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Image-fusion for Biopsy, Intervention, and Surgical Navigation in Urology

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1. Introduction

Due to the recent increased use of diagnostic abdominal imaging and/ or serum prostate specific antigen (PSA) test, both incidental small renal tumors and low-risk prostate cancer are being detected more frequently. This leads to greater numbers of asymptomatic organ-confined early cancers in urology. Treatment strategy needs therefore to be reassessed because of the lack of comparative evidence in effectiveness and the harm of current standard radical invasive treatments especially for such early low-risk asymptomatic cancers (*Hollingsworth et al 2006, Wilt et al 2007*). The precision of the imaging for staging and localization of the diseases is an important problem so that this brings patients a benefit, avoiding the over-diagnosis of clinically insignificant cancer (which does not need to be treated) as well as under-diagnosis of advanced cancers (which definitely need to be treated.) As such, imaging technology is now evolving, and focal therapy for prostate and kidney cancer has attracted attention in urology (*Gill et al 2010, Eggener et al 2007*). Focal therapy aims to achieve targeted control or cure of the malignancy as well as preservation of organ function in order to maintain the QOL of individual patients.

Looking back on the history of urology, there was a definite step when urologists began to practise transurethral resection of bladder tumors (TUR-Bt), and this can be clearly categorised as a type of minimally invasive focal therapy. TUR-Bt can achieve the clinical control or cure of superficial bladder cancer as well as preservation of the bladder in order to maintain QOL, while allowing the patient to urinate through his or her own urethra, avoiding problematic urinary stoma on the abdominal skin. Such focal therapy can be performed generally in the out-patient day surgery, and is also repeatable at a certain interval if indicated. Should the disease become upgraded or upstaged during active surveillance after such focal therapy, the patients would reasonably accept radical treatment when indicated later.

On the other hand, historically we also find shared critical opinion against focal therapy in prostate cancer for 3 main reasons in recent years: firstly, the technological therapeutic difficulty of focal treatment; secondly, the lack of reliable imaging to localize and characterize potentially multifocal and multi-grade prostate cancers; and thirdly, the immaturity of navigation technology to achieve precise 3-dimensional targeting to the biopsy-proven cancer lesion.

However, with increased knowledge of the natural history of prostate cancer, it is now discussed that the prognostic importance of the index prostate cancer, which is a cancer with the highest grade and largest volume in an individual prostate and must determine the individual prognosis of the disease. As such, the important hypothesis has arisen that we might be able to achieve reasonable oncological control by focal therapy, targeting the index-lesion at least, while preserving the healthy parts of the prostate and peri-prostatic tissue that contribute to maintaining urinary continence and sexual function. This would be recommended for patients who are reluctant to accept active surveillance or conservative treatment (*Eggener et al, 2007*).

The current therapeutic standard for clinical localized renal cancer is surgical removal, preferably in the form of nephron-sparing surgery, supported by durable oncological outcomes and overall survival, while active surveillance and minimally invasive ablative techniques have emerged as potential alternatives in carefully selected patients (*Gill et al, 2010*).

Accordingly, for both kidney and prostate cancers, we are facing a real challenge towards endoscopic robotic-assisted surgery, focal ablative therapy, and further computer-assisted, minimally invasive ablation (such as cryosurgery, laser therapy, radiofrequency ablation), or extra-corporeal therapy (such as high-intensity focused ultrasound). A reliable image navigation system would become an essential tool, to facilitate realization of where the surgical pathological targets and vital healthy anatomies are located in the surgical field beyond the surgeon's direct vision or underneath the palpable anatomies. Image-navigation would help intra-operative appropriate decision-making before surgical exposure of the target has even been made, to minimize any iatrogenic injury to the surrounding healthy tissues, and to lead to precise surgical dissection or appropriate delivery of the ablative energy to the surgical target while preserving safe surgical margins. Real-time anatomical and pathological visualization is required for intra-operative navigation, although there may be no perfect single imaging modality to achieve this image-navigation mission. In addition, instead of free-hand control, computer-assistance and robotic control of the surgical instruments or interventional probes could increase procedural accuracy while potentially decreasing the learning curve. "Image-fusion" integrated with such computer-assistance and robotic control would become the key technology.

Active surveillance could increasingly become an important option for the management of low risk kidney and prostate cancers. The optimal biopsy protocol is still controversial in both kidney and prostate, and a new reliable biopsy protocol should be considered since the pathological evidence given by needle biopsy specimens could be one of the key components for determining the oncologic management of these organs.

To obtain reliable information from biopsy sampling, precise spatial targeting accuracy is critical. Since CT-guidance and MR-guidance require expensive facilities and significant expertise in intervention, image-fusion guidance, such as real-time US fusion with previously acquired enhanced CT for the kidney and enhanced MR for the prostate, would provide a clinically relevant opportunity for urologists. The recently emerging technology of "image-fusion" in urology includes the spatial tracking system of a 2D US probe or interventional needle with attached electromagnetic and/ or optical sensors or with robotic control. Another technology involves the acquisition of real-time 3D volume data in order to track with more reality in the spatial targeted fields. This article intends to discuss the advantages and limitations in the current proposed techniques of "image fusion" in biopsy, intervention, and surgery in urology.

Among the various image-guided procedures in urology, percutaneous drainage/ aspiration, percutaneous nephrostomy, percutaneous renal biopsy or renal ablative therapy (for placement of a cryo-surgery probe or radiofrequency probe), transrectal/ transperineal prostate biopsy, and transperineal cryo-surgery or brachytherapy for prostate cancer could be listed as clinically frequent in diagnostic and interventional procedures. Image-guidance in urology could be performed by an urologist with expertise in imaging, but has frequently been performed with the help of an uro-radiologist. The choice of the imaging modality for kidney intervention has been based on the preference of the physicians. For prostate intervention, transrectal ultrasound (TRUS) has been the gold standard as the guidance tool for prostate biopsy delivery. However, controversial issues continue due to a current misjudgment of the true value of TRUS as well as emerging MR technology.

2. Percutaneous renal intervention

Percutaneous imaging guided biopsy and tumor ablation has an increasingly prominent role as minimally invasive management for renal tumors. Precise biopsy needle and ablative probe placement as well as safe and effective ablation are key steps for successful management. In renal intervention such as in the development of nephrostomy, investigators, especially in the USA, considered fluoroscopy as an essential tool for guide-wire introduction, nephrostomy tract dilation, and nephrostomy tube placement (*Barbaric et al 1984, Ko et al 2008*). Others, especially in Europe and Japan, have preferred ultrasound guidance during puncture of the renal collecting system (*Saitoh et al 1982, Skolarikos et al, 2005*). Most often many current investigators now understand the advantages in combining the use of these 2 real-time imaging modalities for renal puncture. Since the pathologic fluid collection or renal collecting system are generally dilated to >10 mm, such a dilated collection system can be targeted so easily that image-guidance at this setting may not require very detailed anatomical signal/ noise ratio or imaging expertise. On the other hand, in order to achieve precise targeting of a small renal mass, renal tumor biopsy and tumor ablative therapy are most often guided by CT fluoroscopy (*Remzi et al 2009, Leveridge et al 2010*), although it may be also precisely guided under US-guidance if performed by US experts (*Atwell et al 2007, Bassignani et al 2004*). Although US visualization of the kidney is excellent, the major disadvantages of US-guidance include the requirement of significant experience in interpretation of the peri-renal anatomy and vasculatures, difficulty of obtaining high-quality images in obese patients, and the difficulty in access of the upper-pole where the US-beam is blocked by the 11th and 12th rib-bones. The major disadvantage of CT fluoroscopy is the radiation exposure for both patients and physicians, and almost all of these CT-guided procedures were performed by radiologists because of its availability. In addition, since percutaneous CT-guided intervention generally uses un-enhanced CT images, intra-renal tumor margins are often hardly identified. Similarly, although the recent introduction of real-time MR is a promising tool, there is also the considerable issue in the availability of such expensive MR-compatible instruments and facilities. As such, pioneer experience of image-guided percutaneous renal intervention required considerable expertise with such high-resolution imaging, and the limited availability of the expensive imaging modality was the significant issue for urologists. There is no doubt that enhanced CT is the most reliable, standard imaging for the diagnosis of renal mass. However, enhanced visualization of the renal tumor is dynamically transient. It does not continue long enough

to be useful during entire interventional real-time procedures, and importantly, it can not be repeated often since the contrast enhancer is harmful to the renal function.

As such, to my best knowledge, the most promising solution for overcoming both the technical difficulties and the lack of availability of enhanced CT imaging is to use image-fusion of real-time imaging with pre-operatively acquired enhanced CT volume data, which can be integrated with a needle/ probe tracking system by GPS(global positioning system)-like technology. Recently, various image-fusion guided techniques have been proposed, which are undergoing research to demonstrate their technical feasibility in preliminary clinical studies (*Ukimura & Gill 2008, Ukimura & Gill 2009, Haber et al 2010*). However, it may be still challenging to achieve clinically relevant accuracy in image-registration as well as in needle/ probe placement, which has to be available during the limited computation time, taking into account each patient's deformable anatomies during the real-surgical procedures.

In 2002, Leroy et al reported a pioneer work on the registration of kidney contours by CT and US images, and also investigated the automated voxel based registration of CT with 3D US, achieving 3.1 mm in registration accuracy, although requiring 80 sec. in computation time (*Leroy et al 2002, Leroy et al and 2004*). In 2004, Osorio et al presented augmented reality visualization that allowed projection of pre-operative CT onto the patient's body, although this system does not achieve real-time monitoring of the procedure (*Osorio et al 2004*). In 2005, Mozer et al evaluated the accuracy of the fusion of CT with real-time US for percutaneous renal access, reporting the encouraging registration accuracy of 4.7 mm between planned and reached targets (*Mozer et al 2005*). They noted that error was mainly due to needle deflection during puncture.

For precise needle/ probe placement, a GPS-like technique for navigation of the needle tract would be ideal in combination with image-fusion guidance. For this purpose, investigators have used an infrared optical tracking system, to track optical sensors which were located 3-dimensionally, and a tracking handle for guidance of the cryoprobe placement (*Haber et al 2010*). Similarly, a magnetic sensor mounted radio-frequency ablative probe can be used for real-time surgical planning to overlay 3D data of the theoretical therapeutic area onto the registered 3D volume of the CT which was pre-registered with real-time US images (*Crocetti et al 2008*).

In the fusion of two imaging modalities, image-registration has been classified as "rigid registration" or "non-rigid registration". Since the urological organs are often shifted by respiration or deformed by surgical manipulation, rigid registration may not be a sufficiently precise image-fusion for routine clinical use in urology. Recent efforts in non-rigid registration between pre-operative high-resolution imaging and real-time imaging potentially provide a new powerful opportunity to take into account the deformation of the organs in image-fusion guided intervention or surgery.

Wein et al reported a non-rigid registration for the image fusion of pre-operative contrast enhanced CT with intra-operative US images at the time of renal biopsy and radio-frequency-ablation, to achieve a fiducial registration error of 5 mm (*Wein et al 2008*). More recently, Oguro et al have proven that a non-rigid registration technique (fiducial registration error of 1.7 mm) was more accurate than a rigid registration technique (fiducial registration error of 5 mm) when fusing pre-procedural contrast-enhanced MR images to unenhanced CT images during CT-guided percutaneous cryoablation of renal tumors (*Oguro et al 2010*). The non-rigid registration technique promises to improve visualization of renal tumors using pre-procedural enhanced imaging during unenhanced CT-guided

cryoablation procedures, although current limitation of the highly precise non-rigid registration does require the significantly long time of 15 minutes to perform. Further technological improvements are being investigated.

3. Augmented reality in surgical navigation

Soft tissue navigation systems in urologic surgery are evolving. The augmented reality surgical navigation technique has been most widely used in the field of neurosurgery (*Iseki et al 1997, Kawamata et al 2002*), in which there is a clear advantage of minimum organ motion in a relatively fixed surgical field within a bony frame, facilitating the registration of the 3D image data. Augmented reality for the management of intra-abdominal soft organs was challenging (*Marescaux et al 2004, Osorio et al 2004, Ukimura & Gill 2007*), because intra-abdominal organs may suffer more from respiratory motion or deformation by manipulation.

Ukimura and colleagues have demonstrated the feasibility of augmented reality in laparoscopic surgery for partial nephrectomy and prostatectomy, using optical tracking systems of the dynamic motion of the surgical instruments, with computer-assisted synchronization of the developed 3D image from the 3D volume data of enhanced CT or intra-operatively acquired 3D volume data of transrectal ultrasound images (*Ukimura & Gill 2007, Ukimura & Gill 2008, Ukimura & Gill 2009*). The approach is technically feasible, but many issues need to be resolved before its clinical wide-spread use in the fields of surgery dealing with soft tissue organs. Nevertheless, recent advancement in augmented reality in urological surgery deserves attention.

Su et al. described a stereo-endoscopic visualization system for augmented reality overlay during robot assisted laparoscopic partial nephrectomy. The stereoscopic system allows the 3D-to-3D registration system of the preoperative CT scan without external tracking devices, using image-based surface tracking technology to track gross movement, with an update rate of 10 Hz and an overlay latency of four frames to place a reconstructed 3D CT image onto the stereo video footage (*Su et al 2009*). Teber et al. reported an augmented reality assisted soft-tissue navigation system using a mobile C-Arm capable of cone-beam imaging, which required the surgeon to insert four or more needle-shaped navigation aids into the target organ (*Teber et al 2009*). Herrell et al. demonstrated an augmented reality guided laparoscopic procedure using tissue mimicking phantoms, to compare their named 'resection ratio', that was defined as the ratio of dissected tissue compared to the ideal resection, between with and without augmented reality image guidance (*Herrel et al 2009*). The resection ratio (3.26) in using image guidance was significantly smaller than that (9.01) in using no image guidance, potentially leading to a decrease of benign tissue removal while maintaining an appropriate surgical margin.

The challenge continues in the real-time tracking of organ motion and deformation, to achieve real-time dynamic navigation through an ongoing surgical procedure. In particular, conventional optical tracking systems and wired magnetic tracking systems are not suitable for tracking internal organ motion. An emerging technology, named the Calypso 4-D localization system (calypso Medical Technologies, Inc., Seattle, WA, USA), is a miniature, wireless magnetic tracking system, which was applied to tracking the prostate motion during external radiotherapy (*Kupelian et al 2007*). We have applied this new technology for an endoscopic augmented reality system to demonstrate real-time dynamic superimposition of the pre-operatively acquired CT image onto the endoscopic image of the moving organ

during advancing surgical manipulation (*Nakamoto et al 2008, Ukimura & Gill 2009*). Such augmented reality image navigation with a 4D-dynamic organ tracking system, being integrated with robotic controlled surgical systems, is likely to herald higher precision surgery in the near future.

4. Image-fusion for radiotherapy, prostate biopsy, and lesion-targeted prostate intervention

Pioneer works in the image-fusion of prostate imaging were reported in the field of radiotherapy including external beam radiation therapy and brachytherapy, using fusions of CT, MR, ultrasound, and/ or fluoroscopy (*Holupka et al 1996, Lau et al 1996, Kagawa et al 1997, Amdur et al 1999, Reynier et al 2004, Daanen et al 2006, Su et al 2007*). In addition, the potential value of image fusion of Doppler TRUS with MRI in the staging of prostatic cancer was discussed (*Selli et al 2007*). However, recent attention to image fusion technology for prostate cancer is more toward its value in improving the quality of prostate biopsy by precisely targeting the image-suspicious area, in mapping the 3D localization of biopsy-proven prostate cancer, as well as its value in navigating image-guided focal therapy (*Ukimura 2010*).

Real-time TRUS has been the gold standard of prostate biopsy guidance, and therapeutic intervention, because of the advantages of its real-time nature, its easy-handling, the fact that it is urologist-friendly, its relatively inexpensiveness, and its non-invasiveness. However, the current role of 2D real-time TRUS imaging to visualize the prostate anatomy as a simple delivery tool of biopsy rarely provides information on the spatial location of prostate cancer. On the other hand, diagnostic multi-function MRI for the prostate has achieved increasingly higher levels of accuracy in detection and localization of cancer in its 3D volume data (*Kirkham et al 2006, Villers et al 2006, Yakara et al 2010*). However, since real-time MR-guided targeted biopsy is still a complicated and expensive procedure, there is considerable interest in a technique of MR/ TRUS hybridized image-guided biopsy.

Reported rigid MR/ TRUS fusion techniques (*Kaplan et al 2002, Xu et al 2007, Singh et al 2008, Turkbey et al 2010*) had a limitation when deformation occurred between MR and TRUS. Importantly, because the 3-D shapes of the prostate at the time of image-acquisition at preoperative MRI are likely to be different from the intra-operative TRUS images, the precise registration of each 3-D volume data is critical. In order to reduce the potential errors in rigid registration of TRUS with MRI, one solution may include preoperative MR images being obtained while a plastic outer-frame, of exactly the same shape as the real TRUS probe, is placed in the rectum, in order to simulate the deformation of the prostate caused by the absence or presence of a TRUS probe during the acquisition of MR or TRUS images (*Ukimura 2010*). For another potential solution, Hu and colleagues described a technique using a patient specific model of MR/ TRUS deformation built from simulated data for image-registration (*Hu et al 2009*). A more attractive developed technique for improvement of registration in MR/ TRUS image-fusion is the introduction of automatic, non-rigid (elastic) registration technology (*Baumann et al, 2009, Martin et al 2010*). This new elastic fusion technique allows making automatic segmentation of the prostate in TRUS images by deforming a patient specific 3D model built from MR image to TRUS data.

As mentioned already, unfortunately, clinical urologists generally use TRUS only as a simple delivery system for systematic sextant biopsies toward the planned segmental locations, with no detailed 3D anatomical records of the sampled localization, and by just

naming the biopsy sample with a rough sextant site for review. Since urologists often need repeat biopsies, this led to the current trend of taking an increased number of initial biopsies, and also to the risk of delivering the repeat biopsy needle to spots that have previously been shown to be negative for cancer, and of failing to make the necessary deliveries for previously un-sampled locations. In order to facilitate the emerging strategy of focal therapy for prostate cancer which may require precise 3D mapping of biopsy-proven cancer, individual recording of the 3D localization of each biopsy would be the key issue. As such, transperineal template grid-based 3D mapping biopsy has been proposed (*Barzell & Melamed 2007, Onik et al 2009*). However, current ongoing transperineal template 3D mapping biopsy may require 5-mm grid based techniques to detect clinically significant cancer, resulting in a tremendous number of required biopsies, for example, over 100 samples in a large prostate. We are hoping that the improved image-fusion technique of MR and TRUS, and the elastic fusion of 3D real-time TRUS for 3D biopsy mapping techniques (*Mozar et al 2009, Ukimura 2010*) could improve the clinically relevant strategy for prostate biopsy, and also the image-guided management of prostate cancer in the near future.

5. Molecular and radionuclide imaging for urology

Targeted radionuclide therapy offers potential determination of targeted cancer specific accumulation by molecular imaging with single photon computed tomography (SPECT) or positron emission tomography (PET). In this decade, computer-assisted integration of anatomical and functional images has been demonstrated as a hybrid of PET/ CT [Townsend, 2001] as well as a fusion of SPECT/ CT (*Schillaci et al 2005*), providing us a new opportunity of interpretation of side-by-side or overlaid dual modalities. Cancer specific molecular imaging and radionuclide therapy is attractive for the early detection and staging of malignancies, and for the precise selection of patients who would benefit from molecular-based targeted therapy and monitoring.

¹⁸F-FDP (fluorodeoxyglucose) PET/ CT has been widely used in the management of various malignancies showing an increase of glucose metabolism leading to uptake of ¹⁸F-FDP, although the urinary excretion of ¹⁸F-FDP and relatively low uptake of ¹⁸F-FDP especially in small sized foci (<5mm) of prostate cancer and some types of renal cancer were a clear limitation of its expansion in urology. At the same time, other PET tracers have recently demonstrated improved accuracy of PET/ CT, which include ¹¹C-choline, ¹⁸F-fluorocholine, ¹¹C-acetate, and ¹⁸F- fluoride that might correlate to prognosis and localization in prostate cancer (*Wachter et al 2007, Bouchelouche & Oehr JUrol 2008, Piert et al 2009, Poulsen et al 2010*).

The fusion image of SPECT with CT might also improve the role of imaging in the diagnosis and therapy of prostate cancer (*Krengli et al 2006, Sodee et al 2007*). The usefulness of pretreatment ¹¹¹-Indium capromab pendetide radio-immuno-scintigraphy plus SPECT co-registration with CT scans has been demonstrated in detection of occult metastatic disease and predicting for biochemical failure in patients who had evidence of that possibility after radiotherapy (*Ellis et al 2008*). This image-fusion capability leads to a new proposed strategy for image-guided radiation therapy to favor dose-escalation to the regions as defined by focal uptake on radio-immuno-scintigraphy fusion with anatomical image sets (CT or MRI) (*Ellis & Kaminsky 2006*).

However, there is still challenge in molecular-based diagnosis and radionuclide therapy for clinically personalized use, which requires improved detection and efficacy in large clinical trials.

6. Conclusions

Image-fusion technology would improve detection of urological malignancies and precision of intervention in minimally invasive urology, and are now increasingly under research for biopsy needle guidance and therapeutic navigation. In particular, the non-rigid image fusion of real-time US with contrast-enhanced CT/ MR, 3-dimensional mapping of biopsy localization, 3-dimensional image-guided lesion-targeted ablation therapy, augmented reality, and tumor-specific diagnostic imaging have been attracting increased attention.

7. Figure legends



Fig. 1. Augmented reality during laparoscopic nerve-sparing radical prostatectomy
The biopsy-proven cancer area (blue), built from intra-operatively acquired 3D TRUS image, was overlaid on the real-time laparoscopic image during laparoscopic nerve-sparing radical prostatectomy



Fig. 2. Augmented reality during laparoscopic partial nephrectomy
The color-coded zonal anatomy (tumor by red, 0-5 mm margin by yellow, 5-10 mm margin by green, beyond 10mm margin by blue), built from pre-operative contrast enhanced CT image, was overlaid on the real-time laparoscopic image during laparoscopic partial nephrectomy



Fig. 3. 4D Augmented reality navigation

Using body-GPS (left, Calypso miniature wireless magnetic tracking system) to track real-time the motion of the organ, 3D model of pre-operative CT was real-time overlaid onto the laparoscopic view during ongoing surgical manipulation (middle, overlaid image at the initial position of the tumor) (right, real-time overlaid image on the lifted-up tumor with safe surgical margin)

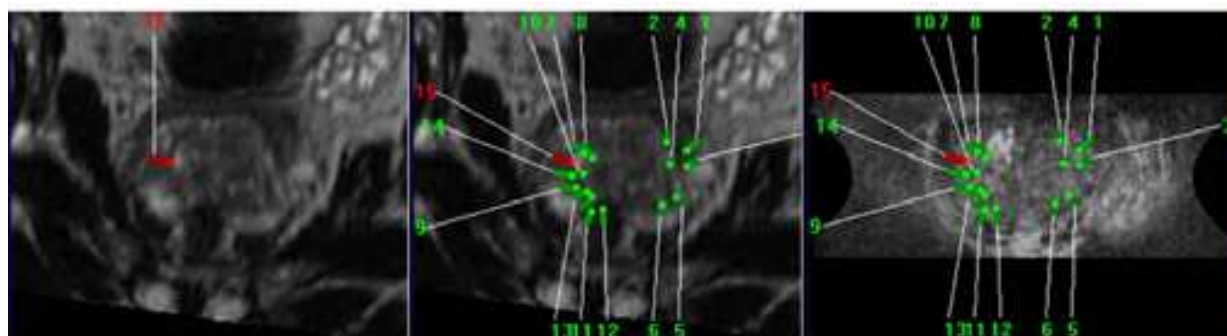


Fig. 4. MR/ TRUS fusion image-guided biopsy with overlaid images of each biopsy trajectory

Left, positive cancer biopsy trajectory overlaid on the MR-visible lesion (low intensity lesion on T2 image)

Middle, overlaid images of each biopsy trajectory on the 3D MR image

Right, overlaid images of each biopsy trajectory on the 3D TRUS image

8. References

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Image fusion technology has successfully contributed to various fields such as medical diagnosis and navigation, surveillance systems, remote sensing, digital cameras, military applications, computer vision, etc. Image fusion aims to generate a fused single image which contains more precise reliable visualization of the objects than any source image of them. This book presents various recent advances in research and development in the field of image fusion. It has been created through the diligence and creativity of some of the most accomplished experts in various fields.

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