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Laser Therapy Combined with Brachytherapy for the Palliation of Malignant Dysphagia

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ABSTRACT

Background/Aim of Study: Laser therapy is effective in relieving malignant dysphagia, but repeated treatments at 4 to 6 week intervals are usually required. This prospective randomised trial is designed to determine if addition of brachytherapy offers any advantages over laser therapy alone.

Methods: Patients with inoperable carcinoma of the oesophagus were randomised to receive either endoscopic Nd:YAG laser therapy alone, or laser followed by brachytherapy. Patients who developed worsening dysphagia during follow-up were offered further treatment as appropriate.

Results: Fourteen patients were randomised to receive laser only, and 12 to receive laser followed by brachytherapy. Of these 12, one was lost to follow-up and four did not receive brachytherapy because they were unfit, had extension into the cardia or had mainly extrinsic compression. These 4 are included on an 'intention-to-treat' basis. The mean therapeutic interval for the brachytherapy group was significantly longer, 83 days compared to 36 days for the laser group (p=0.026). There were no differences in the degree of dysphagia relief, number of endoscopic procedures or survival times.

Conclusion: The preliminary results of this trial suggest that brachytherapy in addition to laser therapy prolongs the first therapeutic interval. However, no long-term advantages have been shown.

Keywords: laser, brachytherapy, oesophageal cancer

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INTRODUCTION

Cancer of the oesophagus remains a disease with a dismal outcome. Fewer than 40% of patients when first diagnosed are suitable for surgical resection[1,2], and the 5-year survival rate is less than 5%[3]. The prognosis has been little improved by chemotherapy or conventional external beam radiotherapy[4]. Hence developments in therapeutic modalities for this disease have emphasised palliation of dysphagia, the most devastating symptom suffered by these patients. There are numerous endoscopic options. Dilatation of malignant strictures provides only transient benefit; intubation by rigid tubes provides partial relief, but tubes are prone to blockage and migration, and the procedure is not without risk[5,6], although modern metal mesh stents may be better. Thermal ablation of tumour tissue is possible with either bi-polar electrocoagulation or by laser light. Laser therapy has received considerable attention and is now well established as a highly effective and efficient means of relieving more than 85% of malignant dysphagia[7,8]. Unfortunately, repeated laser treatments at 4 to 6 week intervals are usually required because of tumour re-growth.

Intracavitary radiotherapy or brachytherapy used alone has been shown to improve dysphagia. This has also been combined with external beam radiotherapy to good effect. The combination of laser with brachytherapy might also be expected to be complementary but there is as yet little experience of this combined modality. We report here the interim results of an ongoing prospective, randomised trial designed to establish whether brachytherapy following laser recanalisation of oesophageal cancer offers any advantages over laser therapy alone.

PATIENTS AND METHODS

The Derby City General Hosptial is a regional referral centre for laser therapy. Patients were recruited through referrals from general practitioners, physicians and surgeons from the region. Patients were included if they had histologically confirmed squamous cell or adenocarcinoma of the oesophagus, but were found to be inoperable by reason either of local or distant spread (detected by imaging, biopsy, laparoscopy or laparotomy) or unfitness for surgery owing to age or medical conditions. Patients were excluded if they had primarily cancer of the cardia extending up into the oesophagus, had non-epithelial malignancies, were terminally ill on referral, had tracheo-oesophageal, mediastinal, bronchial or pulmonary fistulae, or had previous radiotherapy to the mediastinum.

The study was approved by the local ethics committee and all patients gave informed consent prior to randomisation.

Patients randomised to undergo laser therapy only were admitted into the endoscopy unit having fasted since 10 pm the night before. All patients were given intravenous sedation of midazolam 5 mg and also intravenous pethidine 50 mg. All patients were monitored by a pulse oximeter, and had oxygen

through nasal prongs. Endoscopic visualisation of the oesophagus was undertaken using either the Olympus 1T20 or 1T30 gastroscopes. If the tumour stricture did not admit the gastroscope, dilatation to at least 14 mm was done using the Key-Med Advance Dilator System. Laser therapy was then initiated at the same session.

The laser used was a Neodymium-Yttrium Aluminium Garnet (Nd-YAG) laser with a wavelength of 1064 nm, the Fiberlase 100 (Pilkington Medical Systems, Glasgow). The laser beam was transmitted through a 1.85 mm plain tipped Quartz Disposable Surgical Nd-YAG Fibre Delivery System (Surgilase Inc., Warwick), passed through the working channel of the gastroscope. The laser was set for one second pulse durations at an output of 80 watts.

The tumour was ablated from the macroscopic distal tumour margin in a retrograde fashion towards the proximal margin. The tumour was ablated in one or more sessions to within 2 or 3 mm of the normal mucosal margin and to achieve relief of dysphagia. After each session, patients were observed in the ward overnight and if well, were discharged the next morning. Laser therapy was repeated until recanalisation of the oesophagus was achieved (sufficient to admit the gastroscope easily) and the patient had subjective improvement of dysphagia of at least one grade. Dysphagia was graded according to Table I. Response to therapy was defined by improvement of at least one grade.

Table I – Grading of dysphagia

Grade	Description
0	No dysphagia
1	Intermittant dysphagia to solids
2	Dysphagia to solids
3	Dysphagia to semi-solids
4	Dysphagia to liquids

Patients randomised to have combined treatment were lasered in the same way. They were then booked for brachytherapy at the Derbyshire Royal Infirmary 14 days later. Brachytherapy was delivered via caesium remote afterloading (Selectron, Nucleotron, Holland) according to the technique described by Rowland and Pagliero[9]. Each patient was sedated with intravenous midazolam 5 mg, and an oesophageal catheter was inserted endoscopically to straddle the tumour. The catheter was fixed in position via a face mask, and the patient was transferred to the brachytherapy suite and connected to the Selectron treatment unit. Thirty-five to 48 caesium pellets were introduced to achieve a 12 cm long cylindrical dose distribution. A radiation dose of 15 Gy at 1 cm from the central axis was delivered with dose rates varying from 811 to 1178 cGy/hour leading to treatment times of between 1.2 and 1.8 hours. After the procedure, each patient was observed in the ward for a few hours, and if well, was discharged the same day.

Patients were followed up initially at 2 weeks after completion of their treatment, and subsequently every month until their deaths or the end of the current follow-up period .

During follow-up, patients whose dysphagia worsened by even one grade were offered further endoscopy and treatment as appropriate, and monthly follow-up resumed. This further treatment included further laser therapy with or without dilatation and intubation with metal mesh stents.

The therapeutic interval was defined as the time from the end of the treatment regime to the point when further treatment was needed, or until death or the end of the current follow-up period if no treatment was needed until then. The interval between further treatments if given was also noted.

Statistical analysis was done using the Student's unpaired one-tail t-test for comparison of means, and the Chi-squared test for comparison of proportions. A p value of less than 0.05 was considered significant.

RESULTS

Twenty-six patients were randomised. Patient data is given in Table II, and the characteristics of the cancers are given in Table III. The 2 groups are comparable. All patients had successful laser treatment, requiring a mean of 1.7 laser sessions (range 1 – 3 sessions) over a mean of 11.2 days (range 3 – 18 days). The mean total energy required to relieve dysphagia by at least one grade was 11.8 KJ (range 1.2 – 37.33 KJ).

Of the 12 patients randomised to receive brachytherapy following laser, 8 patients successfully received the full dose, and 4 received none: 3 had become too unfit to receive any brachytherapy and one had tumour spreading downwards into the cardia, making brachytherapy technically unfeasible. These 4 patients are included in the analysis on an 'intention-to-treat' basis. One other patient having received combined treatment was lost to follow up and could not be evaluated.

At 2 weeks after completion of the treatment regimes, the mean improvement in dysphagia score for the laser only group was 1.8 grades, and for the laser and brachytherapy group was 2.2 grades (p = 0.21).

Table II – Patient data

	No.	Mean age (yr) (range)	Sex ratio Male	Female
Laser	14	75.5 (62 – 89)	9	5
Laser/brachy	12	73.3 (62 – 83)	6	6

The mean therapeutic interval for the laser only group was 35.6 days (range 6 – 90 days) and for the laser and brachytherapy group was 83 days (14 – 277 days). There was a significant difference in favour of combined therapy (p = 0.026).

Table III – Characteristics of cancers

Treatment group:	Laser	Laser/brachytherapy
Histology:		
Adenocarcinoma	10	9
Squamous cell	4	2
Location:		
Lower oesophagus	12	12
(GOJ involved	11	8)
Middle oesophagus	2	0
Mean length of tumour (cm)	7.2	7.8
(Range)	(4 – 14)	(5 – 14)
Inoperable because:		
Tumour advanced	9	10
Patient unfit	5	2
Pre-treatment dysphagia grade (range)	2.8 (2 – 4)	2.8 (2 – 4)

Table IV – Treatment given at the end of the therapeutic interval

Treatment given	Laser only group	Laser/brachy group
Dilatation only	1 (7%)	0
Laser treatment	4 (29%)	2 (18%)
Intubation (metal stent)	3 (21%)	1 (9%)
None required until death	6 (43%)	6 (55%)
None required until end of current follow-up period	0	2 (18%)

During the follow-up period, 6 of the14 patients (42.8%) who had been treated with laser only did not require further treatment until death or end of the furrent follow-up period. In the laser and brachytherapy group, the number was 8 out of 12 (66.7%) (p = 0.23). The treatment given to patients on recurrence of dysphagia is detailed in Table IV. Further treatments were offered as necessary, for example lasering tumour in-growth through the mesh of the stents. The mean interval between further treatments were 44.2 days (range 7 – 86 days) for the laser only group and 42.5 days (35 – 50 days) for the laser and brachytherapy group (p = 0.47).

The mean number of endoscopies patients were subjected to until their death or end of the current follow-up period were 3.2 (range 1 – 7) in the laser only group and 2.9 (2 – 4) in the laser and brachytherapy group (p = 0.29).

There were 2 treatment related deaths (14%) in the laser only group: One died of perforation of the oesophagus after the second laser session; one died of cardiac failure a day after the second laser session. There were no treatment related deaths in the laser and brachytherapy group. In the laser only group, one patient had transient bleeding after one treatment session, and another was left with symptoms of oesophageal reflux. One patient in the laser and brachytherapy group suffered transient confusion after brachytherapy, probably due to sedation. No radiation side effects were seen.

The mean survival time for the laser only group was 109.7 days (range 8 – 369 days) and for the laser and brachytherapy group was 113.6 days (range 30 – 277 days) (p = 0.46).

DISCUSSION

The persistently poor results of treating advanced carcinoma of the oesophagus has led to much work on improving both single modality treatments, and different combination therapies. The aims have been to produce increased survival times, as well as to offer palliation without undue morbidity in inoperable patients. The mainstays of therapy have traditionally been surgery, external beam radiotherapy, chemotherapy and several endoscopic methods, primarily intubation and more recently, laser therapy. Various combinations of these methods have been attempted, particularly with surgery, external beam radiotherapy and chemotherapy. Results have been varied, and there has been a modicum of success in some trials, but in general, no real breakthroughs have been achieved[10].

External beam radiotherapy used alone has yielded poor results in the treatment of cancer of the oesophagus and has frequently failed to control local disease in up to 80% of patients[11-13]. Radical external beam radiotherapy produces very poor survival, but palliative external beam radiotherapy can be very useful in relieving dysphagia[13,14]. However, several sessions are usually required and improvement takes time. This contrasts with brachytherapy which can be completed in one session and which produces a much quicker symptomatic response.

The first report of intracavitary radiation treatment (brachytherapy) was by Guisez in 1901, using radium[15]. However, technical problems and high risk to surrounding personnel prevented acceptance of this technique until afterloading techniques were developed[16]. There have subsequently been a number of reports on the use of brachytherapy alone or in combination with other therapies, such as surgery, chemotherapy and laser therapy. The greatest number of reports are of brachytherapy and external beam radiotherapy in combination. Unfortunately, there have been very few prospective randomised trials and results are consequently difficult to compare.

Of the reports on brachytherapy used alone, Rowland and Pagliero were the first to show that intracavitary radiation is effective in palliating cancer of the oesophagus, with improvement in dysphagia seen in 65% of their patients, and a duration of relief of 15 weeks[9]. Fleischman et al reported 90% effective palliation in patients who had failed other therapies, an average duration of response of 5.1 months and 60% of patients palliated until death[17]. Jager et al reported 69% palliation, median duration of palliation of 4.5 months and median survival of 4 months[18]. Wee et al achieved 'some improvement' in swallowing in all patients, with a mean duration of palliation of 13 weeks[19].

It was shown by Abe et al that even at a high dose of 50 Gy over 5 weeks, external beam radiotherapy left remnant tumour tissue in the wall of the oesophagus within 5 mm from the inner oesophageal lining[20]. Following maximally tolerable external beam radiotherapy, brachytherapy might be expected to have a role in eradicating any remaining disease near the oesophageal lumen. A number of reports on non-randomised patients have been published evaluating combined external beam radiotherapy and brachytherapy. Most of these trials were looking at curative regimes and some produced reasonable response rates ranging from 53%[21] to 96%[22], therapeutic intervals as long as 68 weeks[23] and survival times up to 19 months for patients with early stage disease[22,24]. Most of these studies however showed high complication rates and patient intolerance which was not always well documented.

Laser therapy is now well established as a highly effective and efficient means of relieving dysphagia, but as a means of localised treatment how does it compare with brachytherapy alone? A prospective randomised trial by Low et al comparing laser with brachytherapy for palliation of oesophageal cancer demonstrated very similar palliation rates, initially of 91% and 81%, and at 2 months, 83% and 75% respectively[25].

When laser is applied, only tumour near the inner oesophageal surface can be removed, and repeated laser treatments at 4 to 6 week intervals are usually required, because of tumour re-growth. Addition of radiotherapy to deal with tumour in depth might be expected to improve results. Sargeant et al added external beam radiotherapy to laser therapy and extended their dysphagia free interval to 13 weeks, at the cost of poor patient tolerance at higher doses of radiation[26]. Brachytherapy might also reasonably be expected to be a useful adjunct to laser treatment, destroying tumour cells in greater depth, with the advantage of not affecting mediastinal tissues and causing systemic side effects.

Bader was the first to combine laser therapy with brachytherapy in the treatment of cancer of the oesophagus and claimed 77% – 80% permanent relief of dysphagia[27,28]. Sander et al[29] followed with a prospective randomised comparison between laser therapy and laser with brachytherapy and found that squamous cell carcinomas benefitted from a prolonged dysphagia free first interval (65 days versus 30 days) but not adenocarcinomas. Overall there was a non-significant trend towards a better median dysphagia free interval for the laser and brachytherapy group (68 days versus 32 days at $p = 0.1$). All their patients suffered re-stenosis in contrast to Bader's good results. Patients receiving laser treatment alone tended to need fewer endoscopic interventions (1.8 per month) than those with combined treatment (3 per month), but there was no difference in overall survival between the groups. It may be that Bader's good results were due to many of his patients also having external beam radiotherapy.

Two other pilot studies of laser with brachytherapy have since been produced. Renwick et al in a non-randomised trial of 21 patients treated with laser and brachytherapy at the same session through a rigid oesophagoscope achieved symptomatic relief in 19 patients. One patient subsequently underwent oesophagectomy, and five others required further procedures after 6 to 44 weeks[30]. Spencer et al treated 14 patients and found that four patients needed no further treatment until death; the therapeutic interval for the rest was 8 weeks with a median survival of 23 weeks[31].

Our choice of brachytherapy regime and dosage reflects the previous experience of other workers. We chose a high dose rate regime of 15 Gy in one session rather than a low dose rate regime over several fractions in order to reduce the number of endoscopic procedures required, since one aim of combined therapy is to try to reduce the total number of procedures patients have to undergo. Our preliminary results show a significant prolongation of the therapeutic interval in the laser and brachytherapy group, 83 days (11.8 weeks) versus 35.6 (5.1 weeks) days for laser treatment alone. This result is consistent with those of previous workers using brachytherapy alone and with Renwick and Spencer's pilot studies. One of our patients having had combined therapy has been well and asymptomatic for more than 10 months. Our patients' cancers are mainly adenocarcinomas and our results stand in contrast to Sander's which showed that adenocarcinomas do not benefit. Rowland and Pagliero's[9,32] and Renwick's[30] non-randomited studies also suggested that histology did not affect results.

The proportion of patients in each treatment group who did not require further treatment was not significantly different, although it tended to favour the laser and brachytherapy group (8/12 compared to 6/14 for the laser only group). Subsequent treatment intervals and survival were not significantly different between the 2 groups and this was also shown by Sander et al with survival figures comparable to ours. This suggests that the difficulty in ablating all tumour tissue in depth by brachytherapy allows eventual proliferation of tumour sufficiently to cause recurrence of dysphagia and full reassertion of the cancer's aggressiveness. The initial prolongation of the therapeutic interval seems insufficient to make an impact on overall survival. It is also disappointing that once there is symptomatic recurrence, subsequent therapeutic intervals appear no different between the 2 treatment groups, suggesting that no long term retardation of tumour growth rate was achieved. The total number of endoscopies patients underwent was also not different between treatment groups.

Perforation is a recognised complication of laser therapy to the oesophagus in between 2% and 10% of patients[8,33,34]. Our perforation rate was one patient in 14 in the laser only group (7%). An

analysis of reported complications due to brachytherapy per se is difficult as trials vary in using high or low dose rate brachytherapy, and many combine brachytherapy with external beam radiotherapy and other treatment modalities. Where brachytherapy has been used alone, complication rates have varied considerably. Jager reported none at all[18]. Mild to moderate oesophagitis was seen in up to 50% with low dose rate regimes[17,19,35] and up to 80% with high dose rate regimes[35]. Oesophageal erosions and ulceration due to high dose rate brachytherapy were reported only by Hishikawa in 86% and 50% respectively[24], an observation not repeated by anyone else. Pagliero reported fistulae and stricture formation in 1.4% each when a high dose rate regime was used, but 5 of the 69 patients had prior external beam radiotherapy and it was not clear if the complications occurred in these 5[32]. Minor symptoms due to brachytherapy are sore throat, epigastric pain, nausea and vomiting[32], chest pain and pyrexia[25]. Low reported transient dysphagia after brachytherapy in 17%[25], but this was not observed where brachytherapy was preceded by laser clearance. Complication rates increased with the addition of laser therapy, with fistulae occurring in up to 16%[29] and strictures in 4.7%[30] to 13.6%[26]. Combining laser with brachytherapy and external beam radiotherapy caused oesophagitis in 46%[36]. None of our patients who had laser with brachytherapy suffered any serious complications. One patient had transient confusion following brachytherapy, but this was more likely to be due to the effects of intravenous sedation with midazolam. Laser therapy also probably prevented transient worsening dysphagia after brachytherapy in our patients.

No purely brachytherapy related deaths have been reported. Our 2 fatalities occurred in the laser only group, one due to a perforation and the other patient due to cardiac failure, giving a mortality rate of 14%. Renwick had a mortality of 10%[30].

Despite initial optimism by Bader, other work and our preliminary results do not suggest that brachytherapy following laser therapy has any long term advantages over laser therapy alone. It may be that brachytherapy alone can produce prolonged relief of dysphagia initially, provided the Selectron applicator can be successfully placed. In this case, the role of laser therapy would be to allow access to the applicator, provide immediate relief of dysphagia and prevent transient worsening of dysphagia which may occur with brachytherapy alone. As patients' quality of life depends to a large part on remaining dysphagia free, it is important to increase the proportion of remaining life, albeit mainly at the start of treatment, in which patients can swallow uninterruptedly. From this point of view, brachytherapy can be regarded as a useful adjunct to laser therapy. It would be interesting to see if adding external beam radiotherapy to laser and brachytherapy might further increase overall benefit. Certainly Bader's patients who received both external beam and intracavitary radiotherapy in addition to laser seemed to do better than other studies using brachytherapy and laser, suggesting that external beam radiotherapy may be useful in this context. A trial to examine this possibility seems the next logical step.

CONCLUSION

Based on the preliminary results of our trial, brachytherapy in addition to laser therapy in the palliation of oesophageal cancer offers only the advantage of prolonging the first therapeutic interval from about 5 weeks to about 12 weeks. We can show no other advantage as yet, but this trial continues until 50 patients have been recruited and followed up until their deaths.

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