博士論文 （要約）

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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Yan Hu, Tokyo, Japan

Abstract

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 surrounding healthy 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 hopeful that this research will open up many novel possibilities for advancement in the application of oncology treatment for intraoperative diagnosis and therapy.

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Context Specific Terms & Disambiguation

Minimally invasive surgery (MIS) in oncology is applied in research and clinic with surgical technique, in which important advances have an effect on primary morbidity caused during the patient's surgical procedure, period of hospitalization time, physical hurting administration, and quality of life outcome.

Computer-assisted surgery (CAS) adopts computer technology for surgical planning, guiding or performing surgical interventions in present clinic surgery.

Photodynamic Therapy (PDT) is the process of *photosensitizer* plus laser light action for tumor/cancer therapy.

Photodynamic Diagnosis (PDD) is the process of *photosensitizer* plus laser light action for local tumor/cancer diagnosis.

Photosensitizer (PS) is such a compound which absorbs light and then launches a photochemical or photophysical response.

Singlet oxygen ($^1O_2$) is molecular oxygen which is in a stimulated or animated state and distinguished by the contrary twirl of a couple of electrons. Thus it is less permanent and more sensitive than the common triplet oxygen (O_2).

Coaxial means the same view field as laser irradiation field in one endoscope.

Chapter 1 Introduction

Generally diagnosis and therapy are necessary for tumor surgery. Present computer assist images like MRI, X-ray and so on just tell surgeon the tumor organ, but the surgeon should distinguish the tumor from healthy tissue in front of endoscope, and photodynamic diagnosis (PDD) based on blue light increases the identification of tumor.

For the photodynamic therapy, it is an effective tool for unresectable tumor tissue, which is close to important-function organ or blood vessel, or unreachable by present cutting appliance. However, present applied endoscope hurts surrounding healthy tissue, such as blood vessel, which maybe cause some serious complications. Thus, target/area-controllable laser endoscope is necessary.

A PDD/PDT integrated laser endoscope could alleviate the burden of patients, and also help surgeon to diagnose the tumor during operation. This chapter introduces following this flow as shown in Figure 1-1.

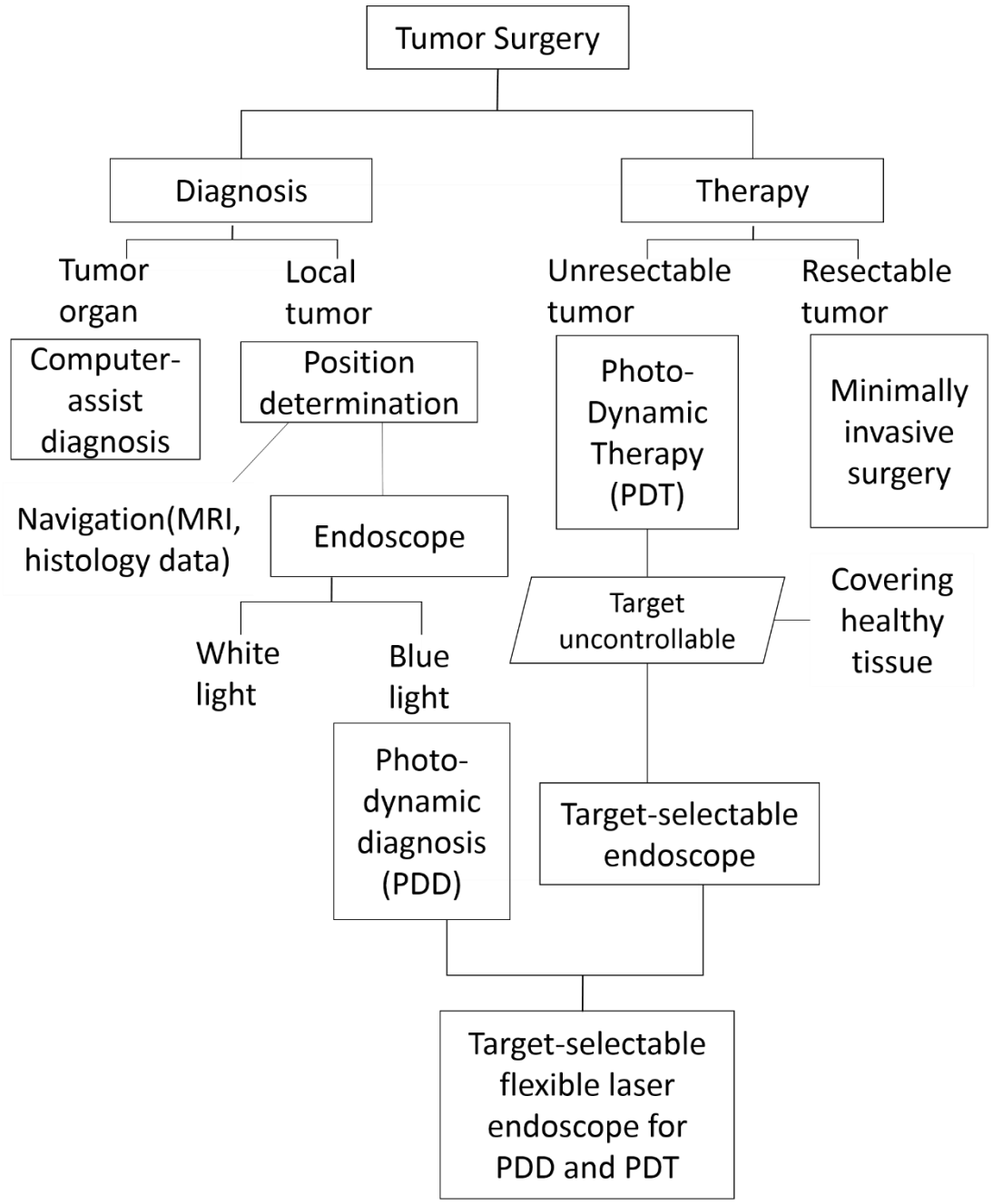

Figure 1-1 Outline of Chapter one.

1.1 *Overview*

In this part, the overview of this research is introduced to get acknowledge of the overall flow of this system. And then I will present background of this research about diagnosis and therapy in oncology.

1.1.1 Overview of the Research

This research is motivated by the clinical needs and technical limitations in the application of laser endoscope of photodynamic diagnosis and therapy in oncology. The purpose is to develop a new kind of device which is able to least-invasively reach and observe tumor, while carrying on part tumor diagnosis under PDD mode and irradiating laser to tumor part during photodynamic therapy.

This system establishes a flexible fiber-bundle endoscope for guiding laser to arbitrary target spots in the view field for kinds of tumor therapy. The spot is selectable by surgeon on visual image during the whole surgery course. To achieve this, integration of image and laser transmission scope is proposed for the development of a coaxial endoscope system, which includes novel features like flexible imaging fiber bundle applied into laser transmission and also laser guiding only to selected target. And also according to the selection mode by uses or surgeons, the camera can capture images for different modes, diagnosis mode and therapy mode. Considering stage moving under condition of standing or horizontal, precision experiments undergo to obtain stable stage placement.

For a comprehensive overview, segments of the “intellectual plot-line” of this research are summarized in Table 1-1 concisely.

Table 1-1 Summary of intellectual 'plot-line' in concise statements

Plot-line	Salient Points	
Motivation	● Address clinical needs • Diagnosis of cancer during operation • Photodynamic therapy for cancer • Laser endoscope challenges ● Bridge research gaps • Flexible & coaxial & laser transmission spot controllable endoscope have not been studied • No related research about PDD and PDT sharing the same scope	
Objective	● Provide flexible coaxial laser endoscope with • Intraoperative diagnosis • Visible image during therapy • Positioning laser only to selected target	
Approach	● Transmit image and laser in the same flexible fiber bundle • Beam splitter to transmit laser and reflect image • XY stage to move laser system automatically • Stage calibration to gain relation between different coordinates • Flip mounter to change suitable filter for diagnosis or therapy	
Scope	Survey → Research &Development → Scientific Investigation → Disscussion	
Research Value	Novelty: ● Coaxial imaging fiber bundle applied into laser transmission ● Intraoperative diagnosis by the same endoscope ● Stage to move laser automatically ● Stage calibration to position laser	Contribution: ● Development and evaluation of a flexible laser endoscope ● Address the needs and limitations in present endoscope technology for photodynamic diagnosis and therapy

1.1.2 Background of the Research

This session introduces contemporary computer assisted surgery for diagnosis of tumor organ and present local tumor diagnosis methods. Then the challenges in minimally invasive surgery in oncology is presented.

1.1.2.1 Tumor Diagnosis Technology

Computer-assisted surgery to assist surgeon the organ tumor part, followed by present local tumor diagnosis technologies, is introduced in this part.

Computer-assisted surgery (CAS)

Computer-assisted surgery (CAS), which adopts computer technology for surgical planning, guiding or performing surgical interventions, is widely applied in present clinic surgery. Invisible internal organ and even deep within the chaos of cancer cells become “visible” for surgeons and researchers, who are able to understand the definite position of the organ or tissue, instead of guessing it by experience and feeling. Safety and accuracy are greatly improved by this “new eye”. Medical imaging, which is an extra necessary tool for cancer diagnosis, is applied to [1]:

- Display, diagnose, and grade of tumor or cancer;
- Navigate tumor or cancer therapies;
- Decide whether a therapy is effective;
- Observe tumor or cancer reappearance;
- Assist medical study, especially in such vital fields as drug invention and medicinal deviation to degrade patients’ fear.

The main medical vision technologies includes Computer Tomography (CT), X-Rays, Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) scans. By enhancing diagnosis and treatment, these are applied to hospital daily work to degrade the fear for tumor or cancer patients.

X-Rays (also called radiographs), which use electromagnetic radiation to make images, are applied in tumor or cancer diagnosing and commonly symbolize a two-dimensional image, taken the machine by the Siemens Healthcare [2] as an example, and the X-Rays image also shown in this website. It is not painful, but the insecurity for patient depend upon the quantity of radiation. In addition because 2D X-ray images only contributes a projective image of the inspected target, it is difficult to represent the positional relationships [3].

Computer Tomography (CT) data symbolizes a sequence of separate X-ray images that are constructed into one 3-dimensional images, which is a very detailed, 3D view of the body's interior, an example and the result image as shown in the website of Siemens Healthcare [2]. Compared with X-Rays, it holds some advantages: localization of anatomical structures, sensitivity and quantitative measurements [3]. So this image could be used to determine exactly where to perform or guide a biopsy procedure, also guide some local treatment, and plan therapy.

Magnetic Resonance Imaging (MRI) applies strong magnets to create detailed, cross-sectional pictures of insides from many angles because distinct tissues (including cancer or tumor) give out an approximately severe signal grounded on their chemical structure [2]. MRI can also produce 3-dimensional images of the body's sections, and it is usually the superior way of discerning and distinguishing tumor or cancer in the bones, muscles, neck and head [1]. Two main types are closed type and open MRI, and one of main manufacture is Hitachi Medical [4].

Positron Emission Tomography (PET) scans, as shown in the website of Hitachi Medical [4] a nuclear medicine vision technique, engender 3-dimensional images of working process, such as metabolistic movement [3]. This technology gives the most precise separate images for envisaging the distribution of tumor/cancer or its feedback to surgery [1].

Locally tumor diagnosis

These above technologies could show us the tumor/cancer position inside the body, and also some technology is essential for surgeon to differentiate neoplastic from plastic tissue while observing the tumor part. Conventionally, diagnosing for tissue, exceptionally for preneoplastic (i.e. before the formation of a tumor) and neoplastic position, depends on histological and cytological examination. However, the main disadvantage is subjective, depending on the examining histologist's perception, and also relying on removed tissue [5].

There are some researches and applications [6, 7], which apply intraoperative MRI image as navigation data to obtain the tumor position. Although the data is taken during operation, it is not real time, and the surgeon should move the patient during operation to take MRI image, which may increase burden for both surgeons and patients.

Moreover, white-light endoscopy for detecting cancer is also one traditional technique. However, it is difficult to tell normal and cancer tissue under white light, and one example of bladder cancer is shown by Sutherland Urology [8]. The tissue inside the yellow circle is cancer, whose color is almost the same as other normal tissue, so such image is not beneficial for surgeon to differentiate the tumor tissue. In addition, Sim et.al [9] proved that under white light, some flat lesions may be undetected.

Therefore, some new technology for tissue diagnosis is necessary to assist surgeons to diagnose locally the tumor tissue inside the organs, which could decrease the recurrence of tumor after therapy rendered by incompletely removed tumor tissue.

1.1.2.2 Minimally Invasive Surgery in Oncology

Benefited from engineering innovations in surgical devices and technologies, surgeons do not directly touch or observe the tissue or structures on which they operate, which guides into minimally invasive surgery world [10]. This could alleviate the patient's pain, discomfort, disability, or other morbidity due to trauma brought by conventional surgery.

At present minimally invasive surgery (MIS) in oncology is widely applied in research and clinic with surgical technique, in which important advances have a consequence on patient's surgical procedure, period of hospitalization time, physical hurting administration, and quality of life outcome [11]. However, there are still some challenges in the present surgery of oncology, for example:

For brain tumor, it is very difficult and dangerous to remove those tumor that are infiltrating brain parenchyma [12], especially near functional brain tissue. But remained tumors are always responsible for local tumor recurrence, repeat operations would give large burden for patients.

For digestive tract carcinoma, unresectable bile duct carcinoma indicates betterment in liver function, patient's quality of life with few complications, and also prolongates patient's survival period [13], so it should not be directly cut by present surgery appliance.

In clinic, surgeons treat lung cancer by combining surgery and either concurrent chemotherapy or radiotherapy, but after surgery, cancer recurrence, newly diagnosed cancer, or considerable pulmonary destruction with losing function often happens [14], especially for peripheral lung cancer [15].

For gynecological disease, radical surgery, as a classical approach to treat injuries and malevolence of the breast, uterus, cervix and vagina, commonly is applied. Whereas possibly remedial destruction of organ service and construction could happen unexpectedly [16], which takes the lives of women or reduces the quality of life.

Therefore, because of some irremovable tissue for better quality of life, or unresectable tissue for the cancer position near important organ function or unreachable by present surgery tools, it is impossible to simply remove these by present medical technique without considering patients' future life quality. In order to cure effectively these hard-treat cases, some other new application is necessary in order to cure the tumor without hurting surrounding tissue.

1.2 *Optical Diagnosis and Therapy in Oncology*

1.2.1 Photodynamic Diagnosis (PDD)

Optical diagnosis, applied in tissue diagnosis for distinguishing neoplastic from preneoplastic, relies on identifying a transformation in the character of light, which is produced by its communication with the concerned subject. Comparing with traditional diagnosis methods, optical diagnostic techniques are more objective and also able to realize real-time by way of minimally invasive courses, which obviate the absolute necessary for removing tissue and supply the surgeon with the required information to instantly operate authoritative treatment [5].

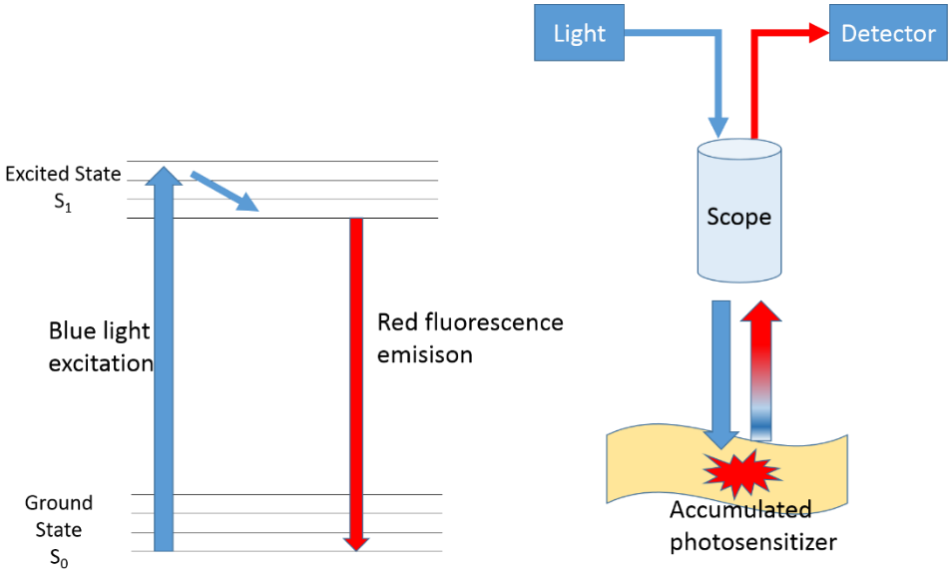

Figure 1-2 Photodynamic diagnosis (PDD) reaction.

Photodynamic diagnosis (PDD) is further expressed as fluorescence cystoscopy. Fluorescence is applied as a conflict instrument in such an optical procedure to signify pathologic tissue, whose principle is the appearance of fluorescent molecules concentrations distinct in healthy and pathologic tissue. As shown in Figure 1-2, the photosensitizer, which mainly accumulates in the tumor tissue naturally, absorbs the appropriate wavelength light to excite the fluorophore molecule's electron vibrational state. Whereas the atom releases to the ground state, a photon is gave out because of the variance of energy. The fluorescent photon holds less power than agitation photon,

and because the light power is contrarily proportionate to its wavelength, the wavelength of emission light is longer than that of irradiation light [17]. Thus, it is possible to distinguish these two types of light [5] as shown in Figure 1-2, the detector is able to capture the image which is mainly red (tumor) and blue (background).

PDD is able to be explained by the basis of two kinds of fluorescent molecules: one is the appearance of innate fluorescent molecules, internal or auto fluorescence; the other one is the administration of agents, like photosensitizers, which augment the performance of fluorescent molecules, exogenetic fluorescence. In this paper, the latter fluorescence is our main focus, combining with PDT to operate therapy in oncology.

To more easily understand the results by PDD, Sutherland Urology [8] gives a bladder cancer image under blue light. Comparing with the image under white light, we can easily differentiate the tumor, red in figure, from normal tissue, blue in figure, so that PDD image is able to present tumor part more clearly than that under white light to assist surgeon determining the tumor position.

1.2.1.1 Photodynamic Diagnosis of Cancer

Photodynamic diagnosis, applying in oncology, adopts photosensitizer and corresponding wavelength light (laser or LED) to enhance the visible difference between benign and malignant tissue. The main photosensitizers are listed in Table 1-2. As shown, the activation light is mainly blue light, and emission light wavelength is in the range of red light.

Table 1-2 Photosensitizer and corresponding wavelength for photodynamic diagnosis.

Sensitizer	Activation wavelength	Emission wavelength
mTHPC	380-430 nm	652 and 718 nm
Protoporphyrin IX	380-470 nm	693 nm
Photoactive porphyrins	380-470 nm	693 nm
Hypericin	385-450 nm	600-640 nm
5-ALA	375-400 nm	600-740 nm
5-ALA hexylesther	375-400 nm	600-740 nm

1.2.1.2 Challenges during Photodynamic Diagnosis

To distinct tumor part inside body, kinds of endoscope, or microscope for tumors, are widely applied.

In 2001, for malignant brain tumors, Zimmermann modified a neurosurgical microscope for mTHPC-mediated photodynamic diagnosis (PDD) and fluorescence-guided resection (FGR) [18]. In this system, a liquid light guide conveys blue excitation light for mTHPC (380-430 nm) to a lens system which is fixed next to the optical carrier of the microscope. The working distance is 30 cm with a homogeneous spot diameter is 5 cm. Optical path adopts an observation filter for the user and the camera in the system. Regional spectral images can be acquired by a fiber joined sensitive spectrometer from the image's heart part. Also to enhance color contrast, filter is applied with triple band-pass design. Then photodynamic treatment is performed by bare fibers, that is to say, the scopes for PDD and PDT are different. And the PDT laser irradiates all parts in front of the lens system, which is the same disadvantage as presently applied endoscope technologies.

For such bladder cancer which is not invasive into muscle, Olympus productions for photodynamic diagnosis (PDD) are shown on the website [19], which is mainly available for 5-aminolevulinic acid (5-ALA) or hexylaminolevulinate (HAL) of PDD. The outer diameter of endoscope is 4 mm. A special yellow filter particularly arranged for photodynamic diagnosis, in order to enhance the weak red fluorescence, is fabricated into the space, so this fluorescence can be distinguished by high contrast, as illustrated in Figure 1-3.

As illustrated above, a yellow filter is usually inserted to emphasize the contrast between red and blue fluorescence light. Therefore, in this thesis, such filter is also applied during diagnosis to obtain high-contrast PDD image.

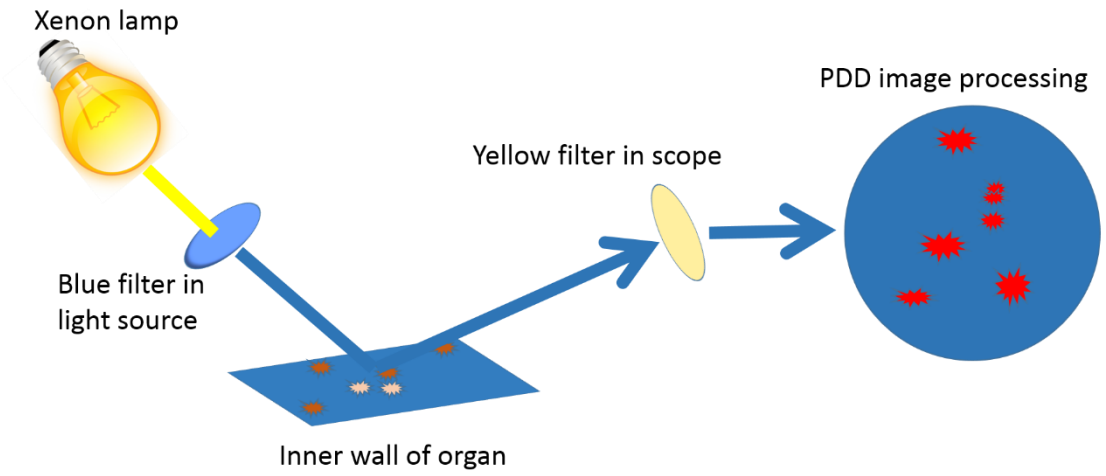

Figure 1-3 Blue filter in light source and yellow filter in scope.

1.2.2 Photodynamic Therapy (PDT)

Photodynamic therapy (PDT), as a modern interest for tumor or cancer therapy, started about 1960 by Lipson et.al. [20], applying a fluorescent tumor-locating combination of porphyrins called "haematoporphyrin derivative" [21]. Subsequently these innovative research, kinds of compounds have been checked out *in vitro* and *in vivo* in some extent of achievement. The fundamental of PDT is the interaction between the light and a photosensitizer that is choicely mainly congregated in the objective tissue (tumor or cancer), leading to tumor-cell destroying in the way of single-oxygen production, which is shown in the following Figure 1-4.

The procedure for PDT damaging tumor cells is like this, and taken brain tumor as an example:

First, the photosensitizer (PS) is administered systemically or optically, which will mainly selectively accumulate in the tumor cell.

Then after a period of time, waiting for systemic PS distribution, corresponding wavelength laser light is used to activate the photosensitizer.

Third, a photochemical reaction is drove on the production of molecular oxygen, and tumor cell is destructed because of irreversible harm to cellular macromolecules. This process is caused by an apoptotic, destructive or autophagic action, which goes

with inauguration of a precision regional provocative reaction. The dead cells are eradicated, healthy tissue equilibrium is recovered and at times the progress of integral immunity, which appear in this reaction [22].

Therefore, photosensitizer which selectively accumulates in tumor tissue, plus laser light produces singlet oxygen, which damages tumor protein causing tumor cell destruction.

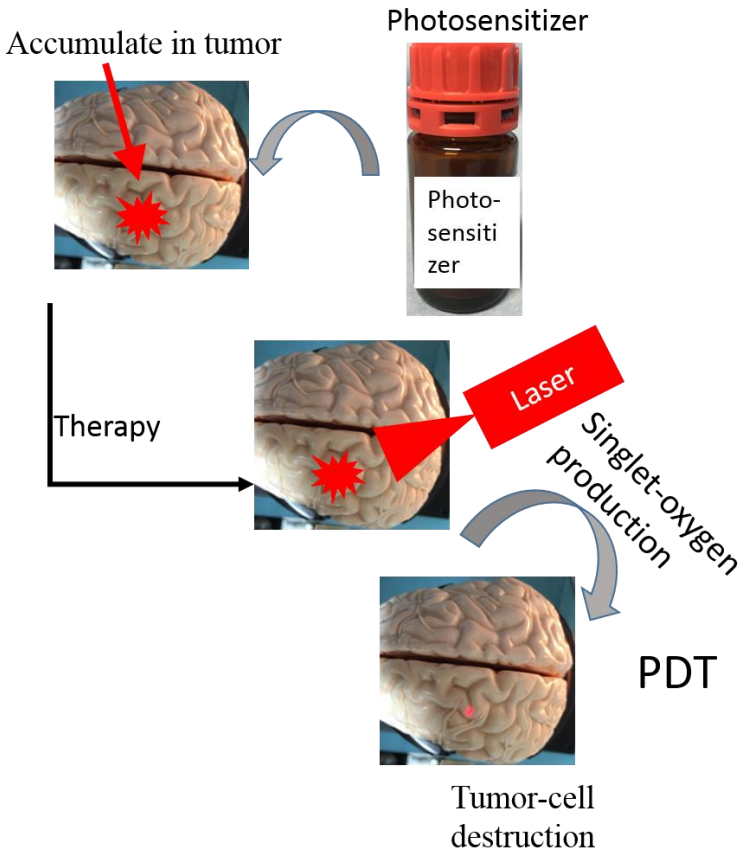

Figure 1-4 The principles of photodynamic therapy.

However, the reason for that PDT cannot heal progressively distributed disease is that the laser irradiation to the whole body of patients by necessary quantity (at least with current technologies) is very difficult [23], which is the limitation of PDT. Therefore, in this research we also mainly aim at photodynamic therapy for local tumor.

Moreover, photodynamic therapy is intimated in both early and advanced stage tumor/cancer, whose diameter is less than 8 mm [24] and depth of about 5 mm [25]

1.2.2.1 Photodynamic Therapy in Oncology

Since photodynamic therapy was considered as an available mechanism in oncology, this implement is presently being extensively applied in the clinic [23]. At present, various cancers, such as the head, pancreas, prostate and skin, are being treated [26]. Owing to researchers and surgeons, more choosy and impressive photosensitizers have been promoted, and are presently under research in clinical trials, and part of the necessary data are shown in Table 1-3, there are more detailed data in this paper [26].

Table 1-3 Photosensitizers for malignant diseases.

Sensitizer	Trade name	Activation wavelength
m-THPC	Foscan	652 nm
5-ALA	Levulan	635 nm (therapy) 375-400 nm (diagnosis)
5-ALA hexylesther	Hexvix	375-400 nm
Taporfin sodium	Talaporfin	664 nm

From the table we can get to know, corresponding different photosensitizer, the activation laser light wavelength is different, and also different potential indications. So for different tumor parts, surgeon is able to select available photosensitizer and laser wavelength, providing some free degree space for surgeons and also researchers. Study about investigating new photosensitizers to improve the tumor specificity is still going on [27, 28, 29].

According to Dolmans et.al. [26], photosensitizers can be administrated by kinds of means, which is also one advantage of photodynamic therapy, such as by intravenous injection to the skin or topical application of drugs. But these alter the biodistribution, which is different from time to time. To regulate the effect of PDT, another way is by controlling the timing of light exposure. The photosensitizer is converted from its

ground state (single state), by absorbing light (photons), into a comparatively long-lasting electronically excited state (triplet state) through a temporary excited singlet state [30]. The excited state is able to endure two categories of reactions simultaneously; category I reaction: producing oxygenated products, category II reaction: transferring energy precisely to oxygen in order to construct singlet oxygen, an extremely reactive oxygen categories (ROS), as shown in Figure 1-5.

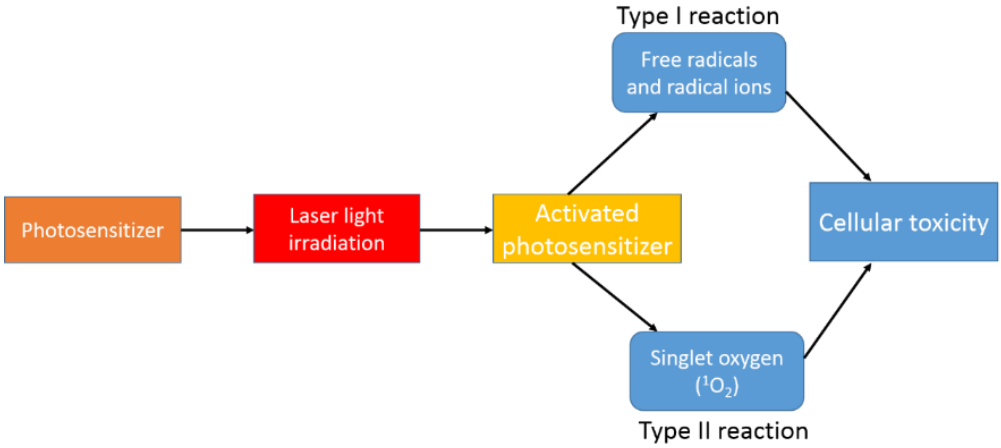

Figure 1-5 Two reactions in photodynamic therapy.

In biological system, the half-life of singlet oxygen is below 0.04 μs, and the action radius of singlet oxygen is less than 0.02 μm [31]. The photo-damage and cytotoxicity degrees are complex. These interdependent factors are listed as below: 1. the category of sensitizer; 2. the sensitizer's extracellular and intracellular location; 3. the administrated whole dose; 4. the overall light exposure quantity; 5. light fluency proportion; 6. oxygen occasion; 7. the occasion after the sensitizer administration and before light exposure [26]. Then photodynamic therapy destructs tumor by destructing tumor cells without delay, destroying tumor-affiliated vasculature, and activating an insusceptible reaction on tumor cells.

Because the essential objective of this research is to develop an endoscope for PDD and PDT, so combined with Table 1-2, we adopt 5-ALA or 5-ALA hexylesther as photosensitizer here, and blue light as PDD light source, red light as PDT therapy laser.

1.2.2.2 Challenges during Photodynamic Therapy

This part introduces some applied endoscope technologies for photodynamic therapy at present, and also their own disadvantages. Then the common disadvantage of present laser endoscope technologies will be presented.

Skin tumor photodynamic therapy technology

During photodynamic therapy for skin tumor, surgeons shines a bright red or blue light on the area which needs to be treated. For the neck tumor, the red laser light irradiates all the field in front of the device [32], also blue laser is applied for the face tumor [33]. As surgeons can see the tumor directly by eye without other instrument like endoscope, during skin tumor therapy. The following devices are applied in clinic and laser applicant just irradiates all skin in front of it. So mild burning sensation during therapy is sometimes produced [34]. And from the application images of the above two device, the laser irradiates not only the tumor skin, but also the surrounding normal skin.

Internal part photodynamic therapy

At present, surgeons always adopt minimally invasive procedure during photodynamic therapy for tumor. To observe the internal tumor, endoscope is always their preferred implement. There are several types of endoscope techniques widely applied in clinic.

One is laser fiber separated from endoscope as shown in the paper by Pettiford [35]. For inserting endoscope and laser fiber, a larger incision is necessary, which would give a lot of burden to patients and also be possible to bring kinds of complications, causing low quality of life. Also, it is not easy to control the laser fiber inside organ.

The second type is multi-channel endoscope, with camera lens channel, light illumination channel and instrument channel which could insert PDT laser fiber during therapy, as shown by Johns Hopkins Medicine Gastroenterology & Hepatology [36].

On the website, there are some images which describes the technology of photodynamic therapy. For such endoscope technology, one channel is video camera lens used as observing the tumor and the captured images are in the below.

This multi-channel endoscope is widely applied during minimally invasive surgery, because it holds an unoccupied channel convenient for inserting necessary instrument for different purpose, such as PDT laser fiber, other coagulation laser fiber, or needle for tumor therapy. However, from the tip of endoscope, the camera channel and laser fiber channel are different, which means the view field is different from the laser irradiation field, so it is possible to lose some tissue irradiated by laser. And this is dangerous for patients, because these uncured tumor tissue may cause tumor recurrence.

In addition, because the laser fiber inserted into the organs is longer than the tip of endoscope, it is dangerous if the fiber touches the organ surface which maybe happen, because the singlet camera cannot effectively estimate the distance between the organ surface and endoscope tip.

The third type of endoscope employs composite-type optical fiberscope [37], which could solve the above problems, including different view field from laser illumination field and laser fiber easily touching organ surface. The laser irradiation part is in the center of the fiber, so that this fiberscope holds the same view field and laser irradiation field. The center of the view field is the laser radiation point. And this fiberscope is applied in photodynamic therapy for peripheral lung tumor.

Common problem

Above three kinds of endoscope exist a common and fatal problem that is the uncontrollable laser irradiation. The laser from fiber irradiating everywhere in front of the laser fiber, not only tumor part but also healthy organ part. According to national cancer institute [38], PDT can result in sears, protrusion, hurt, and scratching in surrounding normal tissue. So such above endoscope technologies would hurt healthy tissue, bringing complications for patients.

Black tape was used by researchers [39] to cover surrounding healthy tissue to avoid laser irradiation. It is available for some tumor, like brain, skin which show healthy and tumor tissue to surgeon directly, but for other tumor which is observed by endoscope, the surgeon cannot cover the surrounding tissue by tape or silver paper.

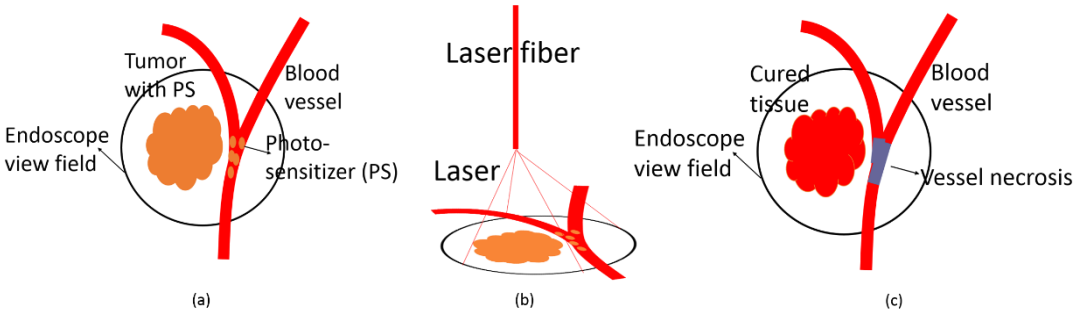

Figure 1-6 PDT laser problem. (a) Tumor near blood vessel containing photosensitizer. (b) Laser irradiating all part in the view field. (c) Blood vessel necrosis after therapy.

More serious consequence is that the uncontrollable laser irradiation may hurt healthy blood vessel, rendering normal blood vessel dead (necrosis). Because after photosensitizer is injected into the bloodstream as shown in Figure 1-6 (a), the blood possesses lots of turning cells (erythrocytes and leukocytes) which could bind these photosensitizer. Then the circulating photosensitizer should adhere the blood vessels' walls. And the nature of the various sizes and characteristics of blood vessels in the tumor and healthy tissues, and distinguished physiological kinds of vessels in varieties of organs are thought to control the place in which photosensitizer locates [40] at a considerable degree. Also parts of photosensitizer may fasten severely to the blood vessel wall, which would cost more time to through the whole blood vessel wall than those binding weakly.

So even after one or three days, some binding strongly photosensitizer may still remain in normal vessel, although most photosensitizer would selectively retain in tumor parts. In addition, it is advised that PDT consequence on healthy and tumor vessels is possible to be qualitatively and quantifiably comparable [41]. Therefore, it is dangerous for patients when the PDT laser irradiates to normal blood vessels, which

maybe cause these vessels necrosis as shown in Figure 1-6 (c). Especially if the tumor is near important blood vessel, the non-selectively irradiating laser endoscope technology would lead patients losing some important function or even their life.

In addition, some peripheral tissue of organ is also not suitable for wide round scope laser irradiation [42]. Also for peripheral cancer, like peripheral lung cancer [43], a widely spread laser would hurt more to normal organ tissue.

Therefore, one laser endoscope technology, which transmits laser only to selective tumor part and observes organ simultaneously, is necessary. As a disadvantage of the first two endoscope listed above, the laser irradiation field is different from the view field, which may cause to lose radiating some parts, thus coaxial, the same view field as laser irradiation field, is necessary to reduce the possibility of tumor recurrence.

All in all, such endoscope is necessary; first, coaxial: laser radiation field equaling to view field; second, laser transmission controllable: transmitting laser only to selected tumor parts: third, flexible: to be able to insert into some internal organ like lung flexibly.

1.3 *Related Researches and Gaps*

1.3.1 Coaxial Laser Endoscope

In 2010, Yamanaka proposed a rigid coaxial laser coagulation endoscope for twin-to-twin transfusion syndrome [44]. This endoscope was used to cut an abnormal blood vessel between twins, and stop unbalance blood transmission from donor to receiver. This endoscope could observe object target, and at the same time transmit Nd:YAG laser to selected target, whose purpose is to avoid hurting baby or other important vessels. The developed endoscope is shown in the following Figure 1-7.

In this system, laser for coagulation of blood vessel was Nd:YAG, 1064nm, in the arrange of infrared light, so hot mirror was applied to transmit outside visible light to camera for image or video, and reflect laser light to grin lens to the object for coagulation. Also galvano mirrors were adopted to change the laser direction to selected object.

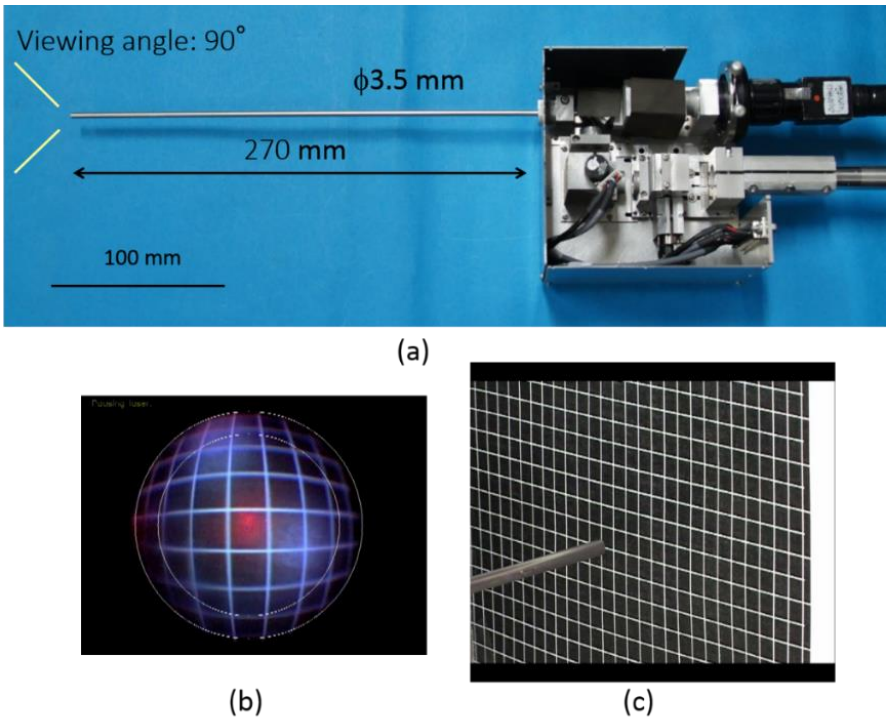

Figure 1-7 Rigid coaxial laser endoscope. (a) Developed endoscope. (b) Endoscope view of grid. (c) External view of grid and endoscope tip.

Although this system could solve aforementioned problems, this system holds its own disadvantages causing that it is not suitable for photodynamic tumor therapy.

- Its scope is rigid, which could not be used for neither some gynecological or lung or stomach therapy. And it is not able to coagulate the object target vessel which is not right in front of the endoscope tip.
- In addition, the laser for coagulation of TTTS abnormal blood vessel is 1064nm, but the laser wavelength for different photosensitizer is in the range of visible light, so the hot mirror cannot split the PDT laser from visible light.
- Galvano scanner is applied in this system, and it generally gives out skew instead of parallel light after changing angle, which is not best solution for flexible fiberoptics.
- One more thing is the camera image as in Figure 1-7 (b), which is distorted too much, bringing some recognition problems to users.

1.3.2 PDD/PDT Endoscope

There is some research also integrating PDD and PDT endoscope into one. Here I will illustrate one of them.

The structure of the endoscope system [45] is not shown in this thesis, but the numbers representation corresponding unit are listed as Figure 1-8 in order to understand the system construction in English. This system is able to observe target during normal observation, PDD mode or PDT mode controlled by system controller. Also it irradiates therapy laser by laser fiber probe for PDT, and light guide fiber bundle is applied to illuminate PDD exciting light source or normal white lamp light, which is controlled by two shutters. In the front of the endoscope, light distribution lens is used to disperse illuminating light, and objective lens system could focus outside light to image sensor, and then signal cable reads RGB signal to color CCD. On monitor, two of three kinds of images that include normal white light image, or PDD mode or PDT mode image, are presented. But under PDT mode, the image is pure white, so that it is unable to observe object target.

Although this system integrates PDD and PDT into one endoscope, there are following deficiencies:

- The fiber probe for PDT laser is arranged adjacent to the channel for image signal transmission, which means the different view field and laser irradiating scope.
- Laser for PDT is fired from a fiber probe, so that there is no control of the laser irradiating field, the same problem as traditional endoscope technology.
- Image under PDT mode is pure white, which makes surgeons unable to observe the object during therapy, thus unable to judge the treatment effect.

10	endoscope	21	timing controller
11	light distribution lens	24	system controller
12	objective lens system	28	focusing lens
13	image sensor	29	beam splitter
14	exciting cut filter	31	collimator lens
15	cable driver	32	rotary shutter
16	light guide fiber bundle	36	shutter
18a, b	signal cable	41	laser fiber probe
19	electrical connector	60	monitor
20	light source equipment		

Figure 1-8 Endoscope system construction.

1.4 *Status of the Present Research and Objective*

This research objective is to develop an endoscope system, which satisfies the following conditions:

- In order to assist surgeons to differentiate the plastic and neoplastic tissue inside body during operation, this system should catch diagnosis and therapy images.
- The scope should be flexible, in order to be suitable for some organ tumor therapy like lung, bladder.
- It is coaxial, meaning the same view field as laser illumination field.
- The laser spot should be controllable, that is to say, laser is fired only to the selected target part. Because as illustrated before, some photosensitizer is possible to be remained in blood vessel, and under the irradiation of laser, it maybe lead to blood vessel dead, which is dangerous for patients.

- ◆ Image under PDT mode should be visible, so that surgeons could control the present condition and select the radiating target.

The specific aims of this thesis are:

1. Propose a diagnosis-and-therapy laser endoscope system.

2. Development of the integrated laser endoscope system which satisfies above conditions.

3. Assessment of above system by performance evaluation and *in vitro* experiment.

1.5 *Scope: Organization & Research Methodology*

The scope of this thesis is organized based on a methodical research approach in sequence of four parts namely A) survey, B) research, development and scientific investigation, and C) discussion and conclusion.

Part A. Survey (Chapter 1)

In part A, the background information, justification and objective of the research will be introduced in Chapter 1. This chapter establishes the required background knowledge and insights to the state-of-the-art relevant for this research.

Part B. Research & Development & Scientific Investigation (Chapter 2 & 3 &4&5)

Part B describes the R & D & S process, which encompasses requirements and specifications of laser endoscope, and the developed system also with its experimental results. Chapter 2 illustrates some requirements and specifications for laser endoscope system. Chapter 3 presents the designing of laser endoscope. The applied system device specifications are listed in the Chapter 4. Then the experimental evaluation is followed in Chapter 5.

Part C: Discussion and conclusion (Chapter 6 &7)

Chapter 6 relates the research observation with important implications and qualifies contribution of this work to existing knowledge. Future work and recommendations on

the research roadmap is also discussed. Finally, Chapter 7 concludes the thesis by reiterating the contribution and highlighting potential impact of the research outcome.

The flow of the thesis reflects the adopted research methodology. The purpose/ scope covered are summarized in Table 1-4.

Table 1-4 Thesis Organization and Scope

Research Element	Thesis Organization	Purpose/Scope
Part A:Survey	Chapter 1: Introduction	➢ Background understanding
Part B:Research & Development & Scientific Investigation	Chapter 2: System specification	➢ Endoscope specification
	Chapter 3: Developed laser endoscope	➢ Developed PDD and PDT endoscope
	Chapter 4: System configuration	➢ System device
	Chapter 5: Experiment	➢ Evaluation on system
Part C: Discussion	Chapter 6: Discussion	➢ Significance of research
	Chapter 7: Conclusion	➢ Conclude findings

Chapter 2 System Specification

In this chapter, the laser endoscope requirements and specifications are introduced, as shown in Figure 2-1. System specifications are mainly about observation optical system, laser induced optical system, beam splitter and filters.

For the observation optical system, the visible light goes into the objective lens system and fiber optics, and then focused by eyepieces onto camera.

For laser induced optical system, laser is focused by lens system into the fiber optics, and then transmitted to target by objective lens system.

To combine the two system, a beam splitter is necessary. Because different purposes on captured images, different filters are necessary. Notch filter is applied to shield the irregularly reflected laser to get clear therapy image. Color compensation filer enhances the contrast between tumor and healthy tissue.

This chapter is written following this order.

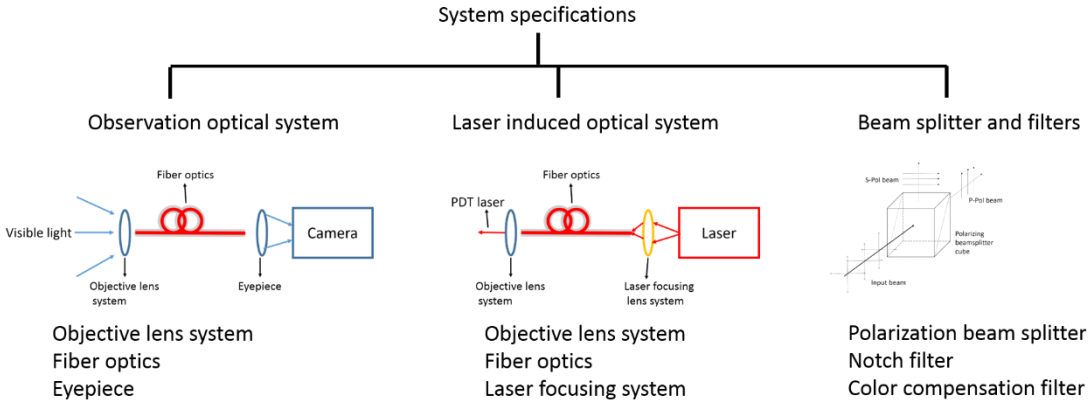

Figure 2-1 Outline of chapter two.

2.1 *Laser Endoscope Requirements*

The future final objective of our research is to establish a laser endoscope which is suitable for photodynamic diagnosis and therapy in clinic, so the following requirements should be satisfied.

Outer diameter of endoscope

When therapy for internal organ tumor/cancer, endoscope is inserted into the body, so if without considering the organ, the outer diameter should be small enough to alleviate patients' suffering. Normally for slender scope, like cystoscope, the outer diameter is usually from 4~5.2 mm, and colposcopy about 4 mm. For some inserted from mouth, such as gastroscopy, the diameter is often 4.9~12.8 mm [46]. If the above endoscope is combined with some laser fiber probe, the outer diameter will be increased to 1.65~3 mm. Then the outer diameter of present endoscope for laser therapy is more than 5.65 mm. Therefore, in this research, the outer diameter attempts to be less than 5.65 mm.

View field of endoscope

The wide view-field of endoscope is able to observe more target area inside body, so that it is beneficial for surgeon to differentiate the plastic and neoplastic tissue. Also, reducing the movement of endoscope inside organ could decrease the danger of touching the organ by endoscope tip. So wide view field of endoscope is desirable. Therefore, the view field of this endoscope system is tried to be larger than 70^{o} [47].

Working length of endoscope

Endoscopes for different purpose need different lengths, such as for stomach and duodenum 925~1250 mm length is applied; for colon and large intestine, the

colonscope is normally longer than 1330 mm; and shorter endoscope is adopted for some other organs, like vagina and cervix about 300~400 mm is enough [46, 48] . Therefore, in this system, because laser is fired from the tip of endoscope, the working length of endoscope promises to be suitable for stomach and duodenum, i.e. no less than 1000 mm.

We also need to transmit laser to the object through the fiber, so the fiber characteristic should be under consideration.

Laser power density regarding irradiation spot

According to the relationship between laser and organ tissue [47], laser power energy density for photochemical reactions is above 10^2 J/cm^2, power density 10^{-2}~10^2 W/cm^2, interaction time 10^1~10^4 sec.

For photodynamic therapy, light dose plus photosensitizer is vital to determine the degree of tumor cells destruction. Different light dose corresponds to different tumor type, such as for brain tumor, light dose is 20-140 J/cm^2, and 300 J/cm^2 is necessary for lung tumor [50]. But according to Mahmound [51], laser power density (PD) should be kept under 200 mW/cm^2, as a higher PD results in unacceptable thermal outcomes.

Therefore, it is necessary to make sure the power density of this laser endoscope adjustable to be not more than 200 mW/cm^2, and the irradiation time about 10-15 minutes.

Irradiation spot diameter and spot (center) position accuracy

The tumor size suitable for photodynamic therapy (PDT) is mainly small, because the disadvantage of PDT is that the necessary laser light to stimulate the greatest photosensitizers cannot be subjected to more than 10 mm of tissue, and also not available for spreading cancer [52]. For example, PDT treats early lung cancer less than 1 cm in surface diameter [53, 54]; after bronchogenic carcinomas therapy, diameter

above 1 cm has been destroyed [53]; and also treatment for inoperable adenocarcinomas, the diameter of 2.5-6 cm is acceptable [56]. In order to be suitable for PDT of lung cancer, the irradiation spot diameter should be less than 1 cm. Moreover the spot diameter should be small enough to avoid hurting the surrounding healthy tissue as less as possible, and also it should be not too small, which would increase the laser scanning time, thus the spot diameter is supposed to be less than 2.5 mm.

In addition, the position of irradiation spot is controlled by computer in this system, and it is thought to higher repeatability than that by surgeons. The goal of laser positioning accuracy is to be less than 1.25 mm, less than 1/2 of required laser spot diameter.

Irradiation distance

Photodynamic therapy for neoplastic tissue, endoscope combined with laser fiber probe is generally above 20mm away from the tissue surface to make sure non-contact between endoscope tip and tissue. Laser radiation is delivered to a distance of several centimeters from the full contact with a tissue [57], also some at a 2-cm distance [58], and some at a distance of irradiation by 5 cm [59]. To avoid the endoscope tip touching the organ surface, which maybe cause bleeding or other complications, the endoscope is able to observe object target clearly at 20~50 mm, and also promise the power density reaching the requirement for therapy.

Optical element

Laser output from endoscope is less than 50 mW, which is not too high for optical lens or filter, so here we do not consider too much about the optical element damage caused by laser. But the laser diode is set with cooler to avoid high temperature. Because the therapy laser wavelength is in the range of the visible light, and we need

to observe object by catching image, some coating for lens is applied to reduce the reflection among optical elements, which would decrease the image quality.

Operability

The endoscope system would adopt some user interface to let surgeons or users easily understand the operation for laser irradiation to the selected target. The user just selects on the user interface to be able to control all the device, laser device to be ON/OFF and change the laser diode current, flip mount to change necessary filter, and camera to capture images.

Cleaning and sterilizing

In the case of clinical use, cleaning and sterilizing are necessary before operation. And it is possible that blood or organ tissue adheres to the endoscope during operation, so that reprocessing is essential. For health-care facilities, the main sterilizing methods are steam under pressure, liquid chemicals and so on. Flexible endoscopes do not endure high-temperature (>60 degree) handling, and are not able to be castrated or sanitized by hot water or subatmospheric steam [60]. Our flexible endoscope can be sterilized by some method like liquid chemicals. So that I need to make sure the contracture of endoscope available to be separated.

2.2 *Observation Optical System Specification*

In this research, I design the endoscope optical system for both observing and laser transmission. For observation optical system, the angle of view, aberration and view field in endoscope image are considered during designing.

A flexible endoscope can consist of a fiber optics, an objective lens system and an eyepiece. Objective lens system and eyepiece are both imaging systems, but the integration of the two is non-imaging system. An optical fiber, as a non-imaging system, is inserted into the objective lens system and eyepiece, then the whole system becomes

imaging system and also ensures the working length of endoscope. Thus, these three parts are designed respectively, and then integrated into an endoscope. In addition, specifications for observing optical system and laser transmission optical system are different, so it is necessary to realize a certain system that shares the objective lens system and bundle of fiber optics, and holds respective eyepiece and laser-induced system.

In the following, to seek the specification of endoscope design, every lens system is considered as one thin lens, and also discussing paraxial geometric optics which uses the principal point of lens. Based on the above specifications, we will design the endoscope optical system.

2.2.1 Objective Lens System

Objective lens system is essential for the view angle of endoscope system.

The objective lens system is used to gather light from the observed object and focus the light rays to produce a real image, which makes wide view field possible. The angle of view is 2α, the focal distance of lens is f_o, the clear aperture is $2*r_o$, then

$$\tan \alpha = \frac{r_o}{f_o} \qquad \textbf{Equation 2-1}$$

As illustrated in section 2.1, the requirement for view angle is above 70 degree, and it is also desired to observe wider view field, so larger view angle is preferable. If the lens diameter is 3 mm, and the clear aperture is 2.7 mm, then the lens focal distance should be less than 1.93 mm. But as the longer the lens focal distance, the image aberration increases. Also, because the laser from fiber would disperse, the lens focal distance should not be too long, which could cause laser loss from fiber to objective lens system.

Moreover, the endoscope should be able to observe some small blood vessel at some distance, such as 1 mm diameter, that is to say, the camera image should show us the blood vessel above a certain size. Therefore, as shown in Equation 2-2, the real vessel diameter is s_o, the distance between object and lens focal point is d, the pixel number of vessel on fiberoptics is p_f, and the pixel number of vessel on camera image is p_o, the

view field radius on image is p_e. As we hope to show surgeons clear image, it is advised to maximum image to two times. So p_o equals to 2*p_f. Then the relationship is as bellows:

$$\frac{s_o}{d\ tan\alpha} = \frac{p_o}{p_e} \qquad \textbf{Equation 2-2}$$

In order to observe the maximum view field by endoscope, the image diameter equals to the short axis of image. Generally, the maximum pixel number is 640. At some distance, if the blood vessel could be shown at a certain size, it will be limit the angle of view. For example, if the distance is 50 mm, and the blood vessel is about 10 pixel on image, visible for user, then the angle of view should be less than 104 degree.

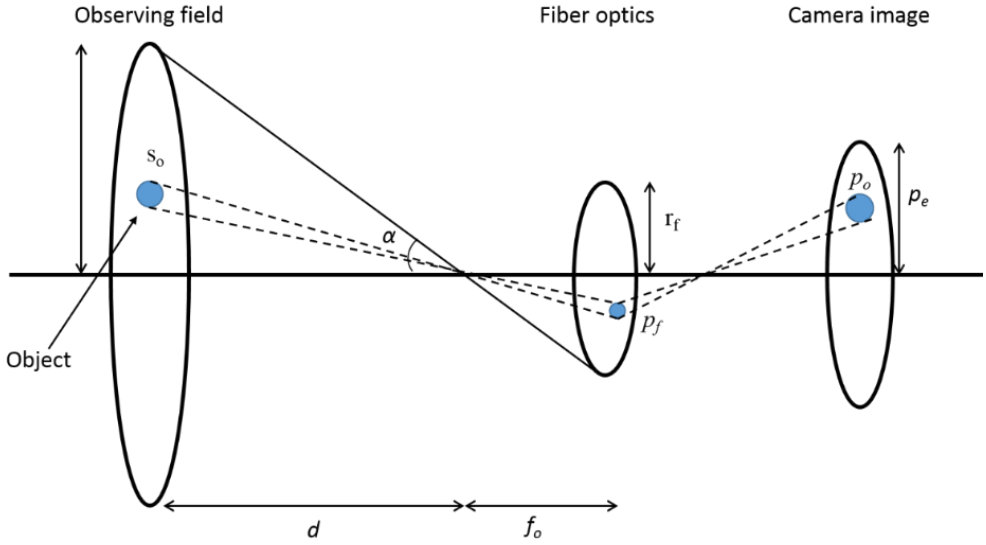

Figure 2-2 Tele-centric lens system pinhole model showing observing field, and object target size on real space and camera image.

2.2.2 Fiber optics

As the endoscope should be flexible, I adopt fiber bundle in this system. It is constructed by numbers of fiber with cladding, outer cladding and interfiber space, as shown in Figure 2-3 (a).

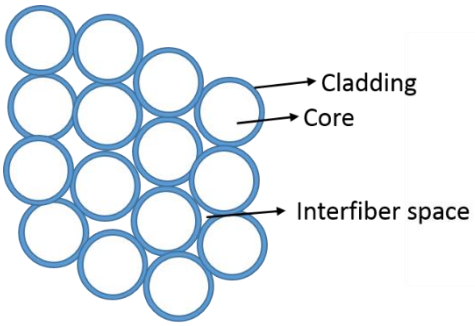

Figure 2-3 Fiber bundle construction

According to the location of fibers, there are three kinds of fiber bundle, standard, randomized and coaxial. To capture image, the fiber bundle should be coaxial. Moreover, as we need to transmit laser to selected target, fiber bundle should hold the position on the input side and output side, i.e. coherent. Thus, in this system, the coherent imaging fiber bundle is applied.

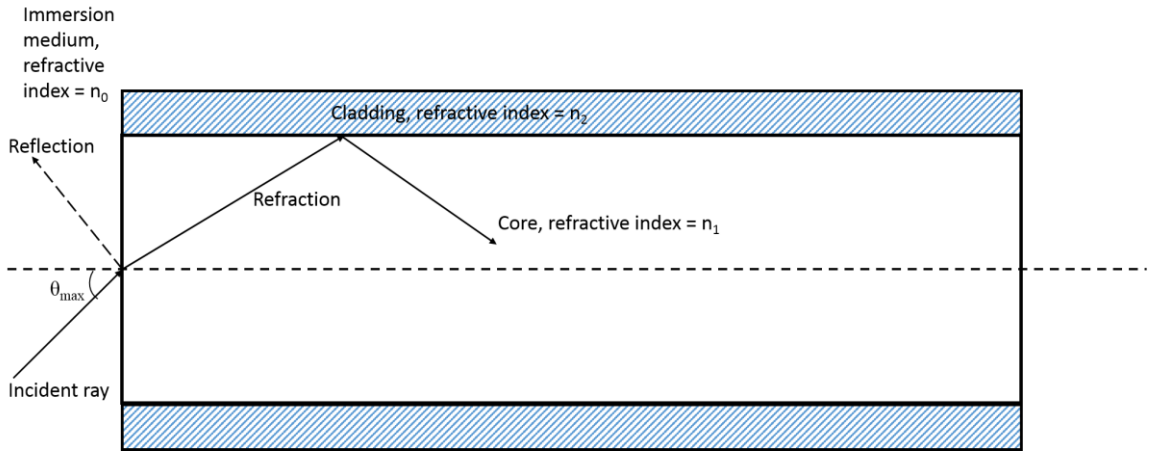

Figure 2-4 Refraction, Reflection and Numerical Aperture

The maximum angle that one fiber in fiber bundle can accept and transmit depending on the refractive indices of the core and cladding, and also the refractive index of the surrounding medium, generally air, n_0 equals to 1, as shown in Figure 2-4. When a ray of light enters into a fiber, part of them are reflected and part of them are refracted into the fiber. Total internal reflection happens if the incident angle is greater than some critical angle [61], which is defined as bellows:

$$\sin\theta_{max} = (n_0)^{-1}\sqrt{{n_1}^2 - {n_2}^2} \qquad \textbf{Equation 2-3}$$

And the numerical aperture is NA $= n_0 \sin\theta_{max} = \sqrt{{n_1}^2 - {n_2}^2}$. Therefore, when the light enters into the fiber bundle, we need to promise the incident angle less than the maximum incident angle. For example, we apply the fiber bundle, whose NA is 0.55, so the incidence angle should be less than 33°.

2.2.3 Eyepiece

Eyepiece is attached in front of the camera to observe target, and it also determines the maximization of image. The ratio between d_f and d_e determines the maximization of image, as shown in Figure 2-5. In this research, to maximize the view angle of eyepiece, it is considered that the height of image equals to the camera sensor. The ray beam from fiber bundle should be all delivered inside eyepiece lens, in order to prevent the light loss for the vignette.

Considering the visual field, the image from fiber bundle should be limited onto the camera sensor. According to the image size, we can refer to the effective radius of fiber bundle, as shown in Figure 2-5. The effective radius of fiber bundle, image height on camera sensor, the distance between fiber bundle and eyepiece, and the distance between eyepiece and camera sensor are represented by r_f, s_r, d_f, d_e respectively. Then the relationship is as

$$s_r = \frac{d_e}{d_f} r_f \qquad \textbf{Equation 2-4}$$

The view field radius pixel number on endoscope image s_i is given by pixel number on short axis of camera sensor p_s, and the ratio between the image size on sensor and the sensor size.

$$s_i = \frac{2s_r}{h} p_s \qquad \textbf{Equation 2-5}$$

In order to limit the all image on camera sensor, the length of the camera sensor short axis should satisfy$s_r \leq {}^{h}/_{2}$.

In addition, the view angle of camera 2 ϕ c meets the following equation.

$$\frac{r_f}{d_f} < tan\varphi_c \qquad \textbf{Equation 2-6}$$

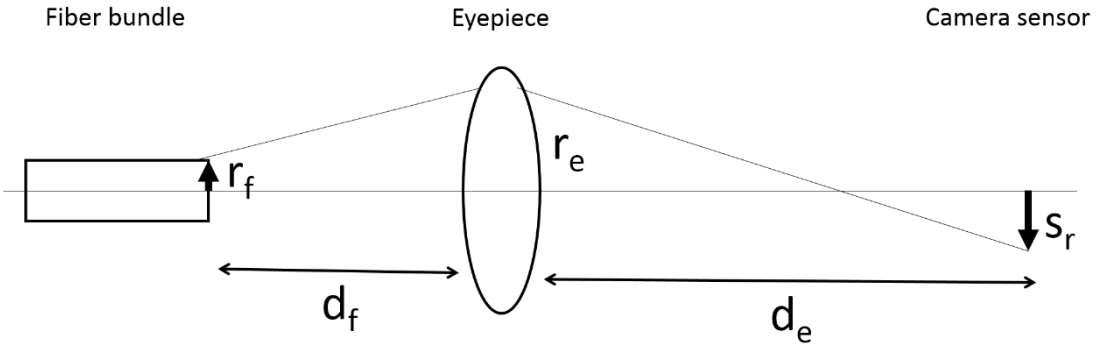

Figure 2-5 Image on a camera sensor transmitted by an eyepiece lens from the imaging point on fiber bundle.

Moreover, to get rid of the light vignette, for the numerical aperture of fiber bundle NA $= \sin\theta$, the clear aperture of eyepiece should meet the following requirements.

$$r_f = d_f \tan\theta \qquad \textbf{Equation 2-7}$$

2.3 *Laser-Induced Optical System*

We examine the laser spot diameter, beam changing angle for laser transmission optical system and laser transmission efficiency for the laser-induced optical system.

2.3.1 Objective Lens System

In paraxial optical system, the laser ray transmission can be expressed by translation and refraction matrix [62]. The laser transmits from fiber bundle to objective lens system, then the angle and height of laser rage are expressed by *u* and *h* respectively. When the laser ray passes through the optical lens system with focal distance of f_0, we assume the laser ray angle as $u' = \tan\theta$, and height as h'. Then we can get the following relationship:

$$\begin{pmatrix} h' \\ u' \end{pmatrix} = \begin{bmatrix} 1 & 0 \\ -\frac{1}{f_0} & 1 \end{bmatrix} \begin{bmatrix} 1 & f_0 \\ 0 & 1 \end{bmatrix} \begin{pmatrix} h \\ u \end{pmatrix}$$

$$= \begin{bmatrix} 1 & f_0 \\ -\frac{1}{f_0} & 0 \end{bmatrix} \begin{pmatrix} h \\ u \end{pmatrix} \qquad \textbf{Equation 2-8}$$

Then

$$\tan\theta = u' = -\frac{h}{f_0} \qquad \textbf{Equation 2-9}$$

The equations tell us the angle of laser output ray does not depend on the input ray angle, just relating to the ratio between the ray height and focal distance. Thus, it is able to change the laser ray output angle by changing the ray height incidence into the objective lens system, as shown in Figure 2-6. Thus, as we use the fiber bundle, we can change the incident height on fiber bundle to change the laser steering angle from the endoscope tip to object.

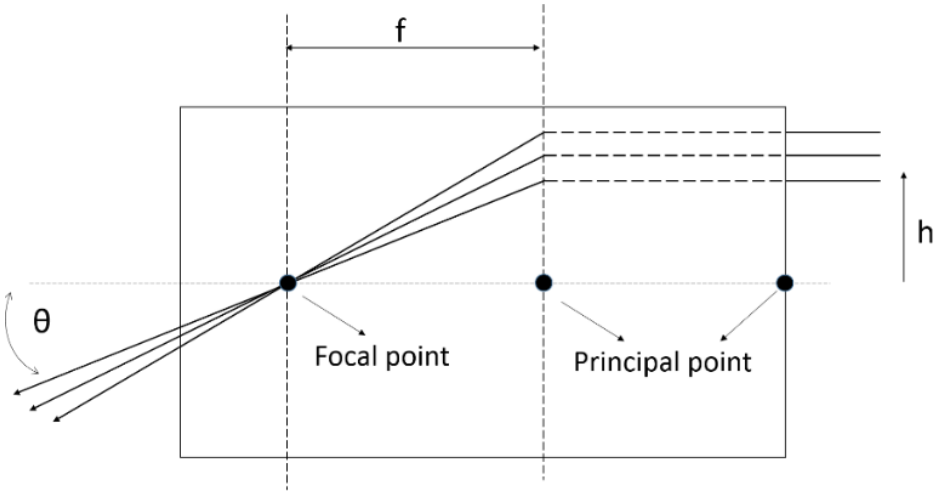

Figure 2-6 Laser beam steering on objective lens system. Steering angle depending on the height of the incident ray on the front focal point.

2.3.2 Fiber Optics

As it is necessary to control the laser transmission spot, the knowledge of the input-output phenomena is essential. If a ray enters into fiber optics at an angle of θ, it will theoretically spread from a fiber at the same angle of θ. In spite, practically, the azimuthal angle on appearance diversifies with θ, the fiber size (length and diameter), etc. that the emergent ray distributes to fulfill a circle of a cone twice of angle θ [63],

as shown in Figure 2-7. But the center of the laser annulus does not change with the angle which is very important for our positioning laser to selected target.

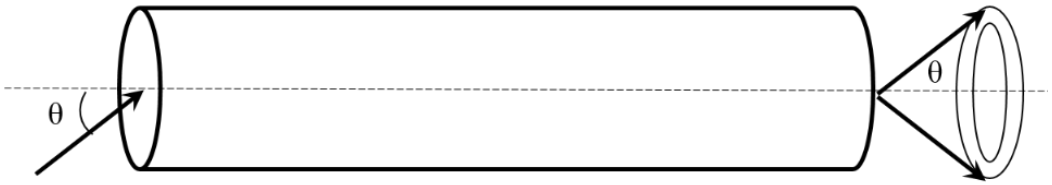

Figure 2-7 Fiber light transmission.

To understand our fiber bundle characteristic for laser transmission, we did experiment about it [64]. While the incidence angle changing from 0° to 33° (the critical angle of fiber), the laser beam diagnostics (Spiricon, SP503U) is applied to catch the laser distribution at the other end of fiber bundle. The specification is list in Table 2-1.

In the following, part of the results is shown in Figure 2-8. The incident laser was Gaussian laser, and the power was very low, about 10 mW to prevent hurting the beam diagnostics sensor.

From the below figure, we get to know the laser disperses with the increase of incidence angle. When the incidence angle is above 7°, the laser output becomes "donuts" circle, which would reduce the laser power density in one point. And also the center of laser spot cannot receive equivalent laser power density, which maybe cause power energy insufficient for tumor therapy. Therefore, in this system, we should try to make sure the laser incident angle into fiber bundle as small as possible, and parallel entering is best.

When selecting the laser scanning system, parallel laser ejection should be an important condition. The galvanometric or polygon scanning system with focusing lens causes serious distortion during laser scanning [65, 66], which is difficult to make sure the laser parallel enter into the fiber bundle. Thus, in our system, XY hollow stage is considered as precision instrument to move laser lens components.

Table 2-1 Specification of laser beam diagnostics [63].

Item	Specification
Model	SP503U
Application	1/2 format, slim profile, wide dynamic range, CW & pulsed lasers
Spectral Response	190-1100 nm
Active Area	6.3 mm W * 4.7 mm H
Pixel spacing	9.9 µm *9.9µm
Number of effective pixels	640*480
Minimum system dynamic range	64 dB
Linearity with Power	± 1%
Accuracy of beam width	± 2%
Frame rates: in 12 bit mode	30 fps at full resolution 60 fps at 320*240
Shutter duration	30 µs to multiple frame times
Gain control	43:1 automatic or manual control
Trigger	3 kinds of methods
Photodiode trigger	P/N SPZ17005
Saturation intensity	1.3 µW/cm^2 2.2 µW/cm^2
Lowest measurable single	0.5 nW/ cm^2
Damage threshold	50 W/cm^2/0.1 J/ cm^2 with all filters installed for < 100ns pulse width
Image quality at 1064 nm	Pulsed with trigger sync – excellent Pulsed with video trigger – good CW – poor
Operation mode	Interline transfer progressive scan CCD
Software supported	BeamGage STD or PRO
PC interface	USB 2.0

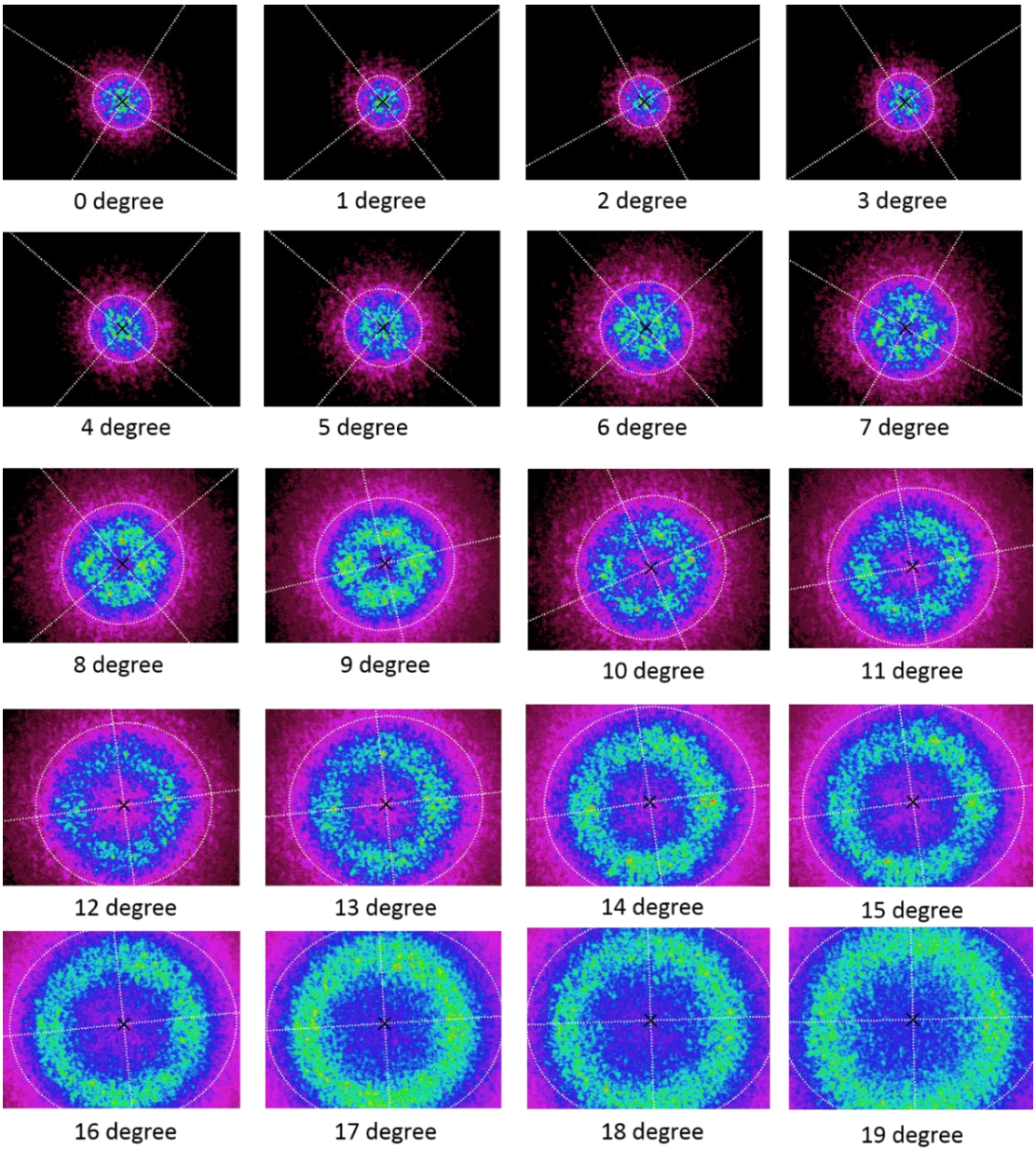

Figure 2-8 Laser distribution responds to different incident angle in fiber bundle.

2.3.3 Laser Focusing System

There are two types of common laser shapes, Gaussian and Tophat. Generally, laser output shape is Gaussian distribution, and the radius of maximum laser output at $1/e^2$ is considered as laser beam radius. Thus, radius is r_o, laser total power P_o, the laser ray output distribution $I(r)$ is expressed as follows [68]:

$$I(r) = \frac{2P_0}{\pi r_0^2} e^{-\frac{2r^2}{r_0^2}} \qquad \textbf{Equation 2-10}$$

The power *I(r)* passing through a circle of radius r in the transverse plane defined by integration is as follows:

$$\mathrm{I(r)} = \int_0^r i(r)dr = I_0(1 - e^{-\frac{2r^2}{r_0^2}}) \qquad \textbf{Equation 2-11}$$

So, when the laser ray transmits through the optical element whose radius is α times of the laser ray radius, the transmission efficiency ρ is defined as:

$$\rho = 1 - e^{-2\alpha^2} \qquad \textbf{Equation 2-12}$$

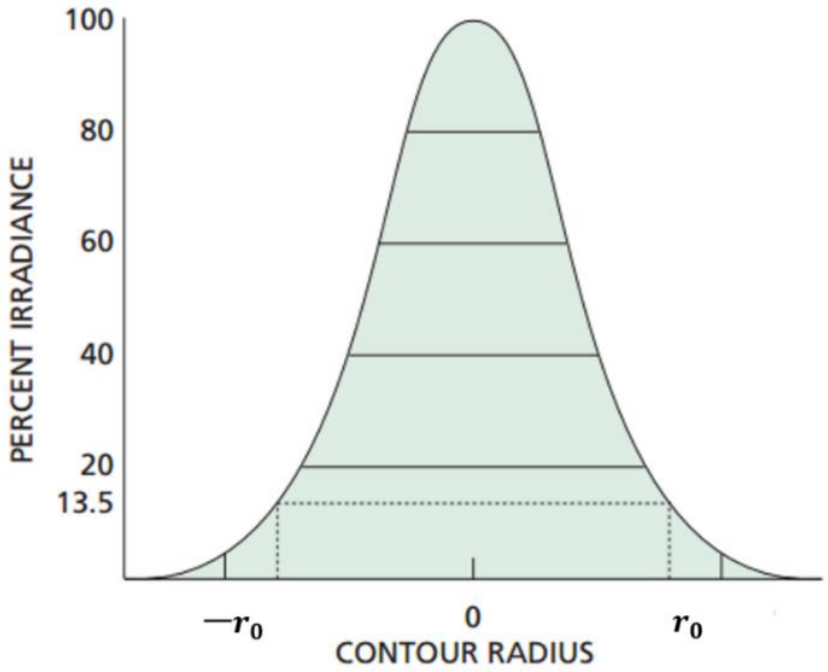

Figure 2-9 Gaussian distribution of laser power.

Therefore, as shown in Figure 2-9, the full output efficiency is 86.5% when the lens radius is less than the laser ray radius. To achieve 95% transmission efficiency, the lens radius should be above 1.224 times of laser ray radius. The diffraction loss caused by lens could be minimized when the lens radius is three times of laser ray radius, and about 98.9% efficiency when the ratio between lens radius and laser ray radius is 1.5

[69]. Thus, to get high transmission efficiency, the ratio between lens radius and laser ray radius should be above a certain value.

2.4 *Beam Splitter and Filters*

2.4.1 Polarizing Beam Splitter

A beam splitter is an optical device that separates a beam of light in two. One of them is polarizing beam splitter, which divides incident ray into p- (parallel) and s- (senkrecht) polarized, as shown in Figure 2-10. Because all the light follow the principle of reversibility, the p-polarized beam which enters into the beam splitter should pass through the beam splitter. Thus in our system, the p-polarized laser passes through the beam splitter, and about 50% laser power is lost. The visible light is reflected by beam splitter to eyepiece, also losing about 50% image light, which leads to low image brightness.

Based on the principle of reversibility of optical path, it is believed that the P-Pol red laser is able to transmit through the beam splitter and then focus into the target.

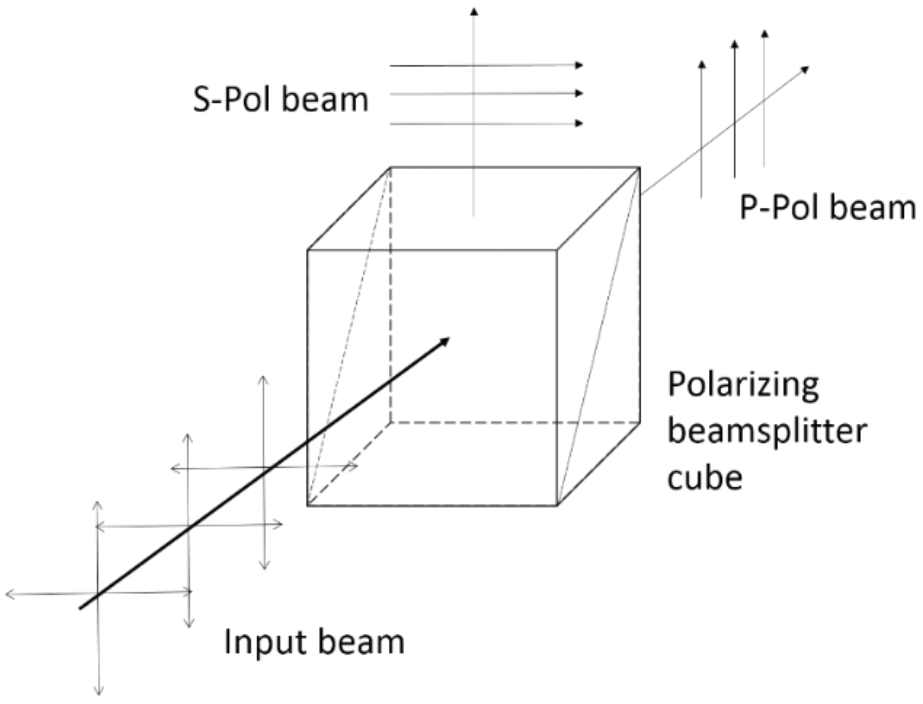

Figure 2-10 Polarizing beam splitter.

The reasons for using a polarized beam splitter are as follows: First, because the PDT laser wavelength (635 nm) is in the wavelength range of visible light, hot and cold mirrors are unable to separate light in the same wavelength range. Second, to provide more information for the surgeon, it is important to obtain color image. Third, the laser is somewhat polarized. Therefore, polarized beam splitter is adopted here.

We adopt polarizing beam splitter from Edmund, and the specification is listed as Table 2-2 Specification of polarizing beam splitter . As the laser power is less than 1 W, the temperature caused by the laser is thought to be very low, thus this beam splitter is able to be applied in such laser transmission condition.

The wavelength range is from 420-670 nm, visible light range. The fluorescent light wavelength by PDD is 600-740 nm, but the main wavelength is around 635 nm, so main PDD image can be transmitted to camera, except part of wavelength over 670 nm.

In this system, the polarizing beam splitter almost reflects half of the laser from focusing lens system, some black material to absorb this reflected laser.

Table 2-2 Specification of polarizing beam splitter [70].

Dimensions (mm)	12.5 x 12.5
Dimensional Tolerance (mm)	±0.2
Clear Aperture CA (mm)	21
Thickness (mm)	0.7
Thickness Tolerance (mm)	±0.07
Surface Quality	80-50
Angle Tolerance (°)	±1
Angle of Incidence (°)	45 ±10
Substrate	Corning Eagle XG
Wavelength Range (nm)	420 - 670
Coating Specification	Surface 2: R_{abs} <0.8% @ 420 - 670 nm
Thermal Expansion	37.6 x 10^{-7}/°C
Operating Temperature (°C)	-40 to +200
Construction	Wire Grid
Type	Linear Polarizer

2.4.2 Color Compensation Filter

Color compensation filters are commonly applied in tuning the color offset of microscope light sources in photomicrography by different color films [71]. The color is managed by such filters by immersing varieties of the green, red and blue portions in the spectrum of the observable light. In principle, the blue (420 nm) is maximally absorbed, and the blue-green-red (500-700 nm) visible light is minimally taken in by yellow color compensating filters.

In this system of photodynamic diagnosis, blue light is adopted to stimulate the photosensitizer, and the photosensitizer absorbing the blue light releases red fluorescence light. Thus, yellow color compensation filter (Thorlab Inc.) is applied in this endoscope, and its specifications are listed as follows. By this filter, the contrast between the tumor and healthy tissue should be enhanced, which is benefit for the surgeon to determine the tumor edge during diagnosing tumor tissue.

Table 2-3 The specifications of yellow color compensation filter [70].

Angle of Incidence	0°
Material	Borofloat Glass
Surface Quality (Scratch-Dig)	80/50 MIL-0-13830A
Clear Aperture	>90% Diameter
Temperature Range	-50 to +80 ºC
Diameter	Ø25.4 mm +0/-0.25 mm
Thickness	2 mm +0.2/-0.5 mm
Transmission	>85% avg. for 550-750 nm <1% avg. for 410-475 nm Cut-on: 515 ± 15 nm

2.4.3 Notch Filter

In this system, it is desirable to observe the object target during photodynamic therapy (PDT), and notch filter is applied to realize the purpose.

As illustrated in Chapter 1, present endoscope technologies cannot capture images during photodynamic therapy, mainly because of the irregular reflection laser. Also in

this system, when the laser is focused onto the fiber bundle, irregularly reflection occurs. The reflected laser makes the obtain image pure white. Thus, in this system, a notch filter for the wavelength of 630~650 nm is used in front of the camera to shield most of the irregularly reflected therapy laser, in order to observe the target tumor and also laser spot position during the laser irradiation. The transmission percentage of the notch filter for the wavelength range of visible light is shown in Figure 2-11. It shields well the 635 nm light, and there is almost no effect for other wavelengths of light (besides visible).

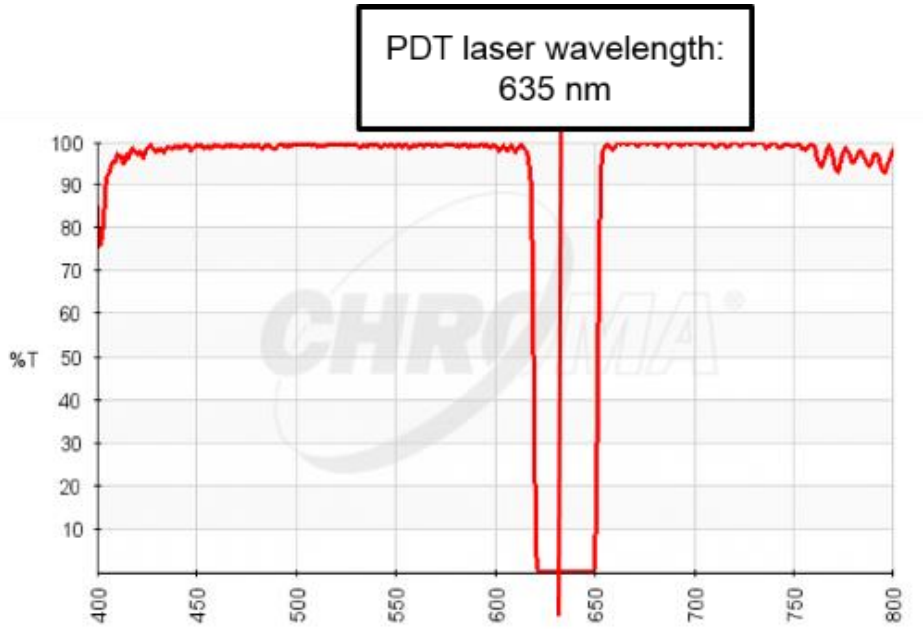

Figure 2-11 Transmission percentage of notch filter [73].

Its specifications are listed as below, and it is supposed to shield the irregular reflection laser on to camera at fiber bundle incident tip from the laser focusing lens system, while almost without effecting the transmission of other wavelength light to provide good quality image for surgeon observing.

Table 2-4 Specifications of notch filter [73].

Angle of incidence (AOI)	**0°**
Center Wavelength (CWL)	635 nm
Full width-half Max (FWHM)	32.5 nm
Transmission	>=95% avg. 410-800 nm outside notch Blocking OD6 abs at CWL
Substrate	Corning 7980 UVFS
Thickness	1.0 mm (+/-0.10mm)
Size	25 mm diameter, mounted to a 3.5 mm thick ring
Clear aperture (CA)	22.5 mm
Surface quality (Scratch Dig (S/D))	40/20
Operating temperature	0-150 ºC
Reflected wavefront distortion (RWD)	<= 1 wave/CA P-V
Transmitted wavefront distortion (TWD)	<= 1/2 wave/CA P-V
Parallelism	<= 2 arc sec

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1. 2012~ present: Japanese Government (Monbusho) Scholarship, The Ministry of Education, Culture, Sports, Science and Technology of Japan.