論文の内容の要旨

Abstract

論文題目　Flexible Coaxial Navigated Laser Endoscope for Minimally Invasive Photodynamic Diagnosis/Therapy

（低侵襲光線力学的診断・治療法のための軟性同軸レーザ誘導照射内視鏡）

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Present computer assisted surgery usually applies some technologies like MRI and CT to aid surgeon to diagnose tumor which tells surgeon the organ and position of tumor inside body. However, it is difficult to differentiate neoplastic from normal tissue even in front of endoscope by white light during minimally invasive surgery. Nowadays, surgeons also adopt tumor navigation based on the MRI and histology images in clinical, but these data are not real time, which may cause wrong determination. Photodynamic diagnosis (PDD) is such a wonderful assistant to show tumor and normal tissue by different fluorescence color in the effect of light illumination and photosensitizer, and it can be applied during operation.

After diagnosis, minimally invasive surgery has been widely applied in oncology therapy which could improve patient’s quality of life. However, for some unresectable tumor tissue which may be tiny lesion or close to some important function organ, some more effective operation appliance should be applied. Photodynamic therapy (PDT) could destroy tiny lesion without tissue removing, which considerably reduces the possibility of tumor recurrence.

There are some main disadvantages for presently applied endoscope technologies: first, it is difficult to control the laser fiber which is separated from the endoscope; second, endoscope neighbored by an instrument channel for laser fiber causes different view field from laser irradiation field; third and the most fetal, the laser irradiation target is uncontrollable, which may damage surrounding normal tissue and blood vessel leading to unexpected complications; fourth, the target is invisible during PDT for present

endoscope as the captured images are pure white; fifth, endoscopes for PDT and PDD are different, so intraoperative diagnosis cannot undergo unless changing endoscope.

Therefore, this research proposes and develops a new kind of diagnosis-and-therapy device, which could minimally-invasively reach and observe the tumor area, while diagnosing local tumor tissue under photodynamic diagnosis (PDD) mode and laser irradiating during photodynamic therapy (PDT).

To be suitable for both PDT and PDD, 5-aminolevulinic acid (5-ALA) series are selected as photosensitizer, 375-400 nm blue light as PDD excitation light, 635 nm wavelength laser as PDT laser to treat tumor tissue.

Analyzing the observation optical system, the view angle is limited by the camera sensor size to be less than 104 degree, and focal distance should be less than 1.9 mm to obtain less distorted image, also the image maximization is confined by the camera sensor size to be 2 times. About the laser induced optical system, first the laser output angle from the objective lens system is only related to the laser incident height from fiberoptics to objective lens system, not dependent on the incident angle. Imaging fiber bundle is applied as fiber optics in this research, which is coherent, meaning the same input and output position, and high temperature transformation, suitable for laser transmission. Thus I can change the laser steering angle by adjusting the laser incident angle from the laser focusing lens system into fiber bundle, which should be achieved automatically by some precision instrument, like stage or galvano scanner. Some experiment proved that the incident angle into fiber bundle should be as small as possible to avoid “donut” of output laser, which reduces the laser power density in the center of laser spot. Because galvano scanner usually provides output laser with skew angle, stage is applied into this laser endoscope in order to offer parallel laser into fiber bundle.

To combine the observation optical system and laser induced optical system together, beam splitter is necessary. Based on the principle of reversibility of optical path, the P-Pol laser beam enters through the beam splitter. Also, polarized beam splitter is applied, because it is not only able to split the therapy laser from visible image light, but also provides color image for surgeon. The wavelength of fluorescent light of tumor tissue is around 630 nm, and that of therapy laser is 635 nm. During therapy mode, the system should provide clear image for surgeon to observe the target by shielding irregular reflection laser. But during diagnosis mode, the 630 nm-wavelength fluorescent light should be caught by camera and also contrast enhanced, beneficial to help surgeon to differentiate tumor tissue more easily. In order to achieve the above two purposes, different filters are necessary, notch filter and color compensation filter. Thus, in order to change the filter according to the surgeon’s selection, flip mount is applied. Moreover, during experiment I find that the laser reflection in the objective lens system renders ghost laser spot, which is reduced by coating lens and black dyed pinhole.

In pursuance of moving laser spot to the selected target, laser focusing lens system and laser fiber header is fixed onto XY hollow stage. Considering the stage’s PID controller parameters are fixed by the maker, the stage precisions of horizontally and vertically placement are measured to select more stable station, which could avoid large laser positioning errors. Experimental results on three kinds of precision prove the horizontally placed stage seems more stable.

Camera inner parameter, estimated by camera calibration, provides less distorted images for users. Similarly, stage calibration is applied to obtain parameters which represent the relation between the stage moving distance and the image coordinate. Because the laser positioning error caused by the objective lens distortion is tolerable, the laser spot on reflected from the imaging fiber bundle of laser incident tip is recorded to acquire the corresponding spot on image to the stage moving distance. After obtaining 10 groups of data, we can estimate the stage calibration parameters.

Thus, the construction of this system is described as: outside visible light (or fluorescent light) is focused by objective lens system, into imaging fiber bundle, reflected by beam splitter, through the camera piece and laser notch filter (or color compensation filter) and finally focused on camera sensor to get therapy image (or diagnosis image). In the therapy mode, laser focusing lens system simultaneously focuses fiber laser, through beam splitter, into imaging fiber bundle and spread by objective lens system only onto selected object target. During therapy, because the photochemical reactions always needs 10-15 minutes to achieve the necessary power energy to kill the tumor cell, in order to avoid wasting time on stage moving, vector laser scanning is applied, which generally costs less time than raster laser scanning. By doing so, it is able to suppress the invasion of normal tissues and blood vessel during operation.

During the experiment, I evaluate the observation optical system by image quality, the laser induced optical system by laser power density, and the laser endoscope by laser steering area, laser positioning accuracy, laser scanning, and in-vitro experiment. The image view field is large enough for 10mm-diameter tumor even at distance of 20 mm, and resolution is five times of standard laparoscopy. And also MTF 50/MTF 20 and chromatic aberration (CA) are used to evaluate the image quality. Laser transmission efficiency is not high, by laser power density is much greater than PDT required value, so the user could get the expected value by adjusting the laser diode current. As the laser spot diameter is changed with the output position from the objective lens system resulted by the lens Petzval field curvature, the laser steering area with relative transmission efficiency about 80% is obtained to ensure the therapy efficiency. Then laser positioning accuracy of this system is evaluated, and the average distance error between the target and the laser spot center is less than 0.4 mm, even at distance of 50 mm, the maximum positioning error is less than 0.67 mm, which is less than the expected value, 1.25. For the laser scanning, the system is supposed to stop laser irradiation automatically once the fired power energy reaches the required value. Thus the iteration counts are related to the required power density and elapsed time for one scan, whose relation with the selected field area and number of scanned points is obtained by experiments. As a preparation for the in-vitro experiment, we set the endoscope on the passive arm and laser irradiates the brain phantom. Finally, the system is applied in-vitro experiment to evaluate the efficiency. Based on the principle of photodynamic therapy, in case no cell or animal, the 5-ALA cannot be transferred to PP IX without biological metabolization. Thus, PP IX is adopted in the experiment as the photosensitizer, and gelatin as the therapy reaction object. The simulated tumor tissue can be distinguished in PDD mode, then the user can select out the red field from the view field, especially after increasing the image contrast. Also the histograms in red channel of the two simulated field prove their difference. But there is no reaction to the gelatin during photodynamic therapy after laser scanning, even by different parameters, such as the concentrations, laser power density, irradiation time, interval time after irradiation.

I also talk over different experiments following the experiment result respectively. First, large field view angle causes large image distortion, and Plössl eyepiece could provide clearer images than Kepler. The laser power is effected by the laser focusing spot size and pinhole size in the objective lens system, which explains the low laser transmission efficiency of the laser endoscope. I also discuss that not only the curvature of lenses in the objective lens system, but also in the laser focusing lens system results in the changing of laser power according to the position of output laser on the lens surface. During the laser positioning experiment, once the stage is not placed straight, even skew less than 0.2 mm, the positioning accuracy would reduce largely, so that during the system construction, it is necessary to make sure the stage moving direction parallel to the camera sensor. Moreover, because the laser spot center is considered as the irradiation target, part of the laser is outside the selected field when laser scans to the edge of the target area. But comparing the view field and the tumor size, this is tolerable. For the in-vitro experiment, the red fluorescent light in diagnosis image is very weak, there are three possible reasons for this: first, the fluorescent light itself is very weak; second, the transmission efficiency of this endoscope system is not high; finally, the illumination power supplied by flashlight, which is not professional medical device, is weak. Responding to the non-reaction of gelatin during therapy, there are two possible reasons: first, the protein type for single oxygen is different, then the live cell or animal for PDT reaction is necessary, which is supposed to be completed in the future.

In the Chapter 6, I discuss that the laser endoscope satisfies all the requirements listed in the introduction part. Then, although the transformation temperature of fiber bundle is very high, the maximum power density at the laser incident surface of fiber bundle may damage the fiber bundle when the laser is focused into the fiber bundle from the laser focusing lens system. I also compare the developed laser endoscope with the previous research, and show the different and improved points respectively. This system is able to complete diagnosis and therapy by itself, and it is also able to combine with other medical appliance. Finally, the future plan for this laser endoscope is provided, which makes this system more suitable for clinical surgery, and also it is available in some other possible field by changing a certain device.

Finally, in the conclusion, the contribution of this thesis is the development of a new kind of flexible diagnosis-and-therapy endoscope. Intraoperative photodynamic diagnosis is realized without changing endoscope. After selecting the tumor target by intraoperative diagnosing, during therapy, the laser is positioned to the selected target spot or scanning the target area while the surgeon could observe the laser moving and object target. By doing so, the therapy laser would not irradiate to surrounding healthy tissue or blood vessel causing burning or blood vessel necrosis or even more serious complications. It is hoped that this study will open up many new possibilities for advancement in the application of oncology treatment for intraoperative diagnosis and therapy.