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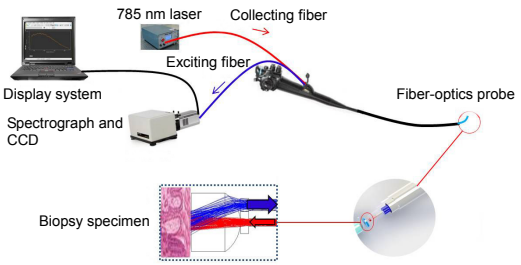
光纤拉曼光谱系统对胃癌的快速诊断的可行性研究



尹立建[1]，饶云江[2]，代剑华[1]，冉曾令[2]，
李卓玥[2]，陈　瑶[1]，彭贵勇[1*]

[1] 陆军军医大学西南医院全军消化病研究所，重庆 400038；
[2] 电子科技大学光纤传感与通信重点教育部实验室，光纤研究中心，四川 成都 611731

摘要： 本文提出了一种能够与胃镜相匹配的光纤拉曼光谱系统和积分能量比相结合来快速诊断胃癌的方法。首先，采用光纤拉曼光谱系统对来自 17 例胃正常粘膜，12 例胃腺癌粘膜的活检组织进行拉曼光谱检测(激发光波长 785 nm，功率 50 mW, CCD 温度-80 ℃，采集时间 1 s)。然后，采用降低基线、快速傅里叶转化(FFT)平滑对拉曼原始光谱进行预处理。最后，根据拉曼谱图特征，分析了拉曼特征峰的归属，比较了胃正常和胃腺癌粘膜的拉曼光谱差异和连续频带内(1500 cm^{-1}~1700 cm^{-1})和非连续频带(1100 cm^{-1}~1200 cm^{-1})积分能量比。结果表明，胃腺癌粘膜位于 1002 cm^{-1}、1073 cm^{-1}、1450 cm^{-1}、1655 cm^{-1} 归属于苯丙氨酸和蛋白质的拉曼峰强度比正常粘膜相对增高，胃正常和胃腺癌粘膜在连续频带内和非连续频带积分能量差异明显(独立样本 *t* 检验，P<0.05)，并以积分能量的比值来作为诊断指标，获得的准确度达到 97.5%~98.5%，敏感度达到 91.7%和特异度达到 100.0%。

关键词： 光纤；拉曼光谱；胃癌；诊断

中图分类号： R445；TN253　　**文献标志码：** A

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A feasibility study of using fiber-optic Raman spectrum system for fast diagnosis of gastric cancer

Yin Lijian[1], Rao Yunjiang[2], Dai Jianhua[1], Ran Zengling[2], Li Zhuoyue[2],
Chen Yao[1], Peng Guiyong[1*]

[1]Institute of Digestive Disease, Southwest Hospital, Army Medical University, Chongqing 400038, China;
[2]Fiber Optics Research Center, Key Laboratory of Optical Fiber Sensing & Communications (Ministry of Education), University of Electronic Science and Technology of China, Chengdu, Sichuan 611731, China

Abstract: A method for fast diagnosing gastric cancer is proposed, by combining optical fiber Raman spectroscopy system matching the gastroscope with the ratios of the spectral integral energy. we complete the detecting of Raman spectra from 17 samples of normal gastric mucosa and 12 samples of gastric adenocarcinoma mucosa using the

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作者简介：尹立建(1985-)，男，硕士研究生，主要从事消化道肿瘤的拉曼光谱的研究。E-mail：lijian.yin@163.com
通信作者：彭贵勇(1963-)，男，硕士，教授，主要从事消化系统疾的内镜下诊治的研究。E-mail：pgy63@163.com

optical fiber Raman spectroscopy system (excitation wavelength of 785 nm light, power of 50 mW, the CCD temperature to 80 ℃, acquisition time 1 s). Then, the original Raman spectra were pretreated, through reducing the baseline and smoothing by fast Fourier transformation (FFT). Finally, according to the characters of Raman spectra, Raman characteristic peaks were analyzed. At the same time, we compared the ratio of integral energy of continuous band (1500 cm^{-1}~1700 cm^{-1}) and non-continuous band (1100 cm^{-1}~1200 cm^{-1}). The results show that the intensity of Raman peak of gastric adenocarcinoma at 1002 cm^{-1}、1073 cm^{-1}、1450 cm^{-1}、1655 cm^{-1} belonging to phenylalanine and proteins are higher than that of normal mucosal relatively. From continuous band (1500 cm^{-1}~1700 cm^{-1}) and non-continuous band (1100 cm^{-1}~1200 cm^{-1}), the ratios of the spectral integral energy of gastric adenocarcinoma were different with normal mucosa markedly(independent samples *t* test, P<0.05), and with the ratio of the integral energy for use as a diagnostic index, obtained the higher accuracy (97.5%~98.5%), sensitivity (91.7%) and specific degrees (100.0%).

Keywords: optical fiber; Raman spectrum; gastric cancer; diagnosis

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1 引 言

在中国，胃癌发病率(29.9/100000 人)和死亡率(221478 人/年)都居高不下，占全球胃癌死亡人数近一半，随着人口增长和老龄化，胃癌将给中国社会造成沉重负担[1-3]。胃癌的诊断主要依靠胃镜和病理活检，由于早期缺乏特异性及内镜检查质量参差不齐，多数患者(>70%)发展为进展期胃癌[4-6]。内镜活检是提高胃癌诊断率的非常重要的方法，但是临床对病变良、恶性的判断过度依赖活检，并且对胃癌的诊断，不同的病理医生依据不同诊断标准作出的诊断差别也比较明显[7]。

拉曼光谱是一种基于分子振动的非弹性散射光谱技术，可以提供组织结构和成分的特异性信息。癌变组织由于其组分含量、结构发生变化，会产生特征性的拉曼光谱[8]。由于具有快速、无创、高度准确、客观的特点，并且不需要对组织进行制备、染色[9]，拉曼光谱非常适合与内镜检查的结合，用于胃癌的诊断并指导胃癌的内镜治疗。

目前拉曼光谱被广泛应用于皮肤、神经胶质瘤、肺癌、胃癌、肠癌等肿瘤诊断方面的研究[10-14]。快速、高效且与内镜相匹配的光纤拉曼光谱系统可用于胃癌的实时诊断，我们采用此系统和不同频谱范围积分能量比作为诊断指标相结合的方法，对胃癌组织进行了诊断价值研究。

2 材料与方法

2.1 光纤拉曼光谱系统

光纤拉曼内镜检查系统如图 1 所示，包括：① 一台近红外半导体激光器(波长 785 nm，长春新产业光电技术有限公司，长春)，② 一台成像光谱仪(安道尔

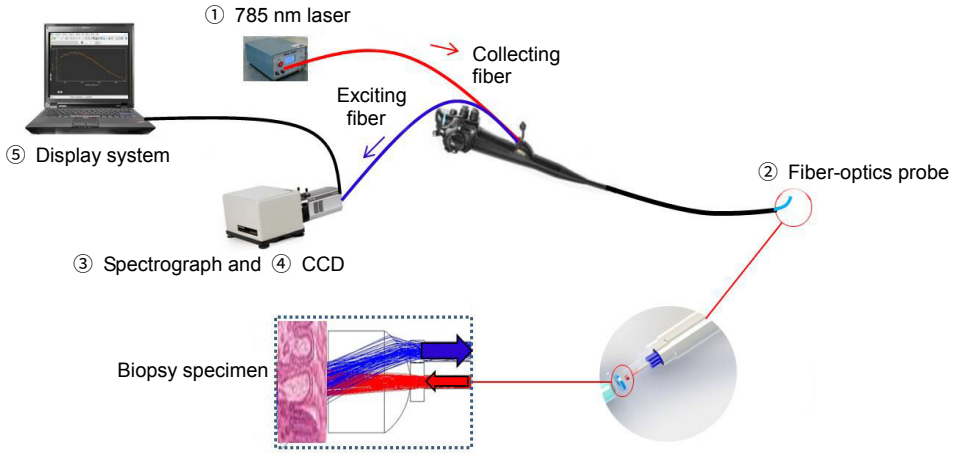

图 1 光纤拉曼内镜检查系统

Fig. 1 Optical fiber Raman endoscopy system

公司，英国)，③ 一台 CCD 摄像机(安道尔公司，英国)，④ 一条光纤拉曼探针(EmVision，美国)，⑤ 一台显示实时拉曼光谱的显示器(Lenovo，中国)。

拉曼光纤束总长度 3 m，外包尼龙保护套，其中央为 1 根芯径 272 μm、0.22*NA* 的激发光纤，由不锈钢材质外套包裹，在其前端耦合一个带通滤波器，周围环绕 7 根芯径 300 μm、0.22*NA* 的收集光纤束，其末端连接一个环形的长通滤波器，滤除激光，仅收集来自于组织的拉曼散射光。

2.2 标本收集与拉曼光谱采集

在经过伦理委员会审查之后，本研究收集了 29 例来自陆军军医大学附属西南医院内镜中心胃镜检查患者的活检标本，其中正常患者 17 例，胃腺癌 12 例，其中男性患者 15 例，女性患者 14 例，患者平均年龄(54.8±12.1)岁，所有参与研究的患者均自愿并已签署知情同意书，本研究符合人体试验伦理学标准，得到医院伦理委员会的批准。

经胃镜活检的新鲜样本，不做任何预处理的情况下，立即送至拉曼光谱采集室，设置激发光功率 50 mW，采集时间 1 s，CCD 温度-80 ℃，活检标本置于镀铝玻片之上，根据标本大小选取 1~5 个点不等，如图 1 所示，将拉曼光纤探头贴紧活检样本，波长 785 nm 近红外激光(红色光束)通过光纤拉曼中央的 1 根激发光纤照射组织标本，然后由周围环绕的 7 根收集光纤收集来自组织的拉曼光谱(蓝色光束)，共采集拉曼光谱 83 个，胃正常 51 个，胃腺癌 32 个。将完成采集的样本立即放入 10%福尔马林溶液固定送病理切片，由专业病理医生对样本进行双盲病理检查，排除不符合标准的标本。

2.3 拉曼光谱预处理与统计分析

如图 2(a)所示，拉曼原始光谱中组织的拉曼光谱信号较弱，包含有较强的组织自体荧光背景、噪声，应用软件 Origin Pro 8.0 通过降低基线去除组织自体荧光背景来提取拉曼信号，采用快速傅里叶转化(fast Fourier transform, FFT)平滑光谱获得了如图 2(b)所示高信噪比的拉曼光谱[15]，在此基础上求得胃正常和胃癌粘膜组织的平均光谱并对胃癌典型拉曼谱峰变化进行归属分析。

应用 Excel 软件对平均光谱进行标准化处理并计算拉曼光谱的积分能量比，应用软件 SPSS20.0 采用独立样本 t 检验对拉曼光谱积分能量比的结果进行统计，检验水准 α=0.05，以 P<0.05，判断差异有统计学意义。应用 Graphpad prism5.0 绘图。

3 采集结果

图 3 所示为经过病理确诊的 17 例胃正常粘膜患者，12 例胃腺癌患者胃粘膜组织平均拉曼光谱图和典型拉曼谱峰。在 1002 cm^{-1}[vs(C-C)苯丙氨酸]、1073 cm^{-1}[v(C-N)蛋白质]、1206[v(苯基环)蛋白质]、1265[无规卷曲 酰胺 III 蛋白质]、1340[v(平面环)蛋白质]、1450 cm^{-1}[δ(C–H2、C–H3)，v(平面环)蛋白质、DNA/RNA、脂质]、1550 cm^{-1}(脂质)、1655 cm^{-1}[(α-螺旋)酰胺 I 蛋白质][16-18]可以观察到显著的拉曼谱峰。各拉曼谱峰归属及振动方式见表 1。

1) 我们观察到在胃正常粘膜和胃癌粘膜积分能量存在差异，采用积分能量比(即不同频带的积分能量之比)作为鉴别胃正常粘膜与胃癌变粘膜的诊断指标，分别比较拉曼光谱连续频带内 E1600 cm^{-1}~1700 cm^{-1}/

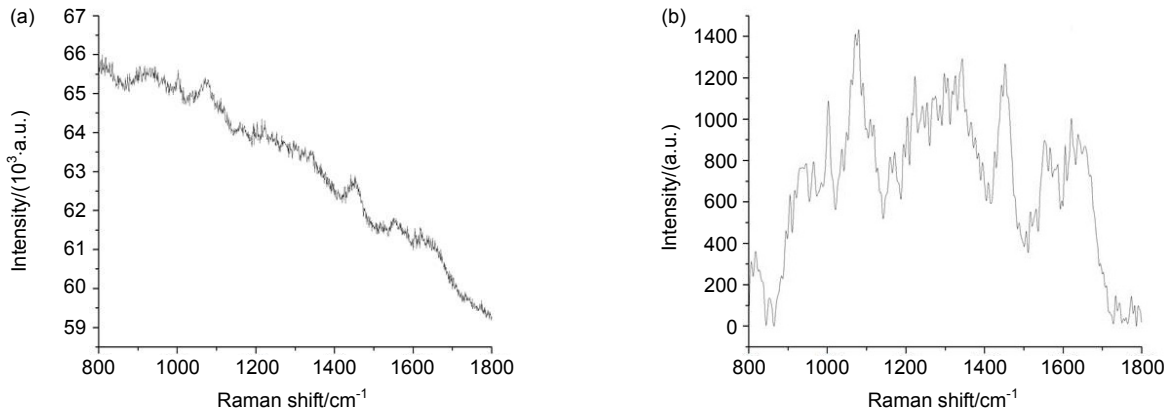

图 2 (a) 原始拉曼光谱；(b) 降低基线、平滑预处理后的拉曼光谱

Fig. 2 (a) Original Raman spectrum; (b) Raman spectra after reduced the baseline and smoothed

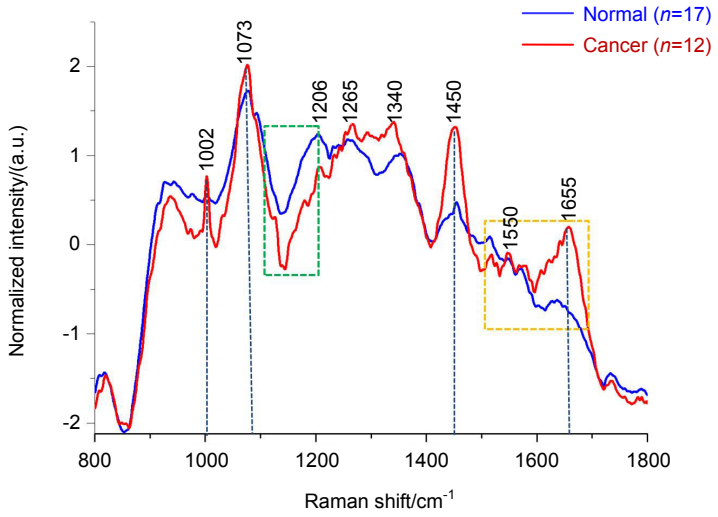

图 3　17 例胃正常患者(蓝线)和 12 例胃腺癌患者(红线)的平均拉曼光谱

Fig. 3　The mean normalized Raman spectra from normal(n=17, blue line) and dysplasia (n=12, red line) gastric mucosa tissue samples

表 1　拉曼谱峰振动方式及其归属

Table 1　Vibration mode and ownership of Raman spectrum peak

Raman peak	Mode of vibration	Ownership
1002	C-C vs	Phenylalanine
1073	C-N v	Protein
1206	Phenyl ring v	Protein
1265	Random coil	Amide III protein
1340	Plane ring v	Protein
1450	C–H2、C–H3 δ Phenyl ring v	Protein、DNA /RNA、lipid
1550		Lipid
1655	α-helix	Amide I protein

Annotation：vs：Symmetrical stretching vibration；v：Stretching vibration；δ：Bending vibration

E1500 cm^{-1}~1600 cm^{-1} (图 3 黄色虚线所标识范围)和非连续频带间 E1600 cm^{-1}~1700 cm^{-1}/E1100 cm^{-1}~ 1200 cm^{-1}(图 3 绿色虚线所标识范围)的积分能量比。

表 2 所示为 17 例胃正常粘膜和 12 例胃腺癌在 1500 cm^{-1}~1700 cm^{-1} 和 1100 cm^{-1}~1200 cm^{-1} 范围内平均光谱的积分能量比结果。

2) 图 4 所示拉曼光谱连续频带内(E1600 cm^{-1}~1700 cm^{-1}/E1500 cm^{-1}~1600 cm^{-1})和非连续频带间(E1600 cm^{-1}~1700 cm^{-1}/E1100 cm^{-1}~1200 cm^{-1})积分能量比作为诊断指标，对胃正常粘膜、胃腺癌做独立样本 t 检验，组间、组内差异明显(P<0.05)，有统计学意义。图 5 所示 E2/E1(E1600 cm^{-1}~1700 cm^{-1}/E1500 cm^{-1}~1600 cm^{-1})诊断胃正常粘膜与胃腺癌的 AUC(曲线下面积)为 0.975，即准确度 97.5%，敏感度 91.7%，特异性 100.0%；E2/E3(E1600 cm^{-1}~1700 cm^{-1}/E1100 cm^{-1}~1200 cm^{-1})诊断胃正常粘膜与胃腺癌的 AUC(曲线下面积)为 0.985，即准确度 98.5%，敏感度 91.7%，特异性 100.0%。

4　讨　论

拉曼光谱是一种散射光谱，不同物质分子都具有其特征的“拉曼指纹”光谱。癌变是一个多阶段的复杂过程，组织细胞在癌变不同阶段中其各种组分(如核酸、蛋白质、脂类、糖原等)的含量、构型、种类、存在状态及组成比例等都可能发生变化，使其产生特征拉曼标志光谱。

1) 拉曼光谱在胃癌诊断方面的研究多应用显微共焦拉曼光谱仪于体外进行研究，对胃粘膜癌变过程中发生的相关分子变化及胃癌诊断模型的建立进行了

表 2　拉曼光谱不同频带积分能量比

Table 2　The ratio of integral energy of different frequency band of the Raman spectra

Normal		Cancer	
E2/E1	E2/E3	E2/E1	E2/E3
0.72	0.40	1.25	1.10
0.58	0.44	1.26	0.71
0.60	0.49	1.21	0.97
0.79	0.40	1.43	0.99
0.58	0.67	1.02	1.20
0.64	0.38	0.89	1.08
0.66	0.55	0.71	1.35
0.59	0.35	1.21	1.64
0.64	0.51	0.87	0.79
0.72	0.40	1.20	0.51
0.58	0.41	1.49	0.80
0.85	0.40	1.08	0.72
0.60	0.37		
0.81	0.37		
0.55	0.35		
0.65	0.27		
0.66	0.62		

Annotation：E1：E1500 cm^{-1}~1600 cm^{-1}；E2：E1600 cm^{-1}~1700 cm^{-1}；E3：E1100 cm^{-1}~1200 cm^{-1}

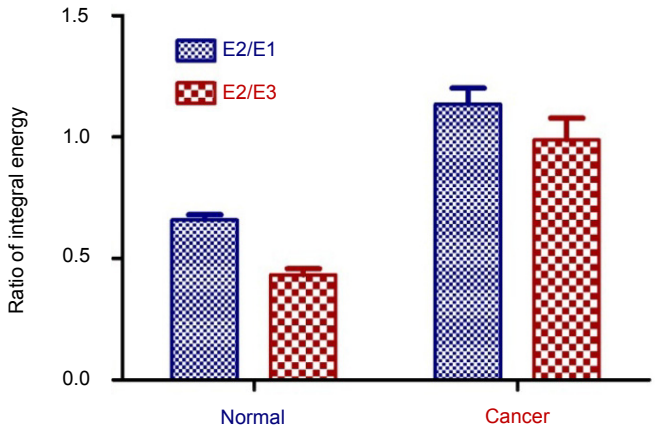

图 4　胃正常和胃癌粘膜拉曼光谱连续频带和非连续频带积分能量比

Fig. 4　The ratio of integral energy of continuous and discontinuous frequency band of the Raman spectra

很好的探索[19-21]，但是显微共焦拉曼光谱仪始终无法应用到体内，从而无法开展临床实时诊断，如图 1 所示，本研究开发的这套光纤拉曼光谱系统能够与内镜检查相结合，能够对癌变的胃粘膜组织进行实时、高效、准确诊断，使拉曼光谱检查的临床应用成为可能，大大提高了胃癌的检出效率和准确率，并能够进一步指导内镜下的治疗。

2）对胃癌血浆中苯丙氨酸及其代谢产物的研究发现[22]，胃癌苯丙氨酸的代谢路径会发生明显改变，导致苯丙氨酸代谢产物苯乙酰谷氨酰胺增多，苯丙氨酸及其代谢产物具有成为鉴别胃癌生物标记物的可能，对尿液中苯丙氨酸的检测证实苯丙氨酸具有作为

肿瘤标志物用于鉴别良、恶性肿瘤的价值[23]。本研究观察到与正常粘膜拉曼峰相比，胃腺癌粘膜位于 1002 cm^{-1}、1073 cm^{-1}、1450 cm^{-1}、1655 cm^{-1} 归属于苯丙氨酸和蛋白质的拉曼峰明显增高(独立样本 t 检验，P<0.05)，可能与癌变过程上皮细胞增生相关的正向调节蛋白含量增加有关[24]。尤其在归属于苯丙氨酸的 1002 cm^{-1} 处，拉曼谱峰尖锐且相对增高更明显，说明此处有较单一的成分富集。光纤拉曼光谱系统能够快速、无创地检测到苯丙氨酸，从而有望应用于胃癌的早癌筛查。另外，位于 1200 cm^{-1}~1400 cm^{-1} 频带归属蛋白质的拉曼峰群向高波数区移动，说明振动的能量增加，可能是引入了新的基团或周边基团的活化使其更加稳定[8]。

3) 以往的研究曾采用拉曼谱峰相对峰强比[25]来诊断早期胃癌，其敏感度(90.5%)和特异性(90.9%)不够理想；应用支持向量机、人工神经网络等算法[26-27]与拉曼光谱相结合，建立模型来对结肠组织进行分类、检测脑肿瘤，一般这些算法都比较复杂，处理难度较大。我们观察到与正常胃粘膜相比，胃癌粘膜拉曼峰强度总体降低，采用拉曼光谱不同频带的积分能量比作为诊断指标来对胃正常和胃癌粘膜进行鉴别诊断。使用这一诊断指标运算简单，并可以取得较高的准确度(97.5%~98.5%)，敏感度(91.7%)，特异性(100.0%)，如图 5 所示。

4) 胃癌按病理变化分为早期胃癌和进展期胃癌，按组织学类型分为腺癌、腺鳞癌、鳞癌、印戒细胞癌等，本研究对处于进展期的腺癌做了探索研究，对早期胃癌和其他组织学类型的胃癌的拉曼光谱学特征尚未进行系统研究，缺少不同阶段和不同组织类型胃癌的拉曼光谱学特征的差异性比对的数据，使误诊的风险增加。由于样本量较小，积分能量比作为胃腺癌的诊断指标的应用价值还需要大量样本数据的支撑。

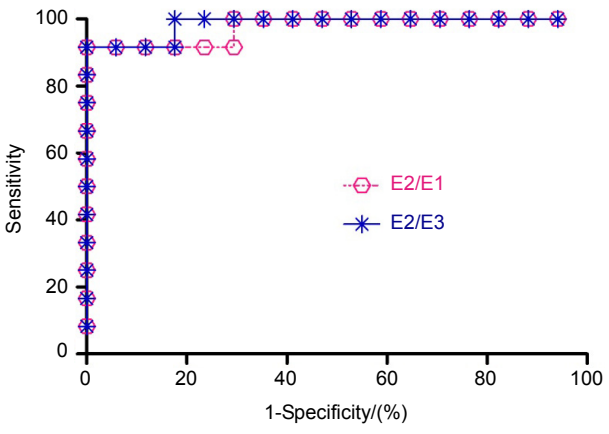

图 5 拉曼光谱连续频带和非连续频带积分能量比的 ROC 曲线

Fig. 5 ROC curve of continuous and discontinuous frequency band of the Raman spectra

用光纤拉曼光谱系统对作为潜在胃癌生物标记物的苯丙氨酸进行了快速检测，并用积分能量比作为诊断指标。该尝试在一定程度上拓展了拉曼光谱用于胃癌诊断的应用。在下一步的实验中，我们将对早期胃癌和其他组织学类型的胃癌的拉曼光谱学特征进行系统研究，并对不同阶段和不同组织类型胃癌的拉曼光谱学特征的差异性进行比对，以降低误诊风险。

声 明

本文中所有参与研究的患者均自愿并已签署知情同意书，本研究符合人体试验伦理学标准，得到医院伦理委员会的批准。

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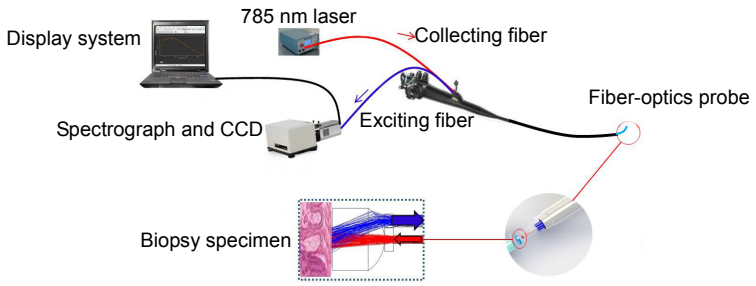
A feasibility study of using fiber-optic Raman spectrum system for fast diagnosis of gastric cancer

Yin Lijian[1], Rao Yunjiang[2], Dai Jianhua[1], Ran Zengling[2], Li Zhuoyue[2], Chen Yao[1], Peng Guiyong[1*]

[1]Institute of Digestive Disease, Southwest Hospital, Army Medical University, Chongqing 400038, China;
[2]Fiber Optics Research Center, Key Laboratory of Optical Fiber Sensing & Communications (Ministry of Education), University of Electronic Science and Technology of China, Chengdu, Sichuan 611731, China



Optical fiber Raman endoscopy system

Overview: Gastric cancer incidence and mortality is high in China. Because of the lack of specificity, the diagnosis accuracy of gastric cancer is not high. Raman spectroscopy is a kind of inelastic scattering spectroscopy based on molecular vibrations, which can provide specific information of structure and composition of tissue. Cancerous tissue can provide characteristic Raman spectra due to its composition content, structural changes. Raman spectroscopy is very suitable for the diagnosis of gastric cancer. Optical fiber Raman spectroscopy system can be used for real-time diagnosis of gastric cancer. The aim of this study was to structure a fiber Raman spectroscopy system matching the gastroscope and combining with the ratios of the spectral integral energy to diagnosis of gastric cancer fast. We used this system to collected 83 spectrum from 29 patients with biopsy examination, including 17 patients with gastric carcinoma and 12 patients with normal gastric mucosa (excitation wavelength of 785 nm light, power of 50 mW, the CCD temperature to 80 ℃, acquisition time 1 s). Original Raman spectrum contained the weak Raman spectrum of tissue itself we needed, the strong autofluorescence background and noise. By reducing the baseline to remove tissue autofluorescence background and using fast Fourier transform (FFT) to increase signal-to-noise ratio, the original Raman spectrum was preprocessed. And then we got the average spectrum of gastric cancer and normal stomach mucosa tissue respectively and analyzed the ownership of the typical Raman spectrum peak. After standardizing the average spectrum， we calculated the integral energy of Raman spectra. Raman spectrum and the ratio of integral energy from continuous band (1500 cm^{-1}~1700 cm^{-1}) and non -continuous band (1100 cm^{-1}~1200 cm^{-1}) were compared. The intensity of Raman peak of gastric adenocarcinoma at 1002 cm^{-1}、1073 cm^{-1}、1450 cm^{-1}、1655 cm^{-1}. Belonging to phenylalanine and proteins are higher than that of normal mucosal relatively. From continuous band (1500 cm^{-1}~1700 cm^{-1}) and non- continuous band (1100 cm^{-1}~1200 cm^{-1}), the ratios of the spectral integral energy of gastric adenocarcinoma were different with normal mucosa markedly (independent samples *t* test, $P<0.05$), and with the ratio of the integral energy for use as a diagnostic index, obtained the higher accuracy (97.5%~ 98.5%), sensitivity (91.7%) and specific degrees (100.0%). Fiber Raman spectroscopy system applied in the clinical diagnosis of gastric cancer had a high value.

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* E-mail: pgy63@163.com