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G. 知的所有権の取得状況

1. 特許取得

なし。

2. 実用新案登録

なし。

3.その他
なし。

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総合研究報告書

レーザー消化管内視鏡治療装置の開発に関する研究

研究分担者　井口　秀人　兵庫県立がんセンター　消化器内科

研究要旨

㈱モリタ製作所、大阪大学、神戸大学で開発してきた試作機に対し、生体ブタを用いた前臨床試験を神戸医療機器開発センター(MEDDEC)において行った。改良試作機はESDの操作に必要なパワーが十分得られた。本炭酸ガスレーザーシステムはin vivo 生体ブタにおいて、胃粘膜層を切開するが、粘膜層通過後粘膜下層注入材によってレーザー光が吸収され、血管や筋層を傷付けずに、安全に粘膜及び粘膜下層のみを選択的に切除することが出来、より安全な消化器内視鏡治療が実現された。また、止血においても、レーザーパワーを5Wに落として照射することにより、止血が十分可能であった。試作機改良を重ね、ほぼ最終のものと判断した。本事業年度内に3度PMDA薬事戦略事前相談を受けることが出来た。

A．研究目的

内視鏡的粘膜下層剥離術（ESD）のハイボリュームセンターにおける経験を下に、生体ブタを用いた前臨床試験により、試作機を評価する。

B．研究方法

㈱モリタ製作所、大阪大学、神戸大学で開発してきた改良試作機に対し、生体ブタを用いた前臨床試験をMEDDECにおいて行った。レーザーシステムの効果を次の点で評価した。

・炭酸ガスレーザー装置の効能
・導光ファイバーの効能
・ガイド光の効能

（倫理面への配慮）

本課題で行う、生体ブタを用いる前臨床試験に対しては、動物実験委員会で審議、承認の上、実験動物に対する動物愛護に対して十分配慮した。

C．研究結果

レーザー装置は、スコープの最大屈曲時にガイド光がやや弱いことが認められたが、十分なレーザーのパワーも有し、操作上に何ら支障が認められなかった。また、止血においても、レーザーパワーを5Wに落として照射することにより、止血が十分可能であった。試作機はほぼ最終のものと判断できた。

D．考察

今後は、最終システム構成を決定し、in

vitro、in vivo 安全性の検証実験を実施し、データーを整理した上で、PMDA の対面相談を受け、臨床試験を実施する必要がある。

E．結論

開発の改良試作機が完成した。今後、in vitro、in vivo 安全性の検証資料を整理した上で、PMDA の対面相談を受け、臨床試験の規模を決定し、臨床試験を実施するとともに、薬事承認申請へと進める。

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2. 実用新案登録

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総合研究報告書

レーザー消化管内視鏡治療装置の開発に関する研究

研究分担者　横井　英人　香川大学医学部附属病院　医療情報部

研究要旨

早期消化管がん治療に有効な内視鏡的粘膜下層剥離術(ESD)において、従来の高周波電気メスに代わる炭酸ガスレーザーを用いたレーザーESD装置開発のための、前臨床試験及び臨床研究の計画支援を行った。開発機器システムの構成の評価、in vitro、in vivo 実験による安全性、有効性の検証方法の計画支援を行い、3 度 PMDA 薬事戦略事前相談を受けることが出来た。

A．研究目的

早期消化管がん治療に有効な内視鏡的粘膜下層剥離術(ESD)において、従来の高周波電気メスに代わる炭酸ガスレーザーを用いたレーザーESD 装置開発のための、前臨床試験及び臨床研究計画を支援することを目的とした。

B．研究方法

開発機器システムの構成の評価を行った。また、ブタ切除胃を用いた in vitro、及び生体ブタを用いた in vivo 実験による安全性、有効性の検証方法を検討した。

PMDA の対面相談に向けて、システム構成、ハードウエアの評価状況、in vitro、in vivo 実験による安全性、有効性を整理した。

（倫理面への配慮）

本課題で行う、生体ブタを用いる前臨床試験に対しては、動物実験委員会で審議、承認の上、実験動物に対する動物愛護に対して十分配慮した。

C．研究結果

ESD にレーザーを使うというところが明らかに既存製品と異なり、この部分は新規事項であり、臨床試験無しというわけにはいかないと考えられた。動物実験のみで、臨床試験不要と主張する場合は、動物実験でその根拠が明確でなければならない。本研究において、平成 24～26 年度で PMDA の薬事戦略事前相談を 3 度受けることが出来、対面相談に向けての安全性・有効性について、以下の事項が明らかになった。

・処置具、ファイバの光学特性、強度・耐久特性、出力特性の評価結果、それに基づいた本ファイバ（処置具）の使用制限等のリスクマネジメント方策についてまとめる。

・動物実験結果のまとめ、その結果から人への外挿性についての考えを整理する。

・電気メスと比較した穿孔リスクや施術容易性についての客観的に説明する（従来法

との比較)。
・レーザーを用いたESDのトレーニング方法を作成すること。
・電気メスと比較した有効性、非劣性の検証の方策について説明する。
・止血、保持用アタッチメントの考え方について説明する。

D．考察

これまでの薬事戦略事前相談において、対面相談に向けての安全性・有効性の必要事項が明らかになった。今後は、最終システム構成を決定し、in vitro、in vivo 安全性の検証資料を整理した上で、PMDA の対面相談を受け、臨床試験計画を作成する。

E．結論

これまでの結果で、開発品の試作機が完成した。今後、in vitro、in vivo 安全性の検証資料を整理した上で、PMDA の対面相談を受け、臨床試験の規模を決定し、臨床試験計画を作成する。

F. 研究発表

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G. 知的所有権の取得状況

1. 特許取得
なし。

2. 実用新案登録
なし。

3.その他
なし。

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
D. Obata, Y. Morita, R. Kawaguchi, **K. Ishii**, **H. Hazama**, **K. Awazu**, H. Kutsumi, and T. Azuma	Endoscopic submucosal dissection using a carbon dioxide laser with submucosally injected laser absorber solution (porcine model)	Surg. Endosc.	27(11)	4241–4249	2013
D. Kusakari, **H. Hazama**, R. Kawaguchi, **K. Ishii**, and **K. Awazu**	Evaluation of the bending loss of the hollow optical fiber for application of the carbon dioxide laser to endoscopic therapy	Opt. Photon. J.	3(4A)	14–19	2013

IV. 研究成果の刊行物・別刷

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Endoscopic submucosal dissection using a carbon dioxide laser with submucosally injected laser absorber solution (porcine model)

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Abstract

Background Recently, endoscopic submucosal dissection (ESD) has been performed to treat early gastric cancer. The en bloc resection rate of ESD has been reported to be higher than that of conventional endoscopic mucosal resection (EMR), and ESD can resect larger lesions than EMR. However, ESD displays a higher complication rate than conventional EMR. Therefore, the development of devices that would increase the safety of ESD is desired. Lasers have been extensively studied as a possible alternative to electrosurgical tools. However, laser by itself easily resulted in perforation upon irradiation of the gastrointestinal tract. We hypothesized that performing ESD using a CO_2 laser with a submucosal laser absorber could be a safe and simple treatment for early gastric cancer. To provide proof of concept regarding the feasibility of ESD using a CO_2 laser with submucosally injected laser absorber solution, an experimental study in ex vivo and in vivo porcine models was performed.

Methods Five endoscopic experimental procedures using a carbon dioxide (CO_2) laser were performed in a resected porcine stomach. In addition, three endoscopic experimental procedures using a CO_2 laser were performed in living pigs.

Results In the *ex vivo* study, en bloc resections were all achieved without perforation and muscular damage. In addition, histological evaluations could be performed in all of the resected specimens. In the in vivo study, en bloc resections were achieved without perforation and muscular damage, and uncontrollable hemorrhage did not occur during the procedures.

Conclusions Endoscopic submucosal dissection using a CO_2 laser with a submucosal laser absorber is a feasible and safe method for the treatment of early gastric cancer.

Keywords Endoscopic resection · Therapeutic upper gastrointestinal endoscopy · Laser · Laser absorbent

Gastric cancer is one of the most common cancers in the world. The development of endoscopic diagnostic techniques led to an increased number of early stage gastric cancers being detected. Subsequently, endoscopic mucosal resection (EMR) was established as a minimally invasive local treatment and is now performed for the treatment of early gastric cancer without lymph node metastasis [1]. The main advantages of the EMR method are that it does not involve laparotomy, the whole stomach is preserved, and it has a less negative impact on the patient's quality of life than laparotomy. Although the possibility of expanding the indications for EMR to resect larger lesions has recently been proposed, conventional EMR cannot be used to resect lesions larger than 20 mm en bloc because of technical limitations [2, 3]. Piecemeal resection does not enable sufficient histological evaluation of the tumor and displays a significantly higher local recurrence rate than en bloc resection [4–6]. Therefore, endoscopic submucosal dissection (ESD), a new EMR technique, was introduced by Hirao et al. [7] and has become widely accepted as a

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standard procedure for early gastric cancer treatment. ESD allows larger lesions to be resected en-bloc. However, in comparison with EMR, ESD requires special skills and involves a long procedure. In addition, ESD carries a high risk of perforation and bleeding. Various devices, such as the insulated-tip knife (IT knife) [4], Flush knife [8], and hook knife [9] have been developed to reduce the complications rate of ESD. When dissection is performed using these devices, which cut using an electrosurgical current, the knife is in direct contact with the tissue. Submucosal dissection using an electrosurgical current requires a high level of skill and carries a risk of perforation because of unexpected incision of the muscularis propria. It was reported that the perforation rate of ESD for early gastric cancer using the IT knife was 5 % [4].

Lasers have been extensively studied as a possible alternative to electrosurgical tools. Various types of laser have been used as surgical tools to incise or excise tissues and achieve hemostasis. For example, potassium titanyl phosphate (KTP), neodymium-doped yttrium aluminium garnet (Nd:YAG), and diode lasers have all been used in endoscopic procedures for treating gastrointestinal tract cancer or precancerous lesions. These laser irradiation therapies vaporize the lesion and coagulate any hemorrhaging blood vessels. The main disadvantage of these therapies is that the lesion is vaporized; thus, pathological evaluations cannot be performed after the procedure. It is important to collect tissue samples from dissected lesions as it allows a precise pathological evaluation and aid decisions regarding additional treatment.

Lasers have various effects on living tissue. Recently, lasers have been widely used in clinical practice for making incisions, inducing coagulation and hemostasis, and vaporizing lesions. The laser energy absorbed by the target tissue is converted into other forms of energy, such as heat or shockwaves, or is used to induce chemical reactions. Lasers of different wavelengths have different scattering, penetration, and absorption profiles, and hence, have different effects on the target lesion depending on the amounts of energy absorbed by elements within tissue [10]. In the mid-infrared range, light scattering is negligible within soft tissue. The surgical performance of mid-infrared lasers generally depends on the light absorption characteristics of water and protein, the main components of soft tissue, at the laser's oscillating wavelength. The CO_2 laser is a gas laser that was originally developed in 1964 and has a wavelength of 10.6 μm [11]. It has been widely used in various surgical treatments in the otorhinolaryngology, dermatology, and oral surgery fields [12–14]. It is a mid-infrared laser, and its energy is strongly absorbed by water and protein, but hardly penetrates deeper tissues [15]. CO_2 lasers can cut tissue precisely whilst causing limited damage to the surrounding tissue [12–14]. Surgical procedures performed with CO_2 lasers are mostly bloodless because the heat produced by the laser seals small vessels [16]. The reduced heat damage inflicted on the resected lesion allows precise pathological evaluations to be performed, and the low level of hemorrhaging increases visibility during the procedure, therefore making it safer. These features of the CO_2 laser are thought to be advantageous for ESD.

In clinical ESD procedures, a solution (usually saline or sodium hyaluronate) is injected into the submucosa to lift the target region of the mucosa, isolate the lesion, and protect the muscularis propria from thermal and mechanical injury, thereby decreasing the risk of perforation. Compared with most other lasers, a large amount of the energy produced by CO_2 lasers is absorbed by water [17]. Therefore, if there is enough water within the submucosa, it is hypothesized that the energy of the CO_2 laser will be absorbed by the water and will not be able to reach the muscularis propria. Thus, performing ESD using a CO_2 laser with saline as a submucosal laser absorbent could be a safe and simple treatment for early gastric cancer. There have been no previous reports of ESD of the stomach performed using a CO_2 laser because usual optical fibers cannot be used to deliver CO_2 laser due to very high internal absorption of the optical fibers. However, the hollow optical fiber that has recently been developed has enabled us flexible delivery of CO_2 laser. We examine whether performing gastric ESD with a CO_2 laser is feasible.

Materials and methods

Measurement of infrared absorption spectra

The infrared absorption spectra of the porcine stomach wall, saline, and 0.4 % sodium hyaluronate (MucoUp; Johnson and Johnson K.K., Tokyo, Japan) were measured using a Fourier transform infrared spectrometer (MB3000, ABB Ltd., Zurich, Switzerland) coupled with an infrared microscope (bi-μMAX, PIKE Technologies, WI, USA). When the absorption spectrum of the porcine stomach was measured, the absorption spectra of each layer; i.e., the mucosa, submucosa, and muscularis propria, were assessed.

CO_2 laser

A CO_2 laser oscillation device (J. Morita Mfg. Corp., Kyoto, Japan) that had been remodeled to increase its output power was used for these experiments. The laser was used in continuous wave mode. The output power of the laser was measured using a laser power meter (30A, Ophir Optronics Solutions Ltd, Israel) and was set at predetermined values.

Hollow optical fiber

A hollow optical fiber (J. Morita Mfg. Corp., Kyoto, Japan) optimized for the wavelength of the CO_2 laser was used in this study [18]. The inner diameter of the fiber was 700 μm, and it measured 2.65 m in length. The fiber was connected to a CO_2 laser oscillation device.

Preliminary study

The speed of porcine gastric mucosal incisions made with electrosurgical knives was measured (data not shown), and it was found that the mean mucosal incision speed was about 1.0 mm/s. Porcine gastric wall samples were placed on an automatic moving table, and the speed of the table's movement was set at 0.5, 1, or 2 mm/s. In the absence of saline injection into the submucosa, the CO_2 laser irradiation was performed at output powers of 6, 8, and 10 W at a distance 2 mm from the mucosal surface. In the presence of saline injection into the submucosa, which was performed to increase the thickness of the submucosa to 5 mm, laser irradiation was performed at output powers of 6, 8, 10, and 12 W. The depth of incision was measured during each procedure.

Ex vivo porcine stomach study

Porcine organs (the esophagus, stomach, and duodenum) were irrigated with water and Pronase MS 400 U/ml (Kaken Pharma, Tokyo, Japan). An overtube (MD-48518 Sumitomo Bakelite, Tokyo, Japan) was fixed onto a plastic box (Pentax Corporation, Tokyo, Japan). The esophagus of the resected specimen was then passed over the overtube, which formed a solid connection with the oral end of the esophagus. Then, the end of the duodenum was tightly attached to the plastic box using a plastic band (Fig. 1).

An upper gastrointestinal endoscope (GIF-Q260J, Olympus, Tokyo, Japan) was inserted into the stomach. To identify the margins of the hypothetical lesions, marking dots were made on the exterior of the target mucosa using a Flush knife (DK2618JN25, Fujifilm) and an electrical generator (vio200S; ERBE, Germany). The marking dots were placed so that the hypothetical lesions had diameters of 2 cm. Saline was injected into the submucosa under the hypothetical lesion with an endoscopic injection needle (01841; Top Corporation, Tokyo, Japan). A hollow optical fiber was passed through the scope channel, and circumferential mucosal cutting was performed using the continuous wave mode of the CO_2 laser at a power setting of 10.0 W. After an additional submucosal injection of saline, the submucosa below the hypothetical lesion was directly dissected using the same CO_2 laser mode. After cauterization, all of resected specimens and ESD sites were collected and fixed in 4 % formalin, and then the diameter of the cauterized area was evaluated histologically.

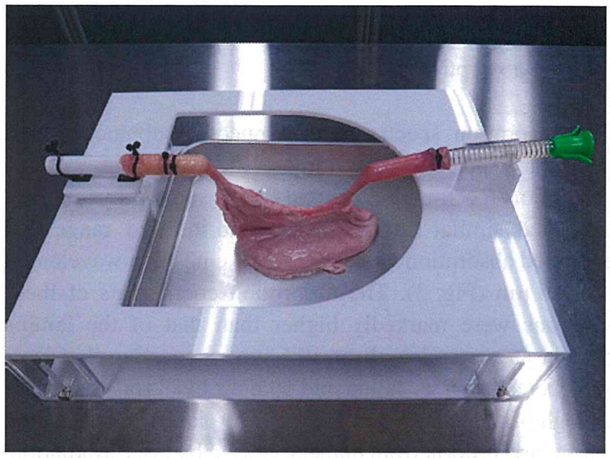

Fig. 1 A porcine stomach was subjected to CO_2 laser ESD using an endoscopy training system. A resected porcine stomach was subjected to CO_2 laser ESD using a training system for endoscopic procedures

Living porcine study

LWD pigs weighing 18.5 kg were used in the study. This study was approved by ethical committee of the animal experimentation facility. The pigs were deprived of food for 24 h before the procedure. The pigs were placed under general anesthesia via the intramuscular injection of 10 mg/kg ketamine plus 2 mg/kg xylazine and endotracheal intubation. Anesthesia was maintained with isoflurane (2.0–3.0 %) and oxygen (2.0–3.0 L/min).

An upper gastrointestinal endoscope (GIF-Q260J, Olympus, Tokyo, Japan) was passed into the stomach with the assistance of an overtube (MD-48518 Sumitomo Bakelite, Tokyo, Japan). Marking dots were made around the exterior of a hypothetical lesion using a FlushKnife (DK2618JN25, Fujifilm) and an electrical generator (vio200S; ERBE, Germany) to identify its margins. Saline was then injected into the submucosa under the hypothetical lesion with an endoscopic injection needle (01841; Top Corporation, Tokyo, Japan). A hollow optical fiber was passed through the scope channel, and circumferential mucosal cutting was performed using the continuous wave mode of the CO_2 laser at a power setting of 10 W. After an additional submucosal injection of saline, the submucosa below the hypothetical lesion was directly dissected using the same CO_2 laser mode. After cauterization, necropsy was *immediately* performed, and all of the resected specimens and ESD sites were collected. The collected samples were fixed in 4 % formalin, and the diameter of the cauterized area was evaluated histologically.