Stimulation of Violet Lasers to Traditional Chinese Medicine Photosensitizer for Diagnosis of Early-stage Gastric Cancer

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ABTRACT

The traditional Chinese medicine photosensitizer (CpD_4) gives off the red fluorescence at a central wavelength 660nm under the stimulation of the violet laser at 405nm. The red fluorescence can penetrate into the tissues deeply, not only in the diagnostic test, but in the treatment as well. The characteristic absorption spectrum and fluorescence emission spectrum of the traditional Chinese medicine photosensitizer are measured, and two violet light sources matching with the spectrums are proposed as well. One is "Hg-Xe" lamp with a special configuration at 433nm at the peak power, and the other is violet LD with a wavelength 405nm at the peak power, which exactly matches the absorption peak of the traditional Chinese medicine photosensitizer.

Keywords: gastric cancer diagnosis, photosensitizer, violet laser

1. INTRODUCTION

The gastric cancer is one of the most common malignant tumors. A key to reduce the mortality is to increase the diagnostic efficiency in its early stage. At present, the detectable ratio for the early-stage gastric cancer is still not quite satisfying. The current PCR technology of the tumor serum diagnosis is applicable to the MGAg immune test and able to improve the detectable ratio, however, it can not be used for the localization of the early-stage gastric cancer operations. Some false negative phenomena occur occasionally. Another popular approach proposed recently for the tumor diagnosis is to use the photosensitizer. People can utilize the photosensitizer's feature that it can gather together selectively inside the tumor tissues to test and treat the early-stage gastric cancer. The conventional photosensitizer in clinic is hematoporphyrin derivative (HPD). In the period of diagnosis and treatment, the vein injection and avoiding illumination are necessary. The HPD diagnosis and treatment in clinic need 3 days and 28days respectively to avoid illumination, which causes the relatively serious photosensitive side effects to the skin. However, the "Violet lasers stimulation to the traditional Chinese medicine photosensitizer" we presented adopts the Chinese medicine photosensitizer that our studied and made specially. It is a type of biological preparation extracted from silkworm excrement and the principal ingredients are the sodium salt of the folic acid α and its polymers, and has a porphyrin circle structure. Unlike the conventional HPD photosensitizer, the Chinese medicine photosensitizer uses the oral dosage, and the time of avoiding illumination for the diagnosis and treatment are only 12 hours and 3 days respectively. The photosensitive side effect to skin is much milder than that of HPD.

We propose in this letter a novel technique and equipment for the diagnosis and treatment of the gastric cancer using violet laser to stimulate the traditional Chinese medicine photosensitizer. And we test the absorption spectrum and the fluorescence emission spectrum and propose two types of violet light source for stimulating the photosensitizer. Furthermore, we utilize the gastroscope and the guide-light fiber to introduce the violet laser into the stomach. The emissive fluorescence from the gastric wall is lead out through the same fiber and observed and analyzed by a video screen finally. The same process is also applicable for the treatment to the early-stage gastric cancer.

2. THE EXPERIMENTAL PRINCIPLE AND PROCESS

The Chinese medicine photosensitizer that is studied and made domestically is a biological preparation extracted from silkworm excrement. That is a kind of the soluble purple black crystalline lens and the principal ingredients are the sodium salt of the folic acid α and its polymers. Its absorption and fluorescence emission spectrum are tested by the ultraviolet spectrophotometer. In the testing process, the dilution density of the sample is 1-2 μg/ml and the naked eyes can observe the light blue-and-green sample solution. The Figure 1 shows the absorption spectrum of the sample. The sample has an intensive absorption peak in the bandwidth 408nm. From the figure the width the peak is around 35nm. The peak wavelength 408nm determines the

bandwidth of the pump light for stimulating the Chinese medicine photosensitizer must in a rang of 390nm-430nm. Hence the choice for the stimulating light source is so significant.

For the conventional light source for stimulating the photosensitizer, people usually choose the spectral line with a central wavelength 441.6nm and transmitting between the Cd^+ energy levels $5S^2(^2D_{5/2})\rightarrow 5P(^2P^0_{1/2})$ that emits from the He-Cd^+ laser. Obviously, the difference of the He-Cd^+ laser central wavelength and absorption

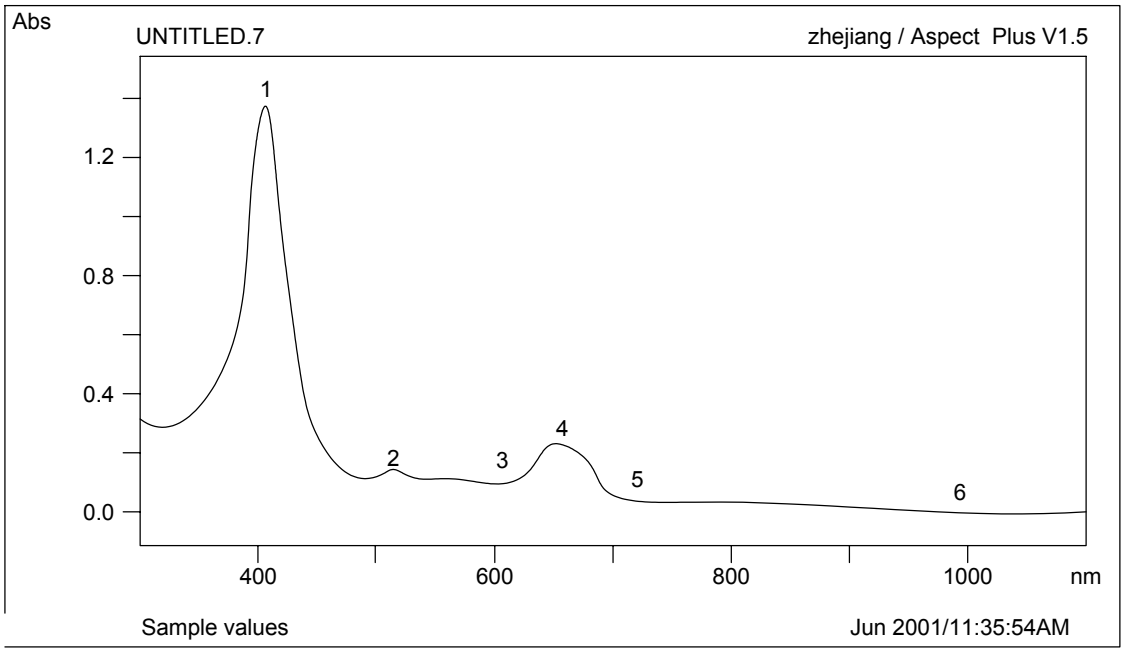

Fig.1 absorption spectrum of the solution sample

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	nm	Abs
1	408.00	1.3715
2	505.00	0.1029
3	595.00	0.0766
4	639.00	0.1985
5	724.00	0.0164
6	950.00	-0.0010

Table 1

wavelength of the Chinese medicine photosensitizer is 33nm. For the 441nm laser from the He-Cd^+ laser, therefore, only a small edge part of laser is effective to the photosensitizer and most of energy is useless. That is the reason why the power threshold of the pump light is quite high (>50mW), but its utility efficiency is every low on the contrary. We adopt two approaches to obtain the high power stimulating violet light source.

The first one is attained by using “Hg-Xe” halogen lamp. The emissive spectrum of the “Hg-Xe” lamp is shown in Figure 2. From the Figure 2, “Hg-Xe” lamp exist four emissive peaks with the respective wavelengths 405nm, 435nm, 520nm, 560nm. The first emissive peak at 405nm completely matches the absorption peak of the Chinese medicine photosensitizer and the simulation efficiency is improved greatly although it is not the most intensive power peak. The practice demonstrates that only a quite low power threshold (10mW) can stimulate the photosensitizer effectively. The better results than that of the “Hg-Xe” lamp are obtained. In order to improve the simulation efficiency further, we design a special optical system and utilize a special filter to filter away the rest of the emissive peaks nothing with the absorption of the Chinese medicine photosensitizer.

Fig.2 emissive spectrum of the "Hg-Xe" lamp

Date: 2001-5-30
LED Model: ma
Peak Wavelength: 433nm
The Half-width of Peak Wavelength: 0nm
Color Coordinate X: 0.209513
Color Coodinate Y: 0.104585
Main Wavelength: 437nm

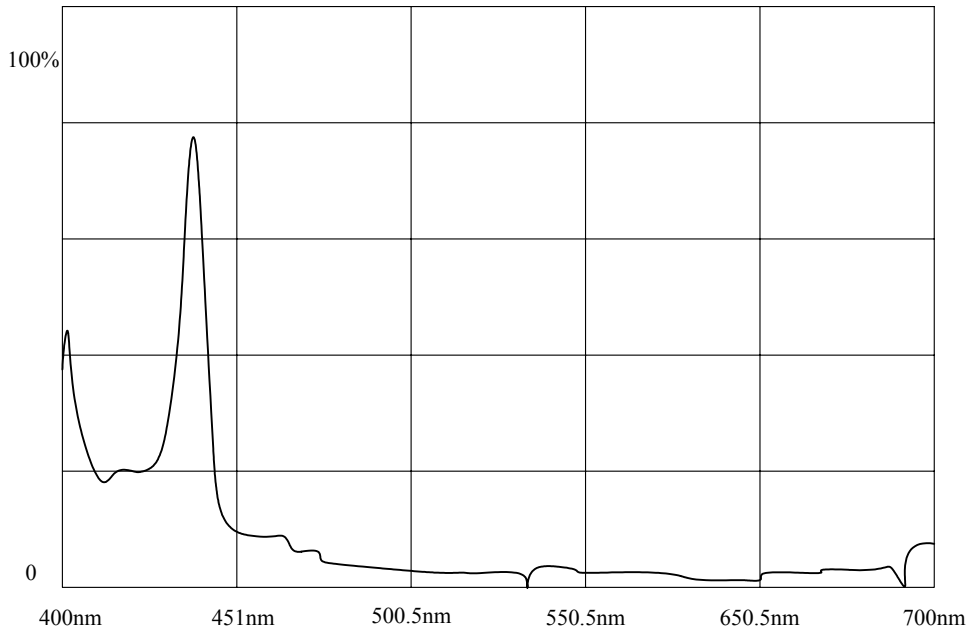


Fig.3 emissive spectrum of the "Hg-Xe" lamp after filter

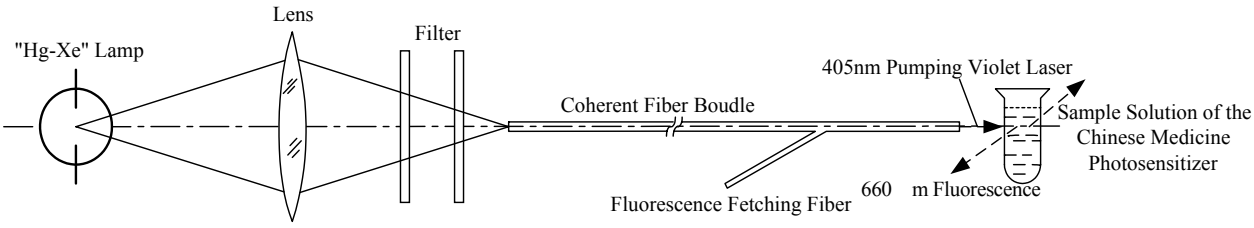
Figure 3 presents the emissive spectrum of the "Hg-Xe" lamp after the filter. Shown from the figure, we preserve two emissive peaks. The one at 405nm matches the absorption peak of the Chinese medicine photosensitizer. The one of the emissive peak at 435nm has also a large part overlapped with the absorption peak of the Chinese medicine photosensitizer. The practice has proved the effectiveness of this violet light source device. In our further experiments, we find the stimulated background light is still very strong although the emissive peaks at 520nm and 560nm are removed. Despite the relative strengthen of the background light is only 2%, the existence of the background light reduces the articulation of the fluorescence because of the bandwidth 440-770nm and the 660μm red light of the fluorescence emission peak of the photosensitizer. So we adopt the further filter measures to achieve the emissive spectrum distribution of the "Hg-Xe" lamp as the Figure 4. In the end, the relative strengthen of the background light is reduced to the 0.01% in the bandwidth 440-770nm, which dramatically improves the articulation of the stimulated fluorescence spectrum of the Chinese medicine photosensitizer.

Fig.4 emissive spectrum distribution of the "Hg-Xe" lamp

The second method is to utilize LD. The central wavelength of the LD produced by Nichia Corporation (Japan) is 405nm which matches with the absorption peak of the Chinese medicine photosensitizer exactly. It has the quite good stimulation efficiency and makes the power threshold of the stimulated light very low (<10mW). Therefore, this type of the violet LD is appropriate to be a stimulation light source due to the over 30mW of its output power. There are many favorable characteristics for using the violet LD as the stimulating light source.

1) Small volume; light weight; safe and compact configuration;
2) Stable output power; no thermal effect;
3) Low working voltage (safe for operators and patients);
4) Long working life (up to 10,000 hours);
5) Cheap expense; It is said that the price of the violet LD (Made by Nichia Corporation) whose output wavelength is 405nm and output power is 30mW is only about 5000 yen (Japanese Dollar).

The Figure 5 shows the equipment system using "Hg-Xe" lamp to stimulate the Chinese medicine photosensitizer. The bandwidth of the output light is 390-440nm after the imaging of a lens and the filtering of two filters. Then the violet laser is introduced into the stomach wall through the gastroscope after coupled in the fiber. Shown in Figure 6, the stimulated output fluorescence at 660μm is fetched through another arm and



then demonstrated on the video screen after the photoelectronic conversion.

Fig.5 experimental setup of violet laser stimulation to photosensitizer using "Hg-Xe" lamp

The configuration of the optical system for the coupling between the violet LD and the coherent fiber bundle is shown as the Figure 6. Through the focusing of the spherical lens and Grin lens, the laser at 405nm emitted from the violet LD is coupled into the coherent fiber bundle.

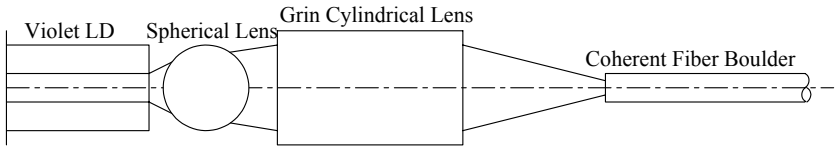


Fig.6 coupling device of the violet LD and fiber

3. EXPERIMENTAL RESULTS

The Chinese medicine photosensitizer can aggregate selectively in the humor tissues. It is able to be stimulated by the laser at a wavelength is same as the absorption wavelength of the photosensitizer to make the little gastro cancer emit the red fluorescence. It will dramatically improve the detectable ratio of the early-stage gastro cancer through the direct biopsy there. At the same time, the cancer tumor focus displayed on the screen has various applicable values, for example, scaling the excision extent in the operation and so on. Experiments show that plenty of the early-stage gastro cancer generates the red fluorescence at 660nm when using violet laser at 405nm to stimulate the Chinese medicine photosensitizer and the mucous layer of the cancerization area and non-cancerization area is distinct. Contracted with the pathologic results, the sensitivity is 94.12% and diagnostic conformity is up to 96.8%.

The clinic study shows that except for a case that the fluorescence in pathological change area demonstrates weak positive reaction, none of the case showing red fluorescence appears and all show negative effect. The pathological conformation ratio is up to 99.96% from the observed 30 cases of the early-stage gastro cancer. For 14 patients (10 late-stage gastro cancer patients, 2 esophagus cancer patients and 2 early-stage gastro cancer) who received our test, the fluorescence observed by the naked eyes shows strong positive effect and

generates red characteristic wave at 660nm, whose conformity ratio is 100% with the pathology.

3. CONCLUSION

Compared with the conventional HPD, the Chinese medicine photosensitizer displays a series of favorable features, like the convenience for dosing, light photosensitive side effect to skin and flexible operation, etc.. That method is absolutely qualified to extensively apply to the routine test for the early-stage gastro cancer and pathological patients. Combined with the violet light or laser at 405nm, it can apply to early diagnosis for the tumor, the malignant tumors that can be found in digestive tract, bladder, bronchus and matrix by various endoscopes. That is also the basis for the treatment to the early-stage cancers and weak cancerization. The two types of the violet stimulated light source we proposed in this letter have the following advantages: the exact wavelength matching, the low power threshold, the good beam quality, the convenience, the security, the compact structure and the cost. The violet LD especially has the advantages beyond the other counterparts. The source of the Chinese medicine photosensitizer: silkworm excrement has the attractive advantages as well, such as the abundance, cheapness, and easiness for extraction. All that proves the brilliant future for the application of this technology.

ACKNOWLEDGEMENTS

The authors are especially grateful to Professor Sailing He for valuable discussions.

REFERENCES

[1] W. Chen, G. Martinez, A. Mulchandani, “Detection of salmonella using a real-time PCR based on molecular beacons”, SPIE 3926, pp. 21-27, 2000.

[2] R. P. Mariella, “Development of a battery-powered hand-held real-time PCR instrument”, SPIE, Vol. 4265, pp. 58-64, 2001.

[3] M. Kwasny; Z. Mierczyk, “Laser fluorescence spectrometers for medical diagnosis”, SPIE, Vol. 4238, Laser Technology VI, pp. 69-79, 2000.

[4] S. Hashimoto, H. Nakajima, K. Yanashima, T. Asatsuma, T.Yamaguchi, H. Yoshida, M. Ozawa, K. Funato, S. Tomiya, T. Miyajima, T. Kobayashi, S. Uchida, M. Ikeda, “GaN-based violet-blue laser diodes”, SPIE, Vol. 4354, Laser Optics 2000: Semiconductor Lasers and Optical Communication, pp. 1-11, 2001.

[5] S. Nakamura, “Present status of InGaN-based violet laser diodes”, LEOS '99. IEEE Lasers and Electro -Optics Society 1999 12th Annual Meeting , 1,pp. 31 -32, 1999.

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