < 0.05.

Table 5: Organ Mean Dose in % of Rx

Plan Type	Heart	Lungs
AP/PA	97.2	44.7
VMAT	31.8	28.4

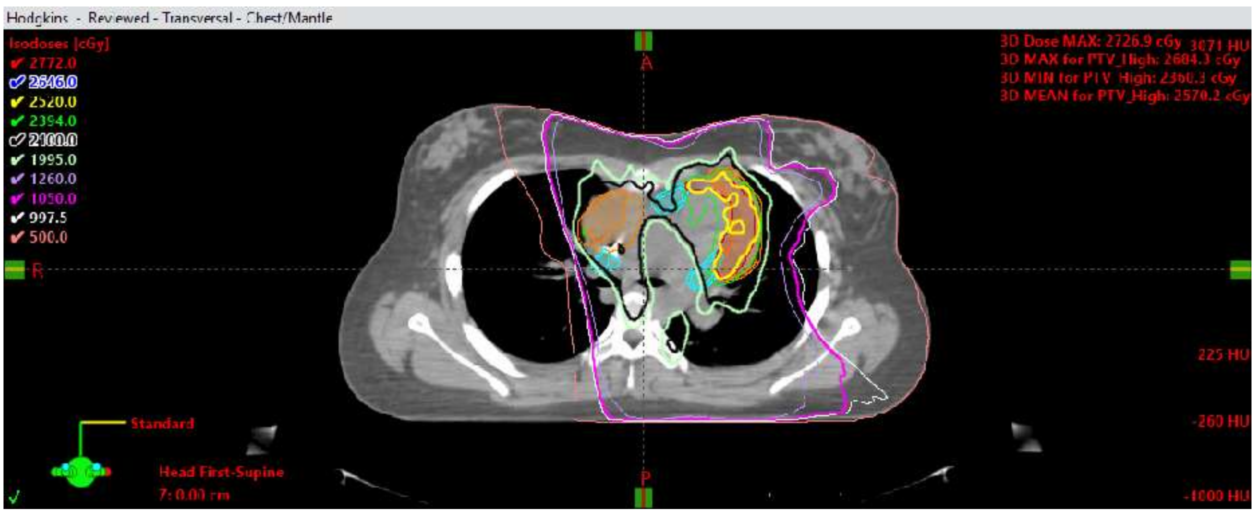


Figure 10: Radiation plan for cardiac avoidance patient 5

Discussion:
Despite continued development and process improvements in systemic, targeted, and biologic therapy for lymphoma management, radiation therapy remains an important component for patient care for consolidation management and primary therapy when appropriate. There are multiple aspects of advanced technology radiation therapy which are important for the management of the modern lymphoma patient.
Volume modulated arc therapy permits treatment to be delivered with intensity modulation while the therapy gantry is moving in rotation. This limits the time of treatment delivery indirectly providing stability in daily positioning by limiting time of therapy. It also permits nimble application of differential dosing to targets defined with risk coefficients in order to treat areas of targets to various doses as part of a single radiation therapy plan, thus saving both time and cost in the delivery of therapy. Lymphoma lends itself to this approach as daily dose fractionation can be applied in a differential manner, unlike most patients with epithelial disease. Planning is done in four dimensions insuring appropriate coverage of the target during all phases of the breathing cycle. Optical tracking systems applied during each treatment insure daily positioning. These process improvements have made a significant difference in the practice of radiation oncology for all patients, however, have become invaluable in the management of lymphoma as medical

oncologists have become more secure in the referral of patients to the radiation service due in large part to applied advanced technology.

The most important aspect to modern planning is the security in defining not only dose to tumor but also dose to normal tissue structures. Dose to normal tissue can now be both defined and modulated by careful planning. Anatomical subsegments can be defined in normal tissue volumes including cardiac chambers, valves, coronary arteries, lung volume etc and these can be displayed to primary care and subspecialty physicians for survivorship care. Therapy modulation with strategic application of dose painting permits normal tissue dose titration with delivery of appropriate dose of tumor targets defined by risk (13-21).

Each patient had benefit from the application of modern therapy both to homogeneous dose to tumor targets and titration of dose to normal tissue. This is important as an increasing number of lymphoma patients achieve both cure and durable response to modern therapy, therefore it is incumbent on the radiation therapy community to optimize care and limit both risk and impact of radiation treatment on normal tissue. Modern therapy has an opportunity to redefine the perception of radiation therapy in this patient population and continued education of providers will insure the continued position of radiation oncology in this disease group.

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