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CASE REPORT

Yttrium-90 Hepatic Therapy and the Importance of Volumetric Voxel-Based Post Therapy Dosimetry: A Case Report on Renal Radiation Dose Volume Analysis with Follow Up

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ABSTRACT

This paper is a follow-up report concerning a patient treated with Yttrium-90 to a hepatocellular carcinoma. The radiation therapy dose distribution was published as a case report in 2022, https://doi.org/10.18103/mra.v10i11.3379. The hepatic target volume for directed therapy abutted the right kidney and this report provides clinical follow up information on the patient relative to renal function on unintentional radiation renal dose. Yttrium-90 therapy has become an important therapy component for patient care directed to multiple malignancies with emphasis on treating lesions in close proximity to the hepatic parenchyma. The targets are treated with an intra-arterial approach with a goal of applying target directed radiation therapy. Historically, prior to the development of voxel-based dose volume computation software, dose to target was prescribed as activity of isotope delivered with a qualitative assessment of isotope delivery based on images obtained from single positron emission computer tomography. As a qualitative image, single positron emission computer tomography served as an image reference and qualitative surrogate for representing radiation dose. Today, commercial software is available to fuse single positron emission computer tomography images into radiation oncology planning images and calculate dose to volume in a manner similar to how radiation oncology physics dosimetry teams calculate radiation dose to target volume for external therapy and brachytherapy with image guidance. In this particular case, we demonstrated that the proximity of the right kidney to the target resulted in unintentional radiation dose to renal parenchyma evaluated using voxel-based dosimetry. In this report, we review progressive decrease in renal function with blood urea nitrogen/creatinine of 45 and 2.75 respectively with continued normal liver function. Although potentially multi-factorial in origin, the decrease in renal function is at a time point consistent with radiation injury. In this paper we review radiation oncology dose volume constraints for renal tolerance and strategies for patient care moving forward. The goal is to provide additional knowledge of this issue and provide an additional knowledge layer for patient safety with emphasis on improving patient outcomes.

Introduction

Radiopharmaceutical therapy is increasing in utility with an expanding portfolio of therapeutic options for patient care in multiple disease sites.[1-3] Historically radioactive iodine was applied for thyroid ablation and treatment of thyroid cancer. With expansion of therapeutic options for radionucleotide therapy, neuroendocrine malignancies are currently treated with I-131 mIBG, Y-90 and Lu-177 Docatate. Lu-177 PSMA is an exciting tool with applications for prostate carcinoma, and Ra-223 is used in multiple disease sites to treat bone metastasis. The United States Food and Drug Administration (FDA) approvals for radiopharmaceutical applications came at a time when radiopharmacy treatments were viewed through a prism consistent with "radio chemotherapy" as treatment delivery could only be measured by the activity of the isotope with limited knowledge of dose absorbed by either the tumor target or normal tissue. In contrast, external radiation therapy and brachytherapy calculations are constructed pre-therapy delivery and executed with image guidance to the target providing assurance that the dose prescribed is dose absorbed. Although tracer studies provide security that the application will be directed to target location, for radiopharmaceutical therapy absorbed dose can only be accurately calculated to tumor and normal tissue after therapy is delivered. Modern commercial software is now available which can calculate dose to target using radiation therapy planning images fused with single positron emission computer tomography (SPECT) scans. SPECT can now be applied and used as a platform to calculate dose to target and create dose volume histograms similar to processes performed in radiation oncology. Although more work is needed to understand the timing and distribution of absorbed radiation dose relative to washout kinetics, the addition of computational software provides an opportunity to study radio-pharmacy through the quantitative prism of radiation therapy.[1-3]

This patient had a simultaneous hepatocellular carcinoma and a high-risk adenocarcinoma of the prostate, clinical stage T2C N2, Gleason grade 8 (4+4) with corrected prostate-specific antigen (PSA) at 8.9. Lymph node involvement consistent with prostate cancer was noted in both the pelvis and superior common iliac system. As part of his staging evaluation, a 12 cm well differentiated hepato-cellular carcinoma was identified in segments 5, 6, and 7. Clinical decision was to move forward with Y-90 directed therapy coupled with hormone therapy in order to address both issues in a simultaneous manner. As previously published, Y-90 was delivered in two sessions separated by 6 months with activity level of 134 mCi and 155 mCi respectively based in part by radiographic review of the response to the initial Y-90 application. Radiation therapy treatment planning required therapy directed to extended lymph node volumes in the retroperitoneum which would come in close approximation to the right and left renal volumes, therefore understanding composite dosimetry and measuring the contribution of dose from the Y-90 applications would influence the approach to treatment planning for the prostate carcinoma. As seen in the initial paper, due to proximity of the hepatic target to the right kidney, there was significant dose delivered to the renal volume with approximately 62.4% of the right kidney receiving in excess of 20 Gy (renal tolerance). The purpose of this manuscript is to provide follow up on patient outcome relative to renal function.

Methods and Materials

The patient is a 79-year-old male with elevation in PSA assay corrected to 8.9 (finasteride). The prostate was enlarged on both physical examination and magnetic resonance imaging (98 ml). Prostate Imaging Reporting and Data System (PI-RADS) identified a 1.6 cm right mid lobe lesion extending to the apex without seminal vesicle involvement or extra-capsular spread of disease. Imaging did reveal adenopathy consistent with disease in the right common iliac region and retrocaval regions extending superiorly towards the inferior axial plane of the kidneys. Biopsy revealed multifocal disease in the prostate with the target lesion demonstrating Gleason grade 8 disease (4+4). The imaging obtained as part of staging also revealed a 12 cm mass occupying levels 5,6, and 7 of the right lobe of the liver and biopsy of this mass revealed a well differentiated hepato-cellular carcinoma. Medical co-morbidities include coronary artery disease, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, impaired glucose tolerance, hyperlipidemia, polyarthralgia, and degenerative joint disease. Medications include Amlodipine, Doxazosin, Metoprolol, Furosemide, Spironolactone, Budesonide-formoterol, Empagliflozin (Jardiance), and Finasteride. Patient was evaluated by multidisciplinary teams both in gastrointestinal oncology and genitourinary oncology and decision was made to treat the hepatocellular carcinoma with Y-90 and Lupron was applied to initiate care for the prostate carcinoma. The initial Y-90 application (134 mCi) was in 8/2021 and a second application (155 mCi) was performed 2/2022 due to concern of persistent disease identified on sequential magnetic resonance imaging. SPECT studies were performed

on the same day post application with images demonstrating activity in the liver. The patient tolerated both the Y-90 and hormone therapy well. He was referred to radiation oncology mid-2022 to plan and initiate definitive management for the primary prostate carcinoma. In order to effectively plan the patient for intensity modulation management directed to the prostate and nodal regions including the common iliac and para-aortic region, radiation therapy planning images were designed to extend above the diaphragm to generate composite dosimetry and integrate dose absorbed from both Y-90 applications into the computational program designed to effectively treat the prostate carcinoma. Although the SPECT images were only obtained at one time point and wash out kinetics could not be assessed, fusing the images into the planning computer tomography study would provide a point of reference to targets including renal and small bowel volumes. This would provide a framework to generate targets of conformal avoidance as part of the development of the radiation therapy care plan and manage expectations for what could be defined as normal tissue metrics for dose recognizing there would be overlap between the Y-90 application and the intended fields of prostate radiation therapy. The plan was developed recognizing there was significant dose from the two Y-90 applications to the renal parenchyma with more than 60% of right kidney receiving greater than 20 Gy (Figure 1). This was important information as the radiation therapy plan was adjusted to minimize the impact on renal parenchyma. Radiation therapy was completed to a target dose of 80 Gy to the prostate target with field reduction at 50 Gy with all treatments delivered in 2.0 Gy fractions. The patient tolerated treatment without incident with current PSA of > 0.01.

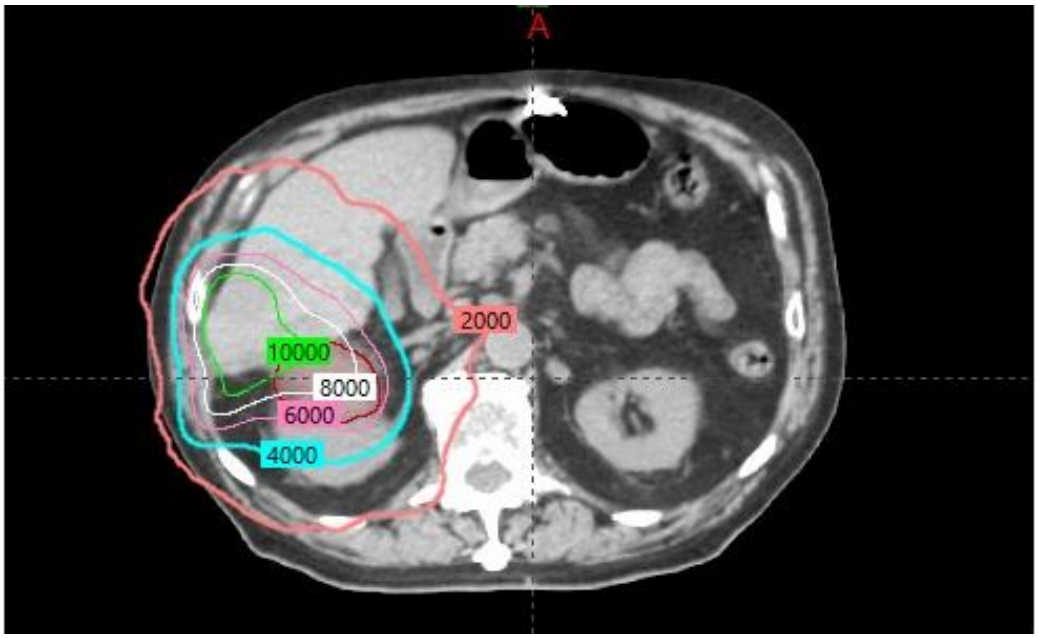

Figure 1. Axial image of percent dose to right kidney for both Y-90 applications.

Results

Understanding the complexity of the case and the need for two multidisciplinary teams to support health maintenance, the patient has been carefully monitored by both hepatic and genitourinary disciplines. This has included serial imaging of hepatic parenchyma, monitoring of PSA, and detailed review of all hematologic and chemistry metabolic indices.

Prior to the identification of both malignancies (3/2021), the creatinine of the patient was 0.84 mg/dl with an upper limit of normal of 1.3 mg/dl. Prior to the initial Y-90 procedure (7/2021), the serum creatinine was 0.88 mg/dl. In July 2022, 11 months after the initial Y-90 application and 5 months after the second application, serum creatinine was 0.87 mg/dl. In January 2023, 17 months after the initial Y-90 application and 11 months after the second Y-90 application, serum creatinine was 0.97 mg/dl. In March 2023, however the creatinine was 1.7 mg/dl, 19 months and 13 months respectively from the Y-90 applications. In July 2023, serum creatinine rose to 2.42 and in October 2023, 26 months and 20 months respectively from the Y-90 applications, serum creatinine is 2.75 (Table 1).

Table 1. Serum Creatinine Levels

Date	Serum Creatinine mg/dl	Months from First Y-90	Months from Second Y-90
March 2021	0.84	Pre-therapy/Not Applicable	Not Applicable
January 2022	0.84	5	Not Applicable
July 2022	0.87	11	5
January 2023	0.97	17	11
March 2023	1.70	19	13
July 2023	2.42	23	17
October 2023	2.75	26	20

Although the hepatocellular carcinoma has recurred by image criteria in a segment not directly treated by Y-90, liver functions have remained within normal limits with no change in medication. The recurrent lesion is amenable to stereotactic therapy (Figure 2).

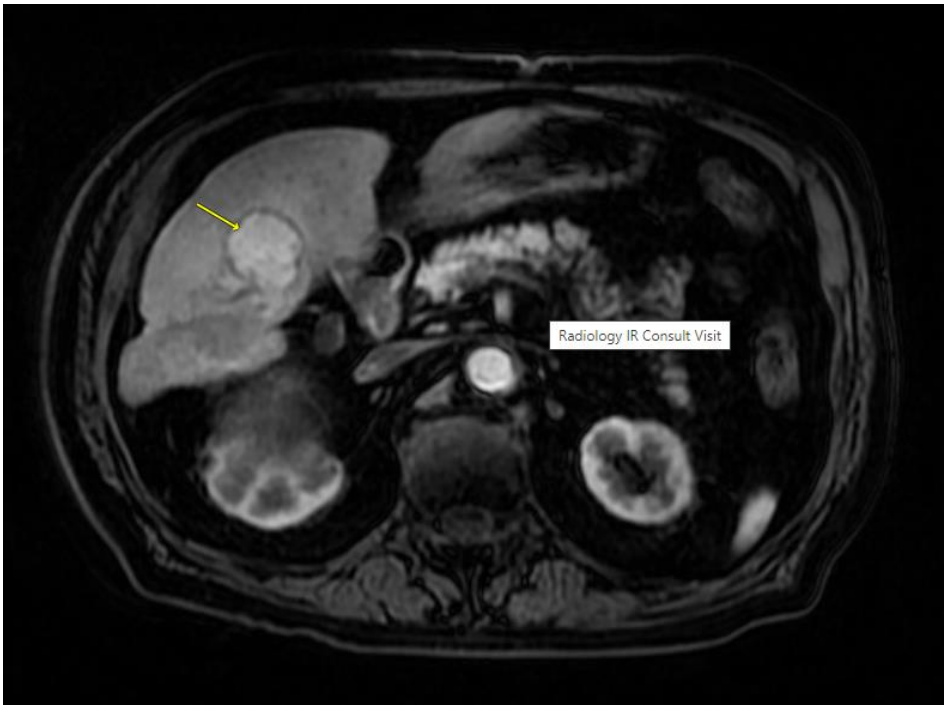

Figure 2. Hepatic recurrence 20 months after the second Y-90 application.

Discussion

Multiple historical and modern studies have demonstrated deterioration in renal function which appears to draw a direct correlate to radiation dose to renal parenchyma. In one study acute effects of radiation therapy were evaluated in 10 patients receiving 2000-2400 cGy to the entire renal volume as part of comprehensive therapy directed towards an abdominal malignancy.[4] Acute changes in renal function as measured by renal plasma flow were seen in radiation doses as little as 400 cGy.[5] In studies including the evaluation canine renal function, doses of 2000 cGy and 1000 cGy were delivered in 200 cGy fractions and doses of 1000 cGy and 500 cGy were delivered in single fraction to a single kidney with results demonstrating a significant decrease in glomerular filtration and renal plasma flow in the irradiated kidneys as opposed to the contralateral unirradiated kidney.[6-10] In a study performed by Luxton, radiation doses of greater than 2300 cGy delivered in 5 weeks to the entire renal volume resulted in acute nephritis in 50% of the treated patients which in the majority of patients led to chronic injury.[11] In these early experiments, recommendations for therapy were established to limit renal doses to 2000 cGy recognizing that chemotherapy can promote injury at lower radiation doses.[4-19] Data from the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) show that 50% of patients develop clinically meaningful renal dysfunction if both kidneys are irradiated with a mean dose of > 1800 cGy[18]. If less than 20% of the renal volume is

treated to 2800 cGy (fractionated RT), less than 5% of patients will develop clinically meaningful renal dysfunction. A publication evaluating renal dose from therapy directed to gastric carcinoma revealed a 2% incidence of renal function deterioration.[12] The volume of renal parenchyma receiving 2000 cGy was a predictive indicator for renal dysfunction. In a paper incorporating para-aortic radiation therapy for patients with gynecologic cancer, patients maintained stable renal function providing the mean renal dose was less than 1800 cGy.[1] In modern departments of radiation oncology, dose volume compliance objectives for each individual patient are composed as part of the written directive for therapy by the radiation oncologist (authorized user-teletherapy). These are written before radiation therapy planning is initiated and must be signed by the radiation oncologist before therapy is initiated. If dose volume objectives cannot be met by the plan, this requires signature of the treating radiation oncologist for regulatory compliance. The dose volume objective template for the abdomen used by the department of radiation oncology at our University is seen in Figure 3. The objectives are a requirement for site accreditation by regulatory bodies including the American College of Radiology (ACR). Because of the uncertainty of dose distribution after infusion, there are challenges adding this process to radiopharmaceutical management, however accountability for dose absorbed by both tumor and normal tissue targets needs to become an expectation for radiopharmaceutical care moving forward.

Dose-Volume Constraints/Objectives for Organs at Risk

Abdomen Conventional Fractionation

Patient: [<Last Name>], [<First Name>] [<Middle Name>]
ID1: [<Patient Id 1>] ID2: [<Patient Id 2>]
[<All Primary Diagnoses - With Staging Info (Default)>]

PTV Margin: [ ] Hot Spot < 110 %

Coverage: % of prescription dose covers at least % of target volume
Result : [choose], Remark (if not met): [ ]

Select OAR	Objective	Priority	Remark (if not met)
Liver	Mean ≤ 30 Gy	(choose)	
Heart	V_{45} ≤ 66% V_{40} ≤ 100% Mean ≤ 35 Gy	(choose) (choose) (choose)	
Lungs	V_{20} ≤ 30% Mean ≤ 18 Gy	(choose) (choose)	
Spinal Cord	Max ≤ 50 Gy	(choose)	
Stomach	Max ≤ 54 Gy V_{45} ≤ 15%	(choose) (choose)	
Small Bowell	Max ≤ 54 Gy V_{45} ≤ 195 cc	(choose) (choose) (choose)	
Kidneys (bilateral)	Mean < 18 Gy V_{18} ≤ 30% V_{12} ≤ 55% If one functional kidney then: V_{18} < 10 %	(choose) (choose) (choose) (choose)	
(add objective)		(choose)	
(add objective)		(choose)	
(add objective)		(choose)	
(add objective)		(choose)	

Physics comments: [ ]

Physician Comments: [ ]

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Figure 3. Dose Volume Objectives for Treatment of the Abdomen, Department of Radiation Oncology, UMass Memorial Health Care and UMass Chan Medical School.

From a clinical perspective, it remains to be determined how acute effects in renal function translate into late effects. Acute morphologic effects are characterized by loss of endothelial cells coupled with interstitial edema of capillary loops. Chronic injury is characterized by fibrogenesis and extracellular matrix deposition with fibrotic reorganization promoting decline in organ function as a late effect. Clinically, after application of radiation therapy to renal parenchyma, there is a latent period of 6-9 months where no specific clinical symptoms or laboratory abnormality can be detected. On occasion during the late latent period at 6-15 months post radiation therapy, physiologic changes can become manifest including peripheral edema, azotemia, proteinuria, and hypertension can be clinically seen. It is not established whether treatment directed to these symptoms of injury can mitigate the appearance of chronic injury as chronic changes will occur even in the absence of visible acute changes. Chronic and late changes become clinically meaningful generally beginning at 18 months post therapy consistent to what is seen in this patient.

It is well understood that chronic renal injury can and is likely multifactorial in origin Medical conditions including hypertension, vascular disease, diabetes contribute in both overt and insidious manners to renal injury. These disease processes can be superimposed with radiation therapy making identification of root cause of injury more challenging to identify. There is evidence, however, in patients undergoing total body radiation therapy as a conditioning regimen for bone marrow transplant that radiation, in isolation, makes a significant contribution to renal injury despite the additional therapies and medical co-morbidities which have the potential of generating nephrotoxicity. Conditioning regimens generally consist of total body doses of 1200-1400 cGy delivered at a dose rate of 5-20 cGy per minute. Renal injury can occur in 25% of patients. Modern bone marrow transplant programs have excluded total body radiation therapy or have applied it in a titrated format for immune suppression (200 cGy) and renal injury is far less common.[13-19] This implies that radiation has influence in the development of injury despite additional medical issues and nephrotoxic agents including chemotherapy and antibiotics in patients undergoing treatment for malignancy.[20-24] This is interesting as we presume renal injury would be less prevalent due both to radiation dose and dose rate during bone marrow transplantation, however in this circumstance injury appears transparent to both dose and dose rate. This may explain, in part, why we see injury with the Y-90 application despite the advantage of dose rate in the radiopharmaceutical application.[23-30]

In our previous publication, we demonstrated the utility of incorporating SPECT imaging into radiation oncology planning imaging and generating dose volume histogram analysis of radiation dose to multiple normal tissue and tumor target volumes from radiopharmacy applications.[30] For patients treated with teletherapy and Y-90 applications, composite dosimetry must be completed to acknowledge potential points of overlap with the radiation fields designed to treat the patient for cancer.[25-30] This was an important step for this particular patient as the teletherapy planned was designed to mitigate the potential of normal tissue injury due to unintentional overlap of radiation dose with both treatments. Although the SPECT studies were both done at a single time point and washout kinetics of dose due to time and decay could not be evaluated, the process of fusing SPECT with radiation therapy planning imaging identified meaningful dose beyond the liver for the Y-90 applications that would likely not have acknowledged otherwise if the assessment and dose volume analysis was not performed. Thus, SPECT imaging studies become an invaluable resource providing quantitative information defining dose to target. With the available information, the radiation therapy treatment plan designed for prostate carcinoma was able to identify the right and left kidneys as targets for conformal avoidance. If the evaluation for dosimetry for Y-90 therapy had been completed after radiation therapy had been delivered to the prostate and extended lymph nodes targets, it is likely additional dose would have been applied to renal parenchyma further increasing risk to normal tissue sequelae for radiation therapy as dose contribution to the renal parenchyma from the Y-90 application would not have been fully anticipated unless computations were completed.[23-30]

From both the nuclear medicine/imaging and radiation oncology perspectives, the case places focus on the need for comprehensive dosimetry for every radiopharmaceutical application. Historically, radiopharmaceutical therapy strategies aligned with prescriptions and directives similar to chemotherapy. There were no vehicles to measure radiation dose absorbed to targets and the prescriptions were largely based on activity of the compound. This was true for I 131 thyroid applications, P32 directed therapies, and more modern applications of Ra-223 and Lu-177. The use of SPECT imaging coupled with the knowledge of compound half-life and washout kinetics with serial imaging shifted the paradigm as absorbed

dose could be measured as a function of activity within the target. Nuclear medicine and radiation oncology colleagues with expertise in computational dosimetry for radiopharmaceutical therapy are essential for designing programs in voxel-based dosimetry to permit absorbed dose to be calculated with the same confidence and rigor currently applied in external radiation therapy and brachytherapy. This is and will be a significant step forward as we can now begin a dialogue about radiation dose to volume when patients are treated with radiopharmaceutical treatment and compare dose to volume with teletherapy, stereotactic therapy, and brachytherapy. We can also begin a dialogue concerning parameters to judge success of an application as well as develop a more comprehensive understanding about radiobiological effectiveness of different applications of radiation therapy relative to radiation dose, method of radiation treatment, and dose rate. Quality assurance programs can begin to become more comprehensive in nature with contributions from multiple stakeholders to optimize patient care.

In this particular patient, the deterioration in renal function correlates to renal volume treated and radiation dose at the time point traditionally associated with therapy associated renal injury. Of interesting importance, the dose to renal parenchyma causing injury in this case resembles dose traditionally associated with injury despite differences in dose rate suggesting, for this case, that radiobiological effectiveness for radiopharmaceutical therapy may not be dissimilar to what we associate for dose volume risks assigned to teletherapy. This is important as modern radiopharmaceutical treatment, including PSMA directed therapy, generates whole organ dose to multiple structures including lacrimal glands, parotid glands, kidneys, and bladder. The bladder in particular, may have already been treated to tolerance levels as part of treatment for prostate carcinoma, therefore composite dosimetry is essential to both understand risk and develop strategies to mitigate risk of radiation injury to normal tissue.[20-30]

Conclusion

Improvements in SPECT imaging coupled with the availability of voxel dosimetry are now important tools to optimize understanding of radiation dose to volume in radiopharmaceutical radiation therapy. For radiopharmaceutical care to move forward at an enterprise level, dosimetry needs to be performed on every patient for each treatment with the same computational rigor as applied to teletherapy and brachytherapy. Radiopharmaceutical therapy is not radiochemotherapy. Because absorbed radiation dose can be measured, radiation dose to both tumor contoured targets and normal tissue need to evolve in a similar manner to current computational analytics and standards applied to radiation oncology with dose to tumor and normal tissue defined through the same prism. Our imaging and computational tools are improving and with these process improvements radiopharmaceutical care will move forward and assume a highly visible and strong position in patient management.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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