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Review

Endoscopic Mucosal Dissection in GI Malignancies

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SUMMARY

In this paper we review the endoscopic mucosal dissection technique for gastrointestinal malignancies in the perspective of the evolution of flexible endoscopic tools to assist in cutting tissue. The available methods as well as the future technology are analyzed in details. It is concluded that the tools for cutting at flexible endoscopy have evolved substantially on recent years.

INTRODUCTION

This manuscript will review endoscopic mucosal dissection for GI malignancies in the perspective of the evolution of flexible endoscopic tools to assist in cutting tissue.

Polypectomy snare cutting

Snare polypectomy was introduced by Woolf and Shinya; working in New York. The idea evolved from snares used during rigid cystoscopy.

The simplicity of this form of cutting and its effectiveness for colonic polyp removal, a very frequently encountered pre-cancerous pathology has contributed to snare resection being the most common form of cutting performed at flexible endoscopy. There has been relatively little evolution in snare design over the years snare shapes have varied to include hexagonal, barbed (to prevent slippage), eccentric with short and long side, pointed to allow different approaches to less accessible polyps and snares which can be rotated.

Most snare resection is performed with coagulative or blended RF current to reduce the risk of bleeding from the vasculature in the polyp's stalk. The use of a "cold" snare technique has been popularised for the removal of small polyps of less than 6mm. In this technique a snare is closed on the polyp but no RF current is applied and the polyp is cut between the closed wire loop and the external plastic sheath using a guillotine–like action. This is thought to be safer than "hot biopsy forceps" which are forceps, which can be closed on tissue such as a small polyp and a monopolar current can be applied to the jaws. This current cuts the tissue leaving most of the small polyp uncoagulated in the jaws and thus assessable at histology.

Sphincterotome cutting

Wire based cutting of the sphincter of Oddi during ERCP to allow the removal of gallstones was first performed in 1975 in Germany and Japan. There have been minor variations in sphincterotomy design.

There include short and long nosed, wire-guided, sharkfin for Billroth 2 cases, articulating, proximal wire insulation for safety, rapid exchange methods. RF current choice has evolved with the popularisation of endo-cut modes which give short bursts of blended current with pauses to reduced inadvertent rapid cutting which was responsible for occasional uncontrolled cutting of the sphincter called a zipper effect.

Needle-knife cutting

Needle-knives were initially improvised by cutting the end off damaged sphincterotomes allowing a short length of exposed wire beyond the cut catheter to be used to cut in order to obtain deep cannulation of the bile duct. This device was found to be useful when cannulation with a ctheter was difficult but was more risky than sphincterotome cannlation risking uncontrolled cutting and bleeding except in expert hands. The wires used at ERCP are thinner and more prone to break than needle or hook based cautery systems used during open surgery and laparoscopy.

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The development of EMR (endoscopic mucosal resection) in the late 1980's and ESD (endoscopic submucosal dissection) about 10 years later especially in Japan, saw a number of new needle-knife designs emerge. These designs addressed some of the limitations of the needle-knives used for sphincterotomy. Most designs were produced by Olympus in Japan. A safety "IT" knife featured a ceramic ball-tip. This allowed the protected tip to be advanced into the submucosa with reduced risk of perforating the target organ (stomach, colon, oesophagus) but could cut laterally or by pulling back effectively and with more confidence. A thin hook-knife was also introduced for safety reasons. The tissue could be hooked and pulled back before RF current was applied reducing the risk of inadvertent perforation. If a medium sized submucosal artery was encountered this could be compressed by hooking it and pulling it back then using spray electrofulguration current arguably allowing sealing of larger vessels than would be occluded with conventional cutting current. A flex knife allowed 2-3 mm of twisted wire to emerge from its catheter and to be flexed in different directions allowing different angles of approach to tissue during endoscopic resection.

A triangular blade on a needle knife was also used for similar reasons especially in esophageal EMR. These needle knives allowed "en-bloc" i.e. complete dissection of mucosal and partially submucosal "early" cancers some of which were several centimetres in diameter from gastrointestinal tissue which is only two or three centimetres in thickness. Safety was increased by the injection of a saline cushion (or other longer-lasting fluids). Sometimes an end cap on the distal tip of the endoscope was used to elevate the tissue or place a rubber band on tissue to improve access, increase safety or reduce bleeding during cutting.

Endoscopic scissors and suture cutters

Endoscopic scissors are a rarely seen device available from Olympus Inc. Their unpopularity in clinical practice may be due in part to their perceived poor cutting capability. Based on reports from the field, the general consensus is that there is much room for improvement.

Still, Miyashita et al. reported in 2003 successful clinical experiences cutting out a superficial gastric cancer with endoscopic scissors developed in collaboration with Olympus Optical Co. Ltd. (Tokyo, Japan).[1]

In the report, they described the use of a two channel gastroscope during the procedure to allow for tissue countertraction with forceps in one channel, while cutting with the endoscopic scissors in the second channel. Application of countertraction or tissue tensioning force, while cutting during flexible endoscopy is difficult and rather uncommon in standard practice, which may help to account for the scissors' reputation for poor performance.

Also, Beilstein and Kochman in 2005, used endoscopic suture scissors (model FS-3L-1 from Olympus America Corp, Melville, NY, USA) to cut through oesophageal scar tissue in a human patient.[2] They were able to cut through the fibrous tissue with "small, repetitive snips" despite the device being designed to cut suture rather than tissue. The straight approach in the esophagus may allow more forward force to be applied aiding successful cutting. Off label use of the suture scissors was chosen over the more traditional electrosurgical needle knife in this application because "of an inability to hold the endoscope in position while visualizing the band and controlling the incision" due to the location of the stenosis, or narrowing of the oesophagus.

Blunt dissection

Blunt dissection devices use relatively atraumatic wedge geometries to stretch, rip and tear tissues along tissue boundaries or at a tissue plane. These devices are commonly used in other specialties, such as in cardiovascular surgery for the harvesting of the saphenous vein for cardiac bypass graft, and in cosmetic surgery during the liposuction procedure. Blunt dissection is also used at laparoscopy as a fundamental surgical technique. Closed laparoscopic forceps or scissors are tunnelled into connective tissue. The jaws, or blades are then opened to stretch and rip tissues apart. In flexible endoscopy, Maloney bougienage, Savary wire-guided bougies, CRE balloons and the Optical Dilator use the same principle of inserting a wedge into a confined space to rip tissue and tear through an anatomical stricture. Blunt dissection also has been attempted in NOTES procedures to tunnel into the submucosa and to separate the gallbladder from liver bed, although it is performed very poorly using currently available endoscopic instruments.

Laser ablation

Lasers – light amplification by stimulated emission of radiation – are optical devices that emit light by a process called stimulated emission.

The emitted light typically is coherent, low-divergence, and monochromatic, and can be used in medicine to cut and coagulate tissues. Many types of lasers have been conceived, and function by various physical means to cause stimulated emission of light – these include traditional gas, dye, metal-vapour, solid-state and semiconductor lasers, as well as more exotic free electron lasers that use relativistic electron beams as the lasing medium, and theoretical lasers like the gamma laser pumped by positronium annihilations and the x-ray laser powered by nuclear explosions. Lasers are used in many clinical applications to coagulate and ablate tissues, and there is ongoing research on using lasers to seal tissues and close wounds. At flexible endoscopy, lasers have been used to coagulate tissue and to treat bleeding ulcers3-5. They also are used in photodynamic therapy in combination with photosensitizing drugs to destroy precancerous lesions. Only a few medical lasers with cutting capability, such the ubiquitous CO2 laser, are used in open and rigid endoscopic surgery. The CO2 laser has not been used in flexible endoscopy in the past because of the difficulties in transmitting far inrfa-red laser light through flexible fibres. However, a new thin, hollow fibre optic based on the omni-directional dielectric mirror technology described by Temelkuran et al. in 2002 can allows endoscopists to explore the use of medical cutting lasers in flexible endoscopy6. Manufactured by OmniGuide (Cambridge, MA, USA), the BeamPath photonic band-gap fibres, are compatible with the standard working channels in flexible endoscopes and allows the endoscopists to use CO2 laser light to burn and cut tissue. Upcoming cutting tools in flexible endoscopy Thought-leading clinicians and medical societies ASGE and SAGES, in partnership with medical device corporations, have invested in developing new cutting devices for NOTES. A number of these upcoming technologies have been published in the literature and discussed at conferences, and undoubtedly more that have not yet been revealed to the medical public are quietly being developed.

An endoscopic toolbox

The advent of NOTES rapidly exposed the difficulty of cutting and dissecting tissue using flexible endoscopic instruments in the abdominal cavity. Thicker diameter hook knives were created which more closely approximated to the hook knives quite widely used at laparoscopy for dissection of the gallbladder. One company (Ethicon Endo-surgery) produced a toolbox for NOTES with contained novel Maryland-type flexible forceps, which perform blunt dissection by splitting planes of connective tissue as they open. Methods of lateral articulation and rotation were applied to needle knives, hook knives and snares to address some of the difficulties of the lack of triangulation associated with the use of accessories passed through flexible endoscopes rather than passed through spaced transabdominal trocars. Flexible scissors, which cut tissue were developed and an RF input added. Limitations of this approach lead to most NOTES cases being performed as a hybrid procedure with one or more transabdominal port or rigid transvaginal instruments being used for more rapid and effective cutting and dissection. The absence of FDA approved or CE marked instruments for dissection and cutting led to improvisation. The dissection and cutting in several human cholecystectomies was performed using a snare with two or three millimetres of wire protruding from the tip because the snare was FDA approved and conventional flexible needle knives approved for ERCP were not robust enough for such dissection.

Mechanized tools

Mechanical tools, like open and laparoscopic stapler devices, simultaneously lay down multiple staple lines and cut through the tissue in between the staple lines to seal and divide hollow organs into two halves. These tools are staples of modern open and laparoscopic surgical technique, and some thought leaders in NOTES have expressed in the literature the desire for replicating stapling capabilities for use at flexible endoscopy.[7] Presently, there are reports of experimental, per-oral, full-thickness gastric resections in animals using flexible linear staplers like the SurgASSIST (Power Medical Interventions Deutschland GmbH; Hamburg, Germany)[8,9] and flexible semi-circular staplers like the experimental, fullthickness resection device (Boston Scientific; Natick, MA, USA).[10]

Gas dissection

High-pressure carbon dioxide (CO2) gas has been use for blunt dissection to separate tissue layers. Sumiyama et al. reported the use of gas blunt dissection to create a submucosal tunnel for gastrotomy and oesophagatomy for transgastric and trasnoesophagal access in pigs.[11-14] The gas dissection was followed by injection of hydroxypropylmethylcellulose (HPMC) and subsequent blunt dissection "cleanup" by a 15mm biliary retrieval balloon.

Chemical dissection

There is a report by Sumiyama et al. reported in 2008 the use of mesna (sodium-2-mercaptoethanesulfonate), a mucolytic drug that is used to reduce mucus viscosity and also as an uroprotective drug in oncology, to chemically assist mechanical dissection of submucosal gastric tissue in pigs.[15] Although the chemical injection was not directly responsible for separating the tissue layers, the investigators reported that it significantly enhanced the technical ease by which submucosal dissection was performed with a blunt dissection balloon.

Articulation platforms

Being able to direct where to cut also is essential, and some of the current ESD and NOTES research has been directed towards developing articulation platforms that provide triangulation and stability to existing endoscopic cutting tools. New devices such as the R-Scope (Olympus Medical, Tokyo, Japan), the Direct Drive Endoscopic System (DDES; Boston Scientific, Natick, MA, USA), the Endosurgical Operating System (EOS; USGI Medical, Inc., San Clemente, CA, USA) and the EndoSamurai prototype (Olympus Medical, Tokyo, Japan) provide greater scope and instrument articulation capabilities that go far beyond that of the current generation of endoscopes.

Robotics

The iconic da Vinci robot for laparoscopic surgery perhaps represents the height of medical robotic technology currently available. Software can augment surgeon skill by filtering out unwanted hand tremors and proportionally amplifying hand motion and strength. In a demonstration of the dexterity and intuitive interface of the surgical robot, Ishikawa et al. reported the use of da Vinci to fold miniature origami cranes from 2cm square sheets of paper.[16] Robotics also have been proposed as a method to improve control of the cutting instruments at flexible endoscopy, and have been implemented in at least one experimental system – the EndoVia endoscopic robot (Hansen Medical).

Cutting tools in rigid endoscopy and open surgery

Medical specialties outside of flexible endoscopy have developed cutting tools specific to their clinical requirements. Perhaps concepts and elements of some of these technologies are appropriate for and can be adapted to endoscope-compatible cutting instruments for NOTES.

Motorized cutters

Motorized or power-assisted cutting tools like surgical drills and grinders, circular bone saws and cartilage debriders have made it much easier to perform tasks in arthroscopy that would be very physically taxing otherwise. Power tools such as these can be found in use, for example, in orthopaedic procedures to replace hip and knee joints. Powered cutting tools also are used when delicate, precise and repeatable cutting tasks need to be performed. Microkeratomes use an oscillating blade to cut corneal flaps of precise thicknesses in the eye before corrective laser eye surgery. Liposhavers – vacuum-assisted tissue shaver with an oscillating blade – are used in plastic surgery to shave and contour fat precisely to improve cosmetic appearance.[17]

Waterjet dissection

Waterjet cutting is a technology that uses a small diameter, highpressure, ultra-coherent stream of water to cut materials like a knife. The technology has been used successfully in industrial applications to cut plastics, soft metals and non-hardened steels, typically with the assistance of fine, abrasive particles added to the water stream to increase the cutting ability of the high-pressure jet of liquid. Medical waterjets have been used to cut soft tissues and debride (remove necrotic tissue from healthy tissue) organs, and these devices usually cut tissue by the mechanical force of the isotonic salt water stream itself without requiring any particulate additives. Medical waterjets have the characteristic of selectively cutting parenchyma, or the functional parts of soft organs, while leaving the structural and connective tissues such as blood vessels intact.

The Móritz 1000 (Euromed Medizintechnik; Schwerin, Germany), Versajet (Versajet, Smith-Nephew; Hull, UK) and Helix Hydrojet (Helix Hydrojet, ERBE Elektromedizin GmbH; Tóbingen, Germany) are examples of commercially available waterjet systems. A number of groups have experimented with miniature waterjets created at the distal end of catheters through explosive vaporization of the water stream by a laser. Eversole et al. reported in 1997 the use of a pulsed erbium, chromium-yttrium-scandium-gallium-garnet (Er, Cr: YSGG) laser to vaporize water vapour to cut dental hard tissues in rabbits and dogs.[18] Nakagawa et al. in 2002 used a pulsed holmium yttrium- aluminum-garnet (Ho: YAG) laser to create a controllable microjet of water fired from a micro-nozzle that subsequently was used to dissect brain tissue in rabbits.[19-21] Fletcher and Palanker in 2001 reported the use of a tungsten-filament. heating element, powered by a high voltage electrical discharge to vaporize water and create a controllable micro-jet of water from a micro-nozzle.[22]

Electrosurgery to cut, coagulate and seal

Radiofrequency electrosurgical devices exist that use the heat generated by electrical currents passing through tissue to form a coagulum to seal tissues. The Ligasure vessel sealing system (ValleyLab; Boulder, CO, USA) uses "an optimized combination of pressure and energy [to create] the seal by melting the collagen and elastin in the vessel walls and reforming it into a permanent, plastic-like seal", according to the product website.[23] Although the Ligasure was designed initially for vessel sealing, with this technology one could envision an electrosurgical supertool that combined the capabilities to cut, coagulate and seal tissues. The Plasma Trisector device of the PK line described above also has the capability to seal vessels.

Plasma dissection

Monopolar fulguration to cut tissue is used in a commercial device that recently has been introduced to the marketplace in the form of the PlasmaBlade (Peak Surgical; Palo Alto, CA, USA). According to the product website, the device uses "pulsed waveforms that produce short plasma-mediated electrical discharges... heat diffusion and associated heat damage to surrounding tissue is limited, resulting in less collateral damage and more precise tissue dissection[24]". Gyrus ACMI, now a part of Olympus Medical, markets the plasma kinetics (PK) technology surgical line (Gyrus ACMI (Olympus); Southbourough, MA, USA) that uses bipolar fulguration to vaporize tissue. Botto et al, published, their experiences in 2004 using the device in prostate surgery,[25] and Abouljoud published their experiences with PK for laparoscopic liver resection in 2008.[26]

Irreversible electroporation

Although not tissue cutting per se, Edd et al, reported a technique in 2006 to use electrical impulses to induce irreversible electroporation, or the formation of permanent nanoscale defects in the bilipid cellular membrane of targeted cells.[27] The process, which leads to tissue necrosis by disrupting the cell membrane, however leaves structures like large blood vessels and ducts intact, unlike electrosurgical coagulation, which indiscriminately "cooks" everything inside a volume of tissue with electrically generated heat. A device based on irreversible electroporation; the NanoKnife (AngioDynamics, Inc., Queensbury, NY/ USA), has been approved for the surgical ablation of soft tissue in the United States.

Ultrasonic dissection

Ultrasonic dissectors can be found in the medical setting to cut and coagulate tissue, and two popular laparoscopic ultrasonic dissectors include the Ultracision Harmonic Scalpel (Ethicon Endo-Surgery, Inc. (Johnson & Johnson); Cincinnati, OH, USA) and the AutoSonix System (AutoSuture (Covidien); Norwalk, CT, USA). Newer iterations of these devices also have the ability to seal small blood vessels. These devices use piezoelectric elements to vibrate cutting surfaces at ultrasonic frequencies to cut, coagulate and seal tissues.[28] According to a 1999 technology review by Cuschieri, low power ultrasonic dissectors operate at around 25 kHz and cleave cells with high water content through cavitation. High power ultrasonic dissectors operate at 55.5 kHz and function mainly through "tissue sawing (high speed frictional deformation) coupled with linear compression of the tissue (by the surgeon)".[29] Advantages of ultrasonic cutters over traditional electrosurgery, according to the website of one manufacturer, include minimal charring and smoke, the passage of no electrical current through the patient, and fewer instrument exchanges because of the devices' multifunctional capabilities.[30]

Laser ablation

The use of medical lasers for cutting tissue is more widespread outside of flexible endoscopy, and correspondingly, there is a wider variety of lasers available for use. Excimer lasers emit light in the ultraviolet (UV) range of the spectrum and are used commonly to resurface tissue in laser eye surgery. Short for "excited dimer", these gas lasers operate by a photochemical effect to ablate tissue, imparting energy directly to breaking chemical bonds in the molecules of surface tissue, which disintegrates into the air. Because cutting is achieved by photochemical means, very little heat is generated that could coagulate and change tissue properties. Excimer lasers also can cause tissue dissection by photomechanical means, although sometimes this can be an unwanted side effect of treatment. Deckelbaum et al. reported in 1995 on the use of saline infusion to reduce the incidence of coronary artery dissections inadvertently induced by excimer laser angioplasty.[31]

Absorption by blood of the laser light was resulting in vapour bubble formation and collapse leading to acoustomechanical damage done to the vessel wall, and their work reduced this effect by displacing light-absorbing blood with saline. Another example of the photomechanical effect is the use of a holmium: YAG solid-state laser with wavelength of 2.1Mm for shattering gallstones, and experiences with this technique were reported by Teichman et al. in a 2001 publication32. 0.6-1.0J of laser energy was delivered to the gallstone surface at a rate of 6-10Hz using an optic fibre to cause this effect. Tissue dissection in surgery of the sort that more resembles cutting with a scalpel, drill or saw are performed with the CO_2 gas laser (10.6Mm), the Er:YAG solid-state laser (2.94Mm) and Ho:YAG solidstate laser (2.1Mm).

These lasers emit light in the infrared region of the spectrum, which is highly absorbed by water, which is the major component of most tissues, as well as hydroxylapatite, a calcium-based mineral that is found in bone, allowing these lasers to be effective for cutting soft tissues, bone and dental enamel primarily by the photothermal effect. Deppe and Horch reviewed the use of CO_2 and Er:YAG laser in oral surgery in 2007.[33] Hollow fibre-optics has been used, and Raananai et al. reported in 1997 their use with a CO_2 laser to harvest the internal mammary artery for cardiac bypass surgery.[34] However, these fibres are too large and too inflexible to fit down even the largest working channel of a flexible endoscope. The Nd:YAG solid state laser (1064nm) also has been used for tissue ablation, although this is more difficult because infrared light at this wavelength is absorbed less by tissue than laser wavelengths produced by the other YAG lasers or by the CO2 laser. Regardless, Price et al. reported in 2007 Nd:YAG laser ablation of a lesion on the vocal cords of a patient with a setting of 30W laser power.[35] Nd-YAG laser treatment became a fashionable treatment for gastrointestinal bleeding and esophageal cancer in the 1980s. It appeared effective in randomized trials but the cost of the laser equipmenr was the main reason for its failure to maintain it position in gastroenterology, It was not clearly superior to thermal proble methods such as bipolar electrocoagulation and the use of esophageal stents and better radiotherapy eclipsed its value for the management of esophageal cancer. Sato et al. reported in 2001 the use of nanosecond, high intensity pulsed laser ablation by a Q-switched Nd:YAG laser to cut porcine myocardium tissue.[36] Based on optical and acoustic emissions as well as histological data, they concluded that laser ablation at 1064nm predominantly was due to photodisruption. The KTP/frequency doubled Nd:YAG solid state laser (532nm) is another popular laser, with its distinctive blue-green light output. Saito et al. reported in 1999 the use of the KTP laser for tonsillectomy in human patients.[37] They cited the faster cutting speed compared to the YAG laser and better coagulation capabilities compared to a CO2 laser as the benefits of the KTP laser.

Future technology

Technologies in other areas of science and engineering may also provide inspiration and blue skies ideas and opportunities for new approaches to cutting tissue at flexible endoscopy.

Feedback control

In many areas such as electronics and mechatronics, the concept of feedback control is popular. This control methodology couples actuators with sensors so that machines have a kinaesthetic sense of where they are and where they need to go. In the context of cutting tissue, the idea can be embodied in coupling diagnostic systems with actuation or cutting systems. Some reports of feedback control, specifically to guide electrosurgical dissection, were found in the literature. Patents describe using tissue impedance (EP1810633), probe motion measured by accelerometers (US7235072), and tissue temperature (US7297143) as control signals for feedback control. As is typical of patents, specific details were hard to find in the claims, and empirical data to back the claims were lacking. One could also imagine using other diagnostic modalities such as reflectance spectroscopy, electrical impedance tomography, and endoscopic ultrasound to direct cutting tools. Information from other tools such as fluorescence and Raman imaging, X-ray fluoroscopy and MRI might be used to guide cutting tools to affect only diseased tissue revealed by the imaging techniques.

Chemically-assisted cutting

There has been much progress in the area of biochemistry as new molecules are being designed and discovered to tag and affect specific cell types. Chemicals and drugs have been used to target specific cell types, particularly cancer cells, as well as enhance ablation in multifactor ablation schemes. Some methods depend on differential uptake of substances by the target and normal cells to “direct” the treatment to the desired locations in the body. Photodynamic therapy using light-sensitizing porphyrin drugs, methylene blue dye and gold nanoparticles in combination with laser light to destroy cancer cells have been described abundantly in the literature. Chemicals also can be injected directly into tissue for direct targeting of pathology. Chen et al in 1996 injected indocyanine green (ICG) dye into mouse mammary tissue to increase the photothermal interaction with an 808nm diode laser.[38] Hino et al. in 2001 injected ICG into tissue surrounding varices at the oesophagogastric junction to enhance the photothermal effect and coagulate tissue in human patients.[39] Arai Hayashi and Sato et al. published four papers in 1997 – 2001 describing their use of ICG to enhance 805nm laser ablation in harvested canine and porcine stomach, percutaneous lumbar disc decompression in canine model, as well as a feedback-controlled system that monitored the presence of ICG dye to control laser activation.[40-43] Yamashita et al. also reported in 1999 ICG-mediated laser EMR in canine model at laparoscopy and human patients at TEM.[44]

Nanotechnology/MEMS

Ultra-miniaturization in the form of millimetre-scale microelectromechanical systems (MEMS) and nanotechnology is an area that holds fantastic promise but most likely is many years away from being realized for clinical use. Still, much progress in the field has been reported in the literature. Son et al described their work incorporating piezo actuators into a silicon needle in a MEMS device that can penetrate skin painlessly. Mathieson et. al published their testing of a fluid-driven micro-turbine 2mm in diameter.

CONCLUSION

The tools for cutting at flexible endoscopy have evolved substantially.

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