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CASE REPORT

Yttrium-90 Hepatic Therapy and the Increasing Role of Volumetric Voxel-based Post Therapy Dosimetry: A Case Report

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Abstract

Yttrium-90 (Y-90) therapy has become an important component to the care of patients with primary hepatic malignancies and lesions that have metastasized to the liver. Therapy is administered through an intra-arterial procedure after an interventional procedure is performed using an albumin labeled product to ensure therapy will be delivered to the target volume of interest with minimal migration from the target of choice. In the past, dose to target has been measured by activity delivered and qualitative deposition of dose on metabolic imaging post application. Imaging tools such as single positron emission computer tomography (SPECT) and digital positron emission tomography have given us insight into quantitative dose to volumetric tumor target and dose to normal tissue. Recent validation of computational software has provided voxel-based dosimetry similar to applied processes established in radiation oncology planning systems. This development presents an opportunity to create dose volume analysis similar to teletherapy and brachytherapy dose delivery for Y-90 therapy. In this case report, we review Y-90 dosimetry on a patient with dual diagnosis of a locally advanced high-risk adenocarcinoma of the prostate which required treatment to the para-aortic lymph nodes located in the same axial plane with renal parenchyma. Although not clinically anticipated, hepatocellular carcinoma was serendipitously discovered at the time of staging for prostate cancer. Treatment dosimetry of the hepatocellular carcinoma is reviewed in retrospect with voxel-based commercial software. Same day SPECT study suggested dose localized to the liver, however voxel planning software confirmed unintentional dose to additional structures including the right kidney and uninvolved liver which influenced radiation therapy treatment planning for prostate carcinoma. With modern available tools, post therapy dosimetry for Y-90 can be performed in a manner similar to volumetric dosimetry used in radiation oncology and provide valuable dose volume analysis of dose delivered to target and additional tissue.

Keywords: Hepatocellular carcinoma, Radiation therapy, Y-90, Radiology, Theranostics

Introduction

Hepatocellular carcinoma (HCC) has become an important worldwide medical disease with increasing incidence.[1-6] Methods of therapy require multidisciplinary interactions among disciplines including transplant surgery, medical oncology, gastroenterology/ hepatology, nuclear medicine, radiology, interventional radiology, pathology, radiation oncology, and supportive care. The care of these patients is highly complex and requires longitudinal participation by all disciplines to optimize treatment and long-term care.[7-14] Often therapies are designed as a bridge to transplant in those medically appropriate. Systemic therapy including targeted treatment in this disease is maturing, however local tumor control remains a primary challenge. Intra-arterial infusion of Y-90 has been successful in treating the disease.[15-22] It requires experienced clinical expertise for colleagues in interventional radiology and nuclear medicine. A mapping procedure is performed before consideration for treatment. This is generally performed by interventional radiology and nuclear medicine to evaluate the potential percent shunting of applied therapy to pulmonary parenchyma. Computational metrics established by the mapping procedure for shunting/delivery of therapy are reviewed for treatment feasibility and patient safety. The procedure defines the vascular anatomy of the tumor and potential approach to care with Y-90. Skilled interventional radiologists and nuclear medicine colleagues are invaluable for successful application and dose delivery. Interventional radiology defines goals for care for dose delivery and volume to be treated. Once the procedure is performed, imaging, including single positron emission computer tomography, is performed to evaluate location of dose.[23-34] Moving forward, additional studies will be integrated with single positron emission computer tomography (SPECT) to apply volumetric dosimetry to the application. Additional therapies, including systemic therapy and stereotactic body radiation therapy (SBRT), can be considered based on response imaging reviewed in a multidisciplinary conference as it is known Y-90 can, on occasion, migrate to additional areas in hepatic parenchyma based on internal tumor anatomy not always well characterized on mapping imaging.[20,21]

In the past several years, theranostics has matured as a therapeutic discipline including Y-90 with multiple therapies expected to move to enterprise function in several disease areas in the near future. One of the historical and current challenges for theranostics has been the need for accurate volumetric computational dosimetry to measure dose delivery to target and unintentional dose to unanticipated additional regions post therapy. Dose to normal tissue is pre-determined by treatment planning in radiation oncology and dose volume metrics to normal tissue can be defined as constraints pre therapy which need to be met for regulatory compliance. This is difficult to characterize pre-delivery for theranostics. This issue was recognized, and effort was designed to develop voxel-based dosimetry processes

to calculate dose to target in closer alignment with computational dose volume processes established in radiation oncology.[32,34-36] There is a need to align therapy computational programs between the disciplines involved in therapeutic radiation and provide appropriate guidance for defining the potential of toxicity from therapy in a similar manner established in radiation oncology. Because systemic radiotherapy can potentially impact tumor and normal tissue dose similar to teletherapy and brachytherapy, the working impression is computational algorithms require as much integration as possible for composite planning. With the groundwork for dose volume analysis of theranostics developed, commercial software computational algorithms are now available to evaluate dose to volume and create dose volume histograms (DVHs) for tumor volume and normal tissue volume coverage similar to processes established in radiation oncology.[35,36] The process requires fusion of images and image objects in radiation oncology treatment planning systems with dose volume histograms being developed after contouring of tumor volumes and normal tissue structures. Processes are maturing due to the recognition by several investigators concerning dose wash out and the need for serial metabolic imaging to improve accuracy of dose with more precision, however the infrastructure is now established to initiate the evaluation and determine dose received to target and unintended dose to normal tissue volumes. In this report, we review a patient with dual diagnosis of hepatocellular carcinoma and high-risk adenocarcinoma of the prostate with both diseases identified at the same time point and how Y 90 influenced renal dose to both the size and location of the hepatocellular carcinoma.

Case Report

The patient is a 78-year-old male who was identified with an elevation in prostate-specific antigen (PSA) corrected on therapy to 8.9 secondary to medication. Physical exam suggested an enlarged prostate and subsequent magnetic resonance imaging revealed an enlarged gland at 98 ml and a Prostate Imaging Reporting and Data System (PI-RADS) 5 lesion measuring 1.6 cm in the right mid lobe extending towards the apex without seminal vesicle involvement or extracapsular spread of disease. Biopsies confirmed two areas of Gleason grade 8 disease in the PI-RADS 5 region with Gleason 7 (4+3) disease in the right lateral mid gland region and Gleason 6 disease (3+3) in the right mid medial region, left apex, and left lateral base. Staging included computer tomography which revealed adenopathy consistent with disease in the right common iliac and retrocaval regions with the superior disease in close approximation to the axial plane of the right and left kidney. The study also revealed a 12 cm by 11 cm lesion in the liver with epicenter at levels 5, 6, and 7 (Figure 1A). Biopsy of the lesion revealed a well differentiated HCC with biomarkers consistent with the primary diagnosis. No additional sites of disease of either malignancy were identified, and the patient had no elevation in liver enzymes or bilirubin with renal function within normal limits. Decision was made by all

involved practitioners from both the hepatic and genitourinary clinic teams to prioritize therapy to the HCC and treat the prostate cancer with hormonal therapy until control of the disease process for the HCC could be established.

Hormone therapy (Lupron) was administered by medical oncology (KM) and attention was given to Y-90 therapy to the hepatic lesion by interventional radiology and nuclear medicine colleagues (HM and RL). After a mapping study which revealed 2.4% pulmonary shunting, Y-90 therapy was delivered in 8/2021 with 134.1 millicurie (mCi) delivered in two segments (anterior/posterior) and SPECT study was performed on the same day to confirm location of dose in the liver with computer tomography performed which served as a platform for retrospective calculations of dose to target and tissue. Follow up computer tomography study was performed in 11/2021 and there was concern for residual disease, particularly at the perimeter of the lesion (Figure 1B). In 2/2022, a second Y-90 application was performed after mapping revealed 9% pulmonary shunting. One hundred fifty-five (155) mCi was administered in three segments to include areas of concern at the perimeter. A SPECT scan was again performed on the same day to confirm location of dose (Figures 2 and 3). For this application, a computer tomography study was also performed with the SPECT study which in retrospect facilitated construction of voxel dosimetry for the application. In June of 2022, patient was re-referred to radiation oncology for consideration of definitive radiation management for prostate carcinoma. Because limited volume disease involved regional and para-aortic lymph nodes, a more extended volume plan than norm was needed for optimal care. Radiation oncology planning computer tomography included the entire liver to integrate Y-90 dosimetry into care plan of the patient for evaluation of composite dosimetry. The software for computational analytics for the department of radiation oncology at our institution is Eclipse (Varian, Palo Alto, Ca), and is fully integrated for Y-90 dosimetry computation. The radiation oncology treatment planning study included the full abdomen and pelvis in order to fuse the SPECT and computer tomography studies into the radiation therapy planning study and compute dose to the liver tumor and adjacent normal tissues structures to provide conformal avoidance and limit risk of overlap or additional dose to normal tissue structures using intensity modulation coupled with motion management and daily image guidance for prostate cancer management. In order to establish dose comparison between therapies, computations were performed using the linear quadratic formula defining the equivalent total dose in 2 Gy fractions (EQD2) which is the accepted standard in radiation oncology comparing therapies of varied dose and dose rate.

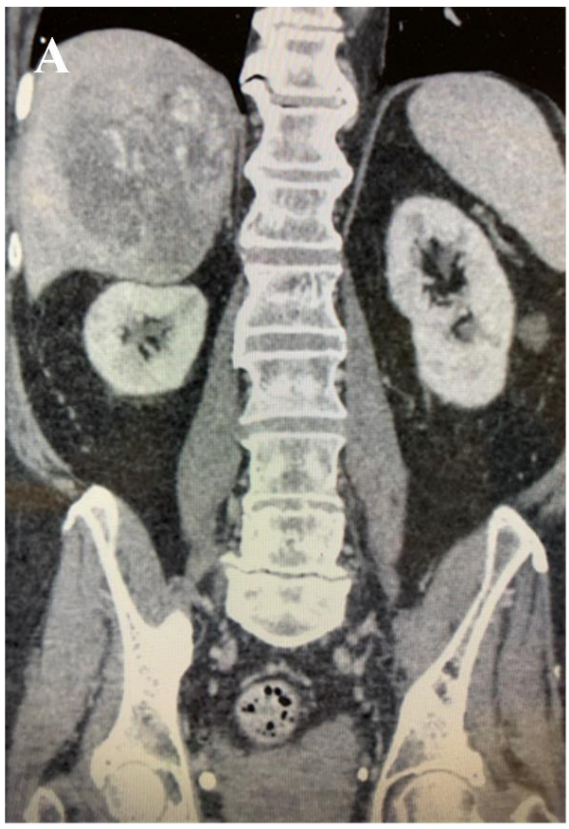

Figure 1A. Hepatocellular carcinoma at presentation.

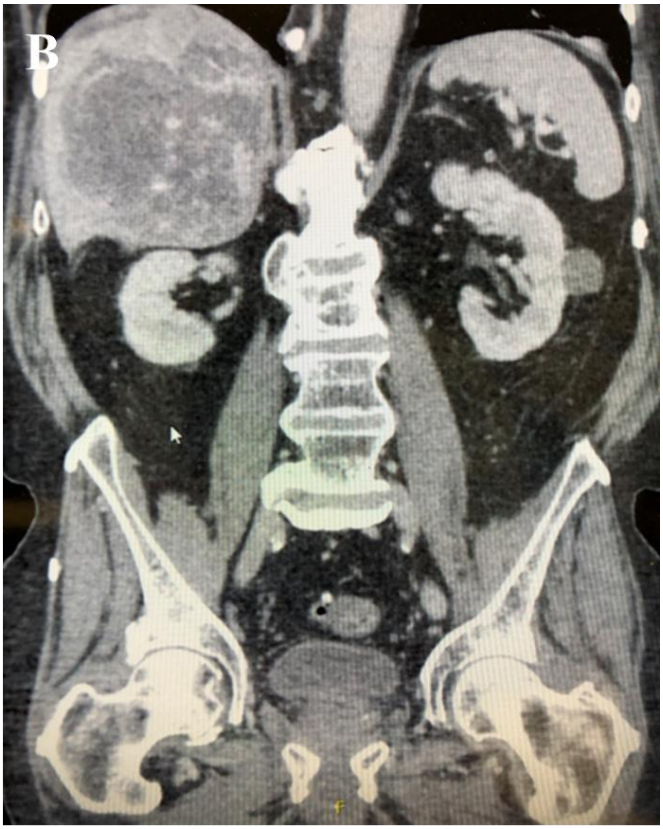

Figure 1B. Coronal view of CT likely residual disease HCC after first Y-90 therapy.

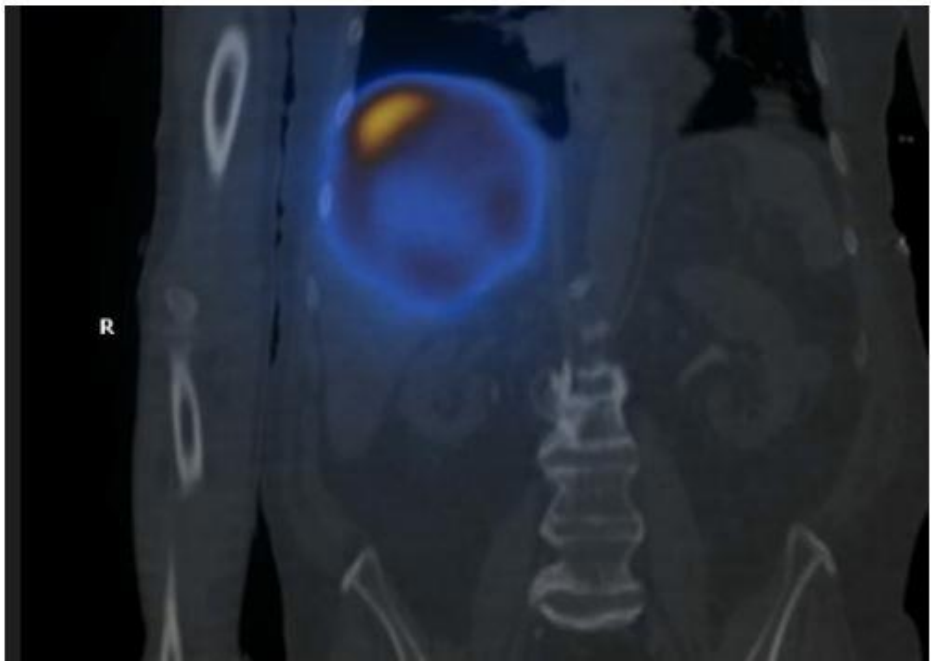

Figure 2. Coronal SPECT Post Initial Y-90 therapy

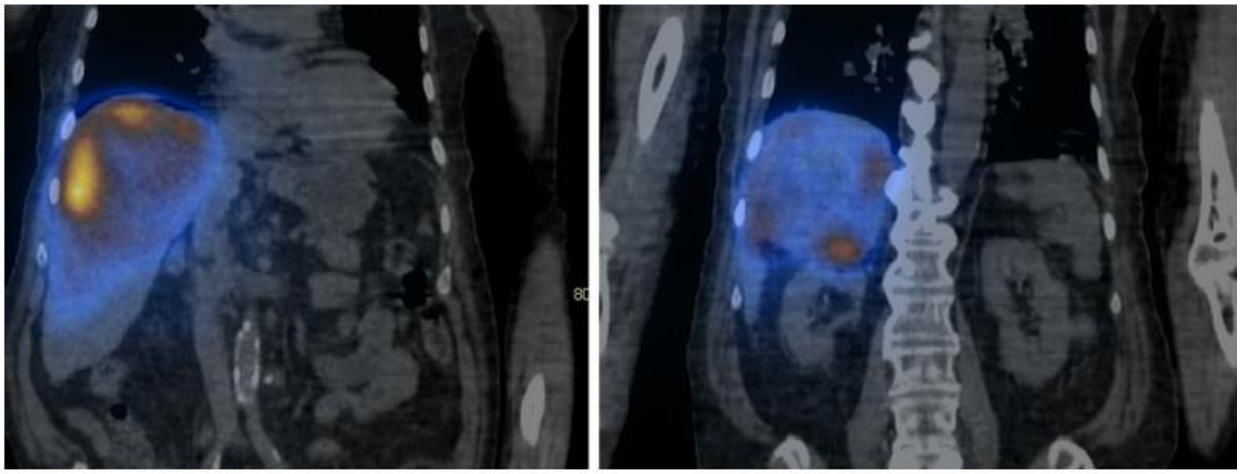

Figure 3. Coronal SPECT Post Second-Y-90 therapy

Findings

Computations of both Y-90 applications were completed and fused into the treatment planning study for delivery of volume modulated arc radiation therapy (VMAT) to the prostate and nodal regions including nodal volumes considered positive at presentation. The anatomy of the hepatic and prostate tumors and normal tissue was contoured per department standard. Dose to contoured tumor, remaining liver minus the CTV, and kidney from the Y-90 applications were calculated with generation of dose to targets in all three planes (Figure 4 A/B) as well as dose volume histograms (Figure 5).

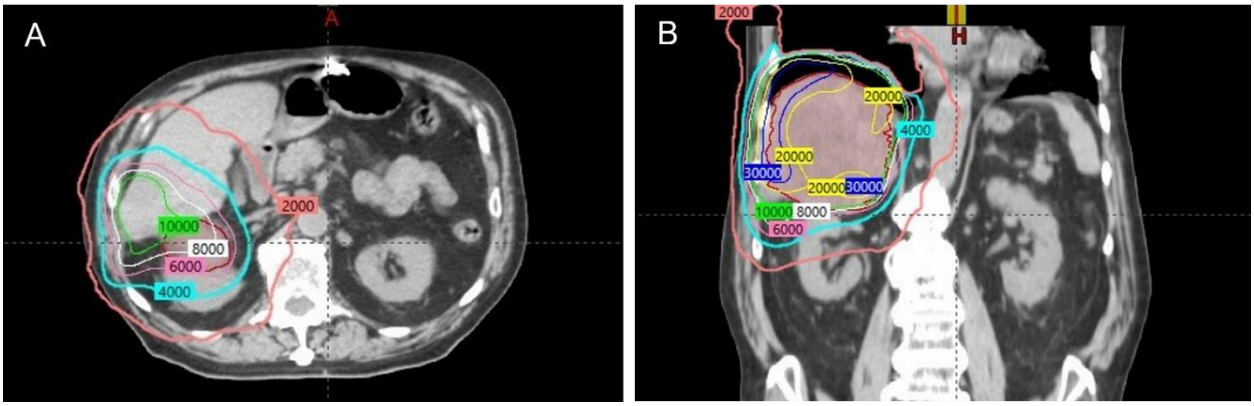

Figure 4A/B. Combined dosimetry from both Y-90 applications.

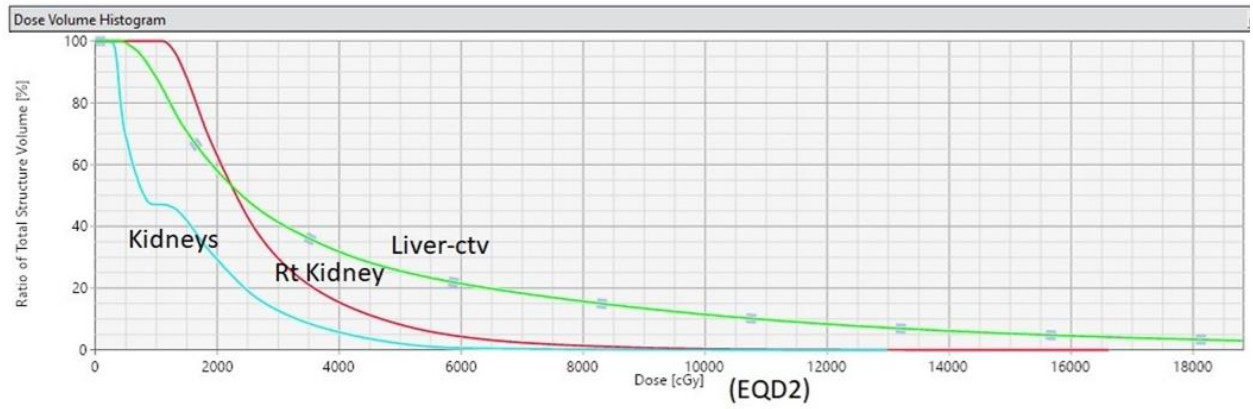

Figure 5. DVH of Normal liver (Liver minus clinical tumor volume) and R/L kidney
Right kidney: V20=62.4%; Mean liver-CTV=4507 cGy;
Y90 injection: 8/2021: 134 mCi; 2/2022: 155 mCi

Dose to tumor and normal tissues can be seen in Figure 4A/B in coronal and axial planes. The location of the target with epicenter in hepatic segments 5, 6, and 7 influenced Y-90 delivered dose to the right kidney and other structures less visible on the SPECT study. The ceiling for renal tolerance is considered to be 20 Gy and likely less with the addition of nephrotoxic systemic therapy and pre-existing renal dysfunction. As can be seen from the dose volume histogram, 62.4% of the right kidney received dose at or greater than 20 Gy from the Y-90 applications. Thirty percent of the combined right and left renal volume received 20 Gy. As can be seen in Figure 5, 40% of the liver minus tumor clinical tumor volume (contoured as normal liver) received 30 Gy and 20% received 60 Gy accounting for the mean liver dose. The mean liver minus clinical tumor volume dose is slightly greater than 45 Gy. For comparison, when applying stereotactic radiosurgery to the liver, department constraints for hepatic mean liver dose for Childs-Pugh A, B, and C are 13 Gy, 9 Gy, and 6 Gy respectively with mean normal parenchymal volume receiving 15 Gy or less > 700 cc. Even for accounting for therapeutic variance in dose rate and radiobiological equivalence, dose to remaining normal liver with Y-90 is significant in this patient and biologically meaningful.

Discussion

Although not anticipated on SPECT studies performed on the same day as the Y-90 applications, post Y-90 dosimetry using voxel-based software revealed that significant radiation dose was delivered to hepatic parenchyma minus the clinical target volume and the right kidney. This is important for both radiation therapy teletherapy planning and downstream general oncology patient care as many systemic therapies have hepatic and renal toxicities which are further influenced by previous cancer therapy and medical co-morbidities. Knowledge of this information provides an opportunity to tailor additional therapy and potentially limit risk of further

injury to tissue receiving unintentional dose from directed therapy to the liver lesion.

The patient has completed radiation therapy without incident with highly favorable PSA (< 0.02) and follow up magnetic resonance imaging of the liver revealed findings consistent with therapy effect with normal liver function tests. The computational evaluation of Y-90 dosimetry was completed in parallel to the development of the radiation therapy treatment plan, therefore the teletherapy radiation plan assigned strict hepatic and renal constraints to limit risk of toxicity and used volume modulated arc geometry to further limit dose to bowel and what was defined as normal liver without visible disease. Because the radiobiological effect co-efficient between external therapy and Y-90 is not known, comparing dose between therapies is not established nor known with certainty. Nevertheless, for teletherapy planning for prostate carcinoma treatment in this patient with high-risk features and need for extended volume care, assigning strict constraints to kidney, liver, and bowel would place additional dose and risk to tissues such as the conus and cauda. Therefore, VMAT was adjusted relative to dose from Y-90 to address this point and limit dose from teletherapy to these structures. The integrated treatment plan was able to limit potential of acute and long-term normal tissue injury risk as this patient required treatment with multi-modality radiation therapy secondary to the established diagnosis of two simultaneous malignancies. The availability of the voxel-based dosimetry treatment planning process invited an opportunity to adjust therapy with decreasing overlap, potentially providing for an improved outcome by decreasing the risk for late effects to tissues of limited self-renewal potential including liver, kidney, and bowel. Moving forward, integration of the strengths of each treatment delivery system may optimize care without additional risk of acute or late injury. Modern dosimetry tools provide insight into what dose was absorbed by tissue. Historically, treatment programs involving radiophramacy could only be measured by the administered dose, not the absorbed dose. Modern dosimetry tools may change how dose is prescribed and how it is measured. This will be essential for clinical trials moving forward as voxel dosimetry will permit evaluation of applications between institutions and find common ground in dose applied to both tumor and normal tissue. With collection of images both pre and post therapy, metrics for both treatment efficacy and normal tissue injury can be established and vetted to outcome.

Y-90 is a powerful tool as exceptionally high dose radiation therapy can be selectively delivered to a target. The challenge for intra-arterial therapy is unintentional dose to targets and the potential of dose migration to non-disease sites of hepatic parenchyma due to tumor vascular anatomy and areas of cellular necrosis. Stereotactic therapy can optimize dose to normal tissue and dose painting can be assigned to high-risk tumor targets defined by radiomics, however motion may influence successful application of stereotactic therapy and must be carefully

managed with cone beam computer tomography, fiducial placement, and optical tracking. Accurate computation of radiobiological effectiveness (RBE) of each delivery system remains to be defined. Further improvements with accelerated dose rate delivery systems with flattening filter free technology and ultra-high dose rate (FLASH) systems may also influence choice of therapy and further re-define RBE moving forward. In challenging situations such as this patient, both Y-90 and stereotactic therapies can be applied in sequence with strategy. SBRT offers confidence that the intended radiation dose to target, and dose delivered can be executed in alignment with the treatment plan with dose to normal tissue pre-determined by accurate radiation therapy planning. Y-90 can "boost" and supplement therapy to high-risk areas potentially less achievable with SBRT dose painting assuming accurate mapping and delivery of dose to the target. In turn, SBRT can supplement Y-90 therapy by adding dose in a strategic manner to areas less well treated by Y-90 due to anatomical constraints. The therapies are not mutually exclusive and can be designed to optimize dose to tumor and normal tissue in challenging situations.

The case provides an opportunity to further optimize care moving forward. As tools for voxel-based volumetric dosimetry are now commercially available, developing both a protocol-driven and institutionally focused quality assurance program for theranostics and treatment delivery is now available and can be built with confidence for clinical trials and institutional application of radiopharmacy. At national and international level, the Imaging and Radiation Oncology Core (IROC) has responsibility of managing imaging and radiation oncology quality assurance programs for the National Clinical Trials Network (NCTN-TJF). IROC writes guidelines for imaging and radiation oncology into each NCTN trial and will soon establish guidelines for clinical trials involving theranostics including credentialing for institutions to participate in developing hepatic radiotherapy trials and trials involving systemic radiotherapy. As disease incidence increases including supplemental upfront radiation therapy care for patients with oligometastatic disease, there is a need to move treatment programs forward in a thoughtful and deliberate manner to optimize care, manage toxicity, and optimize dose volume normal tissue constraints for the written directive. Each form of therapy provides strength and protocols for care plans can mature with data management programs in place to optimize treatment and analyze outcome.

The development of computational dosimetry tools for theranostics will have a long-standing impact on clinical trial development and patient care. Although there is historical experience in systemic radiation therapy delivery strategies for Iodine-131 (I-131) and Radium-223 (Ra-223), the assessment of these systems and impact of dose to target with modern dosimetry can now be re-visited and a more comprehensive management strategy can be applied with added with certainty as dose to volume is calculated with accuracy including total body and unintended dose targets not anticipated at the time of

administration. This is important in order to define dose absorbed and the unintended downstream consequence of dose to normal tissue. This will improve the approach to treatment as the advantages of both infusional therapy and stereotactic therapy can be applied and compared to outcome as additional programs with Lutetium (Lu-177) mature. Our understanding of radiomics will mature as dose-to-image findings can be reviewed in follow-up image sets and an improved assessment of disease and treatment effect can be established. This will be essential moving forward as our understanding of treatment effect in liver is currently limited and will also provide a better understanding of distinguishing treatment effect from disease progression. Similar to follow-up imaging for SBRT to pulmonary targets, treatment effect can mimic disease which is why follow-up imaging needs to be part of protocol management and outcome assessment and viewed through the prism of the therapy plan to assess disease status. Voxel-based dosimetry will support this analysis and other important research pathways exceptionally well and patient care will improve.

Conclusion

The future of patient care is improving with the addition of theranostic tools. Now that computational dosimetry is available, departments of radiation oncology and radiology can apply strengths of service to optimize and improve patient care.

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Conflict of Interest:
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