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Invited review

Lasers in Gastroenterology: Current Status and Future Perspectives

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Lasers are sophisticated sources of monochromatic light in the visible and near infra-red part of the optical spectrum. The one that has been used most by gastroenterologists is the Neodymium yttrium aluminium garnet (NdYAG) laser, which emits a near infrared beam at 1064nm. This penetrates living tissue well and can be transmitted via a thin, flexible fibre, so can be used with flexible endoscopes. Short, sharp shots from this laser cause thermal contraction in soft tissue, which provides good haemostasis. Longer shots at high power can vaporise tissue and coagulate the underlying layers, which is effective for debulking and recanalising advanced cancers. At much lower powers, the same laser can be used to coagulate a larger volume of tissue without vaporisation. More recently, there is increasing interest in photochemical effects, where red laser light is used to activate previously administered photosensitising drugs (photodynamic therapy, PDT).

HAEMOSTASIS FOR BENIGN LESIONS

The first interest in the use of lasers in gastroenterology was for the control of haemorrhage from peptic ulcers. In the mid 1970's when flexible endoscopes were first coming into widespread use, innovators were searching for technology that could treat as well as just look at the lining of the gastrointestinal tract. At this time, lasers were also becoming more available with the possibility of fibreoptic delivery systems, so powerful light beams could be delivered through the biopsy channel of flexible endoscopes. The "James Bond" factor played a significant part in bringing the 2 technologies together.

It had been known for years that only a small proportion of peptic ulcers rebleed after an index bleed. The interest in developing endoscopic techniques for haemostasis, in particular with lasers, provided the incentive for a series of studies to identify which ulcers were at highest risk of rebleeding. The answers were clear. Ulcers in which a "visible vessel" could be identified in the crater were the ones at highest risk. The NdYAG laser was a convenient technique for thermally sealing these exposed vessels. Several trials showed that the laser treatment significantly reduced the incidence of rebleeding after haemorrhage from peptic ulcers.[1] However, later studies showed that injection sclerotherapy worked just as well, and was simpler and cheaper.

The only benign lesions for which endoscopic laser therapy retains an important role for control of blood loss are vascular lesions like hereditary telangiectasia, angiodysplasia and water melon stomach (GAVE, gastric antral vascular ectasia). The natural history of these is to bleed with increasing frequency and severity over a period of months or years. The aim of endoscopic therapy is to ablate the fragile microvessels and replace them with a scar, which is much less likely to bleed. Even after apparently successful laser treatment, new areas of ectasias may develop over the course of several years, so a simple endoscopic treatment that can be repeated if new lesions develop at a later stage is much more attractive than more drastic options such as a surgical antractomy.

In a series reported by Sargeant et al,[2] 41 patients with transfusion dependent bleeding from vascular ectasias of the upper gastrointestinal tract (16 with water melon stomach), were treated with the NdYAG laser. Overall, 61% (including 12 of 16 with water melon stomach) required minimal or no transfusion after laser treatment and a further 22% were controlled with repeat

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courses of laser treatment. These results are at least as good as those achieved with other endoscopic techniques. More recently, the argon plasma coagulator has been used for this indication. The effect is more superficial than that of the laser, but for these superficial lesions, the results are comparable. These lesions can be managed by sclerotherapy and various other thermocoagulatory modalities but non-contact laser treatment is effective and simple to apply, especially when multiple lesions are present.

PALLIATION OF ADVANCED CANCERS

The main role of high power, thermal lasers like the NdYAG in current practice is for palliation of advanced, inoperable cancers of the upper and lower gastrointestinal tract. Under direct vision, nodules of exophytic tumour can be vaporised and underlying tumour coagulated either to relieve obstruction or to reduce blood loss. The incidence of complications is low, although it often takes several treatments to achieve optimum recanalisation.

PALLIATION OF ADVANCED MALIGNANT DYSPHAGIA

Most patients with cancers of the oesophagus or gastric cardia present when the disease is too advanced for there to be any prospect of cure and the main aim of treatment is to relieve dysphagia as simply and rapidly as possible. The main endoscopic options are stent insertion and laser therapy. The early laser papers reported effective recanalisation of advanced cancers with a major exophytic component, providing rapid symptomatic relief.[3] However, regrowth from cancer in the wall of the oesophagus is inevitable and leads to recurrent symptoms in an average period of about 6 weeks. Laser treatment can be repeated as often as required, but combining it with radiotherapy is better.

Radiotherapy has been a mainstay of the non-surgical management of oesophageal cancer (squamous and adenocarcinomas) for many years. Some of the long term results, particularly for squamous carcinomas, have been very good, but for cancers that are causing severe dysphagia at the time of initial presentation, radiotherapy often does not provide good symptomatic relief.[4] Thus a logical approach is to achieve initial recanalization with the laser and then to add radiotherapy. This has now been done using both internal and external irradiation. In a controlled study comparing laser palliation alone and in combination with a palliative dose of external beam radiotherapy (30 Gy in 10 fractions over 2 weeks), the average interval between laser treatments increased from 5 to 9 weeks, although there was no difference in the survival time. The results were the same for both squamous and adenocarcinomas.[5] This was encouraging, although it was inconvenient to need 10 fractions of radiotherapy. More recently, a study has been reported comparing laser alone with laser plus brachytherapy (intraluminal irradiation). This is simpler as only a single, day case treatment is needed for brachytherapy and the results were dramatic. Only patients able to eat solids after initial laser treatment were included, but those receiving brachytherapy were palliated for an average of 19 weeks compared with 5 weeks in the laser only control group.[6] However, once dysphagia did recur, retreatment was required every 5-6 weeks, suggesting, as might be expected, that the brachytherapy only treated tumour immediately adjacent to the oesophageal lumen. Perhaps the best solution lies in using some combination of external beam and intraluminal radiotherapy after laser, although this has not yet been reported.

For many endoscopists, the first choice for palliation of malignant dysphagia is stent insertion. This is a one stage procedure, but the results are far from always satisfactory. The two techniques are complementary – laser is better for eccentric, exophytic cancers and stents are better for extrinsic tumours with no obvious laser target. It is likely that if there is a large, bulky tumour, reducing the volume of this with the laser initially will make stent insertion easier and more effective. Recently, expanding metal stents have dominated this field. Once inserted, many stents function reasonably well for the rest of the patients' life and undoubtedly, they are simpler and safer to insert than the old silicon rubber stents. Nevertheless, the harder one looks at the long term results, the more it becomes clear that the quality of palliation is often nothing like as good as had been suggested when these devices were first introduced.[7] There is sometimes an extended period of pain after their insertion, which in about 6% of cases may last for the remainder of the patients' life. It is now clear that there is no technique that is suitable for all patients. These patients are best treated in a hospital that is able to use all these techniques, alone or in combination.

PALLIATION OF ADVANCED RECTO-SIGMOID CANCERS

Most colorectal cancers are best treated by surgery. However, there is a small group of patients who are not fit for definitive surgery of advanced cancers arising in

the rectum or distal sigmoid colon. In some cases, obstructive symptoms are relieved by a defunctioning colostomy, but the main bulk of the tumour remains where it arose. This can often lead to distressing symptoms of rectal bleeding with mucus discharge. In other cases, the bowel remains in continuity without obstruction, but an inoperable cancer causes tenesmus, diarrhoea and bleeding that can be relieved by debulking the cancer. The same may be true for large villous adenomas which can produce copious quantities of mucus, but which progress quite slowly in elderly patients who are otherwise reasonably well.

Treating such lesions with endoscopic laser therapy can be undertaken in exactly the same way as for advanced cancers of the upper gastrointestinal tract, usually as a day case procedure with minimal sedation.[8] Often the bulk of these cancers is large, but access is usually relatively easy. Many endoscopists use various forms of snare polypectomy and diathermy excision to reduce the bulk of these tumours and for large exophytic nodules, this may be the best way to start. The value of laser therapy lies in the greater precision available as the effect of each laser shot can be seen immediately. This makes the laser option safer and it is really the only endoscopic technique that can be used safely above the peritoneal reflection (apart from the argon plasma coagulator, which is very slow for treating bulky lesions).

Laser therapy provides effective palliation for most of these patients by debulking the tumour either in a defunctioned pouch or in an intact bowel, but as in the upper tract, the effect can only be expected to last for a few weeks before further treatment is required. It has been shown that the effect can be prolonged by giving a palliative course of external beam radiotherapy after laser treatment.[9] Recently, expanding metal stents have been introduced for palliation of obstructing symptoms in the distal colon. In appropriate cases, these are most effective, especially for lesions above the peritoneal reflection where there is more risk of perforation from thermal treatments, but they cannot be used safely if the lower end of the lesion is less than about 6cm from the anal margin.

INTERSTITIAL LASER PHOTOCOAGULATION (ILP)

For endoscopic applications of the NdYAG laser, the high power laser beam (typically in the range of 30-70W) is transmitted via a flexible fibre surrounded by a thin catheter through which a slow stream of air passes continuously. This acts to prevent any of the luminal contents of the gastrointestinal tract contaminating the end of the fibre. If this happened, the laser energy would be absorbed in the debris and could destroy the fibre tip. The laser energy is transmitted in short bursts of 1-2 seconds and the effect on the tissue can be observed directly by the endoscopist. In 1983, an alternative way of using this laser was first described.[10] Instead of using the laser at high power and transmitting the beam via a fibre probe that is held a few mm above the surface of the target tissue, a bare fibre without the surrounding catheter and gas flow was used, which was inserted directly into the target tissue. By this means, the laser beam could be delivered to the centre of a solid organ without producing any effect on the surface. To achieve this safely, the power had to much lower (2-3W instead of 30-70W, to avoid any immediate tissue vaporisation leading to mini explosions within the tissue), but with continuous treatment over a period of 10-15 minutes instead of discrete shots lasting only a couple of seconds. This is the "slow casserole" effect rather than the "stir fry".

In gastroenterology, the potential application of ILP that has attracted most interest is the percutaneous treatment of small tumours in the liver. Much of the early experimental work on ILP was done on normal animal livers, as the liver is such a forgiving organ and heals well after thermal insults. These studies showed that it was possible to produce a sharply defined zone of necrosis up to 1.5cm in diameter around a single fibre. These lesions healed completely with regeneration of normal liver and no general upset to the animal.

As ILP produces its effects in the middle of a solid organ, it is completely dependent on imaging to define the location and size of the lesion to be treated, to insert the needles through which the laser fibres can be positioned in the target lesion and to monitor the effects of treatment. The first studies used ultrasound as the imaging technique for needle insertion, which worked well, although ultrasound was not very accurate for monitoring. Contrast enhanced CT scans taken a day or two after ILP have proved better for assessing the results. The first clinical studies were for the treatment of isolated metastatic tumours in the liver, most often in patients who had previously had cancers of the colon removed surgically. Amin et al[11] described their experience in the treatment of 55 liver tumours in 21 patients. 82% of patients fulfilled the UICC criteria for at least a partial response (>50% reduction in tumour volume). A recent paper described the long-term outcome in over 500 treated patients with a median survival of 27 months and a 5-

year survival rate of 26%. This is compared with patient outcomes following operative treatment for metastases at the same institution, of 33 months median survival and 30% 5 year survival respectively.[12]

Monitoring ILP in real time as the laser is firing would be the ideal approach as it would make it possible to adjust the treatment time and needle positions to be sure that adequate treatment has been delivered at all relevant sites, without any normal areas receiving unacceptable amounts of heat. However, this has proved to be difficult. The most promising approach is with magnetic resonance imaging (MRI) as this can detect temperature changes in tissue, although for meaningful results, a high magnetic field scanner is required (1-1.5 Tesla).[13] Unfortunately, this is only widely available in closed scanners and few open scanners (needed for it to be practical to manipulate needle positions during treatment) have a field higher than 0.5 Tesla. This problem may be overcome with future scanners.

ILP is not used widely for treating small primary or secondary tumours in the liver as relatively few patients are suitable. In addition, there are several other percutaneous techniques that can be used in a similar way (interstitial radiofrequency heating, injection of absolute alcohol or chemotherapy agents etc), but nevertheless, it is an elegant concept that has stimulated research into percutaneous, image guided treatment of lesions in a range of organs.

PHOTODYNAMIC THERAPY (PDT)

The most exciting use of lasers in gastroenterology in the next few years is likely to be in photodynamic therapy (PDT), especially for the treatment of pre-malignant and early malignant lesions in the luminal gut (particularly dysplasia in Barrett's oesophagus). Recent work has also shown its possible role in the treatment of cancers of the pancreas.

PDT is a way of producing localised tissue necrosis with light (most conveniently from a laser) after prior administration of a photosensitising agent, in the presence of oxygen.[14] The cytotoxic intermediary is thought to be singlet oxygen. As the biological effect is photochemical, not thermal, there is little damage to connective tissues like collagen and elastin, which helps to maintain the mechanical integrity of hollow organs like the gastrointestinal tract.[15] Further, as the light used is non-ionising, PDT does not carry the cumulative toxicity associated with radiotherapy. Once a PDT treated area has healed, it can be treated again, if necessary. Much of the early interest in PDT centred around the selective retention of photosensitisers in malignant tissue compared with the adjacent normal tissue in which the tumour arose as this raised the possibility of selective destruction of cancers. Unfortunately, although there is some selectivity of uptake, this is rarely enough to make selective tumour destruction feasible and there is essentially always some necrosis in adjacent normal tissue where normal and neoplastic tissue meet. Nevertheless, if necrosis of normal tissue heals safely without loss of the mechanical integrity of the organ, then PDT may have an important role to play in the local destruction of a range of cancers. PDT and ILP are compared and contrasted in table 1.

TUMOURS OF THE LUMINAL GUT

PDT is an attractive option for treating small tumours of the gastrointestinal tract in patients who are unsuitable for surgery. In a series of 123 patients with early but inoperable oesophageal cancers treated with PDT using the photosensitiser porfimer sodium (Photofrin), a complete response (no evidence of tumour on endoscopy or biopsy) was seen in 87% at 6 months.[16] Although the overall 5 year survival was only 25%, the disease specific survival was 75%. Thus effectively, in half the patients, the cancer was not the main cause of death. These individuals died of the other conditions that made them unfit for surgery. Care must be taken not to treat too extensive a lesion as circumferential scarring in the muscle layer can cause a stricture. Strictures occured in 35% of the patients in this series, although they did all respond to dilatation. PDT can be applied at any endoscopically accessible site in the upper or lower gastrointestinal tract, but it cannot treat any lesion that has spread beyond the site of origin as, for example, to local lymph nodes. Although the light for PDT is applied locally, the drug is given systemically, which means that the whole body is photosensitised, including the skin. This can be a problem, as there is a risk of skin damage due to drug activation by ambient light. With the photosensitiser porfimer sodium, patients must avoid bright sunlight for up to 3 months, although with the sensitiser mTHPC (meso-tetrahydroxyphenyl chlorin) it is 2-3 weeks and with ALA (5-amino laevulinic acid), it is only 1-2 days.

PDT has been proposed for the palliation of advanced malignant dysphagia. This was the first application for which PDT was licensed in the USA and the UK (using porfimer sodium). PDT does provide some relief in this situation, but there are very few cases that can be helped by PDT if NdYAG laser therapy or stent insertion fail,

Table 1. Comparison of Interstitial Laser Photocoagulation (ILP) and Photodynamic Therapy (PDT)

	ILP	PDT
Nature of biological effect	Thermal	Photochemical
Effect on connective tissue	Destroyed	Largely unaffected
Healing	Resorption & scarring, some regeneration	Regeneration, sometimes with scarring
Selectivity of necrosis between tumour and tissue of origin of tumour	None	Minimal
Selectivity of necrosis between tissue of origin of tumour and other adjacent tissues	None	Possible between mucosa and underlying muscle in hollow organs
Cumulative toxicity	None	None
Wavelength of Infrared (805-1064nm) light used	Red (630-760)	
Typical laser power per fibre	3-4 W	0.1-0.3 Q (higher for illuminating hollow organs)

and it is certainly not desirable to make patients photosensitive for much of their remaining life.[17] PDT may be relatively simple for the physician to deliver, but it often causes the patients considerably more discomfort than NdYAG laser therapy in the first couple of weeks after light application. The problems include chest pain, pleural effusions and pyrexia. PDT may be of value to treat tumour that has grown over or through a stent that cannot be adjusted and which cannot tolerate the heat from a NdYAG laser (such as a covered expanding metal stent). In general terms, it seems more logical to licence PDT for treating early oesophageal cancers, as has been done by the Japanese authorities.

PREMALIGNANT LESIONS OF THE GASTROINTESINAL TRACT

The management of Barrett's oesophagus is one of the most difficult problems in current gastroenterology, particularly as the incidence of adenocarcinomas in these patients is increasing so fast. Low and high grade dysplasia are well documented as precursors of invasive malignancy, but the only definitive treatment available at present is oesophagectomy, which carries considerable morbidity and up to a 5% mortality. It would be much more attractive to find a simpler and safer, endoscopic option. The challenge is to destroy all the Barrett's mucosa, which may contain patchy, occult areas of dysplasia, without damaging the underlying muscle.

Thermal ablation with an argon plasma coagulator or KTP laser involves moving a small therapeutic beam across the area to be treated under direct endoscopic vision. It is easy to under treat, and leave abnormal mucosa, or over treat, with the risk of muscle scarring or even perforation. With PDT, balloon light delivery systems are available which illuminate all the relevant mucosa evenly, and there is very little risk of perforation, but using porfimer sodium, there is a risk of a stricture as there is no selectivity of effect between the mucosa and underlying layers.[18]

Another photosensitising agent that looks promising for this application is 5-aminolaevulinic acid (ALA). In vivo, this is converted to the photoactive derivative, protoporphyrin IX (PPIX, part of the natural route for the synthesis of haem). In contrast to photofrin, which can be found in all layers of the oesophageal wall, PPIX localises mainly in the mucosa and experimental studies have shown that this can be exploited to give selective necrosis of mucosa without damage to underlying muscle.[19] This is exactly what is required to treat circumferential zones of Barrett's oesophagus. Two important clinical studies have been published using ALA.[20,21] Neither described any strictures after treatment, which suggests that the muscle layer is not affected, but both reported residual Barrett's glands under areas of regenerated squamous mucosa, so the problems are not yet all solved. More research is needed to find reliable ways of ensuring that the full thickness of the abnormal mucosa is ablated. Options being explored are to add an iron chelating agent (which slows down the final conversion of PPIX to haem and so increases the tissue level of PPIX)[22] and to fractionate the light dose, as experimental studies have shown that a single break of 150 seconds part way through illumination can increase the area of necrosis produced by a factor of four. However, these possibilities have not yet got beyond animal studies.

In the current state of knowledge, it is doubtful wheth-

er any form of endoscopic therapy for Barrett's oesophagus is appropriate other than in the context of clinical trials unless there is evidence of severe dysplasia and the patient is considered a high risk for surgery. In the latter situation, endoscopic destruction of the mucosa by either thermal or photodynam.ic therapy can give worthwhile results.

PHOTODYNAMIC THERAPY FOR CANCER OF THE PANCREAS

One of the most dramatic possible future applications of PDT is for the treatment of cancer of the pancreas. Even though pancreatic cancer is one of the top ten leading causes of cancer death, less than 10% of cases are suitable for potentially curative surgery. Options available for the treatment of inoperable patients are largely limited to radiotherapy and chemotherapy and few patients respond well to either or both. Overall, the long-term prognosis is poor with a 1-year survival rate of no more than around 10%. For non-metastatic disease, the median survival is 6-10 months although for those with metastatic disease at presentation, median survival is a dismal 3-6 months.[23] A new minimally invasive treatment capable of local destruction of pancreatic cancer with low morbidity may have a place in the treatment of this unpleasant disease.

In view of the close proximity of the pancreas to vital structures such as the stomach, duodenum, biliary tree and major blood vessels, it was essential to understand how well these structures could tolerate PDT before contemplating clinical studies. Several groups undertook studies on normal hamsters to do this using a range of photosensitising drugs: The results were broadly similar with all of them. Necrosis could be produced in normal pancreas, stomach, duodenum and common bile duct but this healed safely with the exception of the duodenum where some free and sealed perforations were seen. In the arteries, there was endothelial loss and loss of smooth muscle in the media, but the endothelium regenerated within a few days and there was no thrombosis or weakening of the arterial wall. Experiments on cancers transplanted into the hamster pancreas showed that it was possible to produce necrosis in the cancer and there was even some selectivity of effect between the cancer and adjacent normal pancreas. This was thought to be due not to selectivity of retention of the photosensitiser, but to a constituent of normal pancreas that reacted with singlet oxygen, perhaps glutathione, that was not present in the cancer. One randomized study showed a significantly increased survival time for PDT treated, tumour bearing animals compared with untreated controls.[24]

Subsequent to these encouraging experiments, a recent paper has described a pilot clinical study on 16 patients.[25] This used the photosensitiser mTHPC as this gave the largest zone of necrosis around a single treatment fibre (up to 12mm in diameter) in the animal cancers and also because this drug requires the lowest light doses, which would mean a shorter treatment time.

All patients had histologically confirmed adenocarcinomas localised to the region of the pancreas, presenting with obstructive jaundice, which had been relieved by insertion of a biliary endoprosthesis and were considered unsuitable for surgery. Three days after administration of the photosensitiser, up to 6 needles were inserted into the tumour percutaneously using a combination of ultrasound and CT guidance. Through these, the fibres for delivering laser light to the cancer were passed.

All patients had abdominal pain after the procedure, most requiring opiate analgesia for the first few days, but none had any clinical or biochemical evidence of pancreatitis. There was concern that treatment of a tumour that encased or was in close proximity to a major blood vessel might lead to intra-abdominal or gastrointestinal tract haemorrhage. The only 2 clinically significant bleeds associated with PDT induced tumour necrosis were into the gastrointestinal tract and were from the gastro-duodenal artery, which was documented to course through the treated cancer in both cases. Contrast enhanced CT scans taken a few days after PDT showed new areas of non-enhancement, due to PDT induced necrosis. There was no CT or ERCP evidence of a pseudocyst, abscess or pancreatic duct leak in any patient at any time after PDT. In 3 cases, no definite cancer could be seen in the head of the pancreas in the early follow up scans and in 3 others, only tiny areas of viable cancer were seen. The median hospital stay after PDT was 7 days (range 5-9 days). The survival time from PDT for all patients in the study ranged from 4 to 30 months (median 9.5 months), with one patient still alive at 31 months. The median survival from the time of diagnosis ranged from 6 to 34 months (median 12.5 months), with one patient alive at 35 months.

This study confirmed the feasibility of applying PDT to cancers of the pancreas. There was no treatment related mortality, most patients were out of hospital less than 10 days after treatment and the morbidity was considerably less than would be expected after surgery. Larger scale studies are now required.

PDT has also been used in the management of advanced cholangiocarcinomas.[26] Remarkably encouraging results have been reported for the relief of obstructive jaundice in intrahepatic bile ducts in locations that could not be stented.

FUTURE APPLICATIONS OF PDT

A logical application of PDT is as an adjunct to surgery, to destroy small tumour deposits that are not visible to the naked eye or which involve areas that cannot be resected, although this may be quite difficult to apply in practice. One randomised trial has been reported looking at PDT as an adjunct to resection of rectal cancers, but there was no difference between the two groups in the incidence of local recurrence.[27]

A more speculative application of PDT is for the treatment of *helicobacter pylori*. With the increasing incidence of antibiotic resistance, it would be attractive to have an alternative therapy and all sites colonised by *h. pylori* are easily accessible endoscopically for light delivery. The organism is certainly sensitive to PDT in culture, using methylene blue as the photosensitiser, and preliminary *ex vivo* experiments have also given encouraging results,[28] but it would take considerable technical ingenuity to get adequate drug and light to all relevant sites to make this worth trying clinically.

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