4. *Let's Fly Smoke-Free*. Brussels, European Bureau for Action on Smoking Prevention, 1991.
5. Australian Federation of Consumer Organisations Inc. vs. Tobacco Institute of Australia Ltd., 1987. Federal Court of Australia, Judgement by Mr Justice Morling, 1991.
6. Australian court rules that passive smoking causes lung cancer, asthma attacks, and respiratory disease. *Br Med J* 1991, **302**, 943–945.
7. Environmental Protection Agency. *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*. Washington DC, US Environmental Protection Agency, 1990.

Acknowledgement—This paper was written while the author was the recipient of a Senior Visiting Scientist Award at the International Agency for Research on Cancer, Lyon.

Eur J Cancer, Vol. 27, No. 11, pp. 1350–1352, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00
Pergamon Press plc

Palliation of Malignant Obstruction—Use of Lasers and Radiotherapy in Combination

TO THE PRACTISING radiotherapist, the availability of new techniques to provide rapid reversal of an obstructed upper digestive tract or airway offers exciting prospects for more effective treatment [1, 2]. In the past the use of radiotherapy, even to modest palliative doses, has sometimes been rendered difficult, even impossible, because of the poor general condition of many of these patients, either through malignant cachexia, obstruction of the oesophagus or a major airway, or other associated medical problems [3, 4]. The morbidity of radiotherapy in these seriously ill patients can be considerable and is poorly documented in the literature. In a recent paper [3], Caspars *et al.* showed clearly that patients with severe dysphagia at presentation gained little from radiotherapy alone, regardless of the patients' general condition and the decision to treat with radical or palliative doses of radiation. In contrast, those with only mild impairment of swallowing at presentation did very much better.

Laser therapy, though employed only relatively recently as a means of luminal debulking, has already become established since it provides rapid reversal of obstruction in a high proportion of patients with a low incidence of complications [5–7]. Unlike conventional radiotherapy, which even if effective may take several weeks to relieve dysphagia, laser therapy provides an almost immediate effect. The laser therapist treats the tumour under direct vision, so treatment can be applied to the parts of the tumour causing the worst obstruction. Some parts can be vaporised instantly, although other parts are necrosed *in situ* and will slough over a period of a few days. Recanalisation can usually be achieved by one or two treatments, re-establishing a partial or sometimes physiologically near-complete passage and which may lead to sufficient improvement in function to allow for a more definitive treatment. This means, for example, that patients with complete dysphagia who were generally felt unsuitable for irradiation, can now be considered as potential candidates for treatment.

In contrast to external beam irradiation, brachytherapy may also relieve obstructive symptoms within a few days [8]. It is likely that laser therapy and brachytherapy will prove complimentary. With brachytherapy, irradiation is delivered circumferentially, so it is particularly suitable for annular lesions of the oesophagus and gastric cardia. Tumour necrosis can be produced at depths of up to 1–5 cm from the lumen. If normal tissue is exposed to the radiation, there is a risk of radiation-induced oesophagitis which can be persistent and troublesome and may later progress to stricture formation. Laser therapy carries the two advantages of more precise control of the treated area together with the lack of cumulative toxicity, but cannot safely penetrate so deeply, making it more suitable for exophytic tumours. If both techniques fail to provide adequate recanalisation, there remains the option of inserting a prosthetic tube, although this inevitably reduces the quality of swallowing [7].

For small and localised cancers, it has long been taught that surgery gives the best prospect of cure, although there has never been a formal trial comparing surgery with radical radiotherapy [9, 10]. However, for many patients with locally advanced cancer of the oesophagus, a nihilistic therapeutic approach has become increasingly common over the past few years. It has been widely felt that even in patients considered technically fit for surgical resection, there is no evidence that the results are any better than in those treated by radical irradiation alone [9, 10] or indeed that either is any better than less radical techniques for palliation of dysphagia for which the morbidity and mortality are so much less. For the majority of patients with carcinoma of the oesophagus, palliation of dysphagia is all that can realistically be attempted, though a small minority of cases should undoubtedly be treated more intensively [11]. The quality of life in most patients is very poor if no attempt is made to improve the inevitably progressive dysphagia and although a number of techniques exist, the long-term success rate is only modest. A recent review of the competing approaches to palliation of malignant dysphagia with surgery, radiotherapy, laser or prosthetic intubation highlighted the difficulties [1] and also pointed out that surgical removal of the primary tumour in its entirety gives the best relief of dysphagia, though the morbidity and mortality are too high to regard this technique as appropriate other than in special circumstances.

Whilst laser therapy is valuable for direct tumour debulking, it has nothing to offer as a means of controlling the cancer beyond the confines of what can be treated within the lumen itself. Patients often need to be warned of this as the tumour is

Correspondence to S.G. Bown.
Received and accepted 25 July 1991.

likely to extend both intramurally and of course beyond the organ. However, for carcinomas of the oesophagus, bronchus (non-small cell) and trachea, the anatomy of local direct and nodal (regional) spread is such that these areas can often be encompassed by a moderately sized, and generally well tolerated, radiotherapy field—particularly if a palliative tumour dose is all that is being attempted. For this reason, laser and external beam radiotherapy are conceptually highly complementary in that the laser can provide rapid intramural tumour debulking and symptom relief, whilst radiotherapy has the potential for treating all the tumour bulk in the organ of origin including the local regional draining sites. With the rapid improvement in general condition, patients initially regarded as untreatable or, at best, suitable for only palliative doses of radiotherapy, may in some cases be suitable for a more definitive radiation dose once the early laser-induced improvements in nutrition or respiratory capacity have been achieved. In general, the response of these tumours to chemotherapy has been disappointing, but the same principles apply and symptom relief with laser therapy may render patients fit for more intensive chemotherapy.

Most patients with end-stage obstructive non-small cell bronchial carcinoma are referred after full external radiotherapy, such that laser alone or laser with brachytherapy has been the preferred method of management [2]. In contrast, with oesophageal carcinomas, most patients obstruct early and are referred untreated, allowing the option for laser plus external irradiation.

Very few studies have yet assessed the potential role of the laser/radiotherapy combination in patients with carcinoma of the bronchus or oesophagus. For most of those with bronchial carcinomas, no other treatment modality, except possibly chemotherapy, has been considered as a realistic alternative and the projected survival in most cases is under 6 months. Previous work over the past 10 years, using laser therapy alone in these circumstances, has demonstrated its short-term effectiveness in large airway obstruction; indeed, the more proximal the obstruction the more likely is the technique to prove valuable, often with re-establishment of a satisfactory air flow pattern [12, 13]. Complications of laser therapy do not appear to be significantly increased in patients who have been treated previously with radical external irradiation for carcinoma of the bronchus or trachea. However, the frequency with which laser therapy may have to be repeated clearly limits the technique, and it is possible that a planned combination of laser and radiotherapy, perhaps using brachytherapy, may even in these difficult circumstances lead at least to a reduction in frequency of laser sessions required. Early studies from the USA using brachytherapy and laser resection in combination have been encouraging. Macha *et al.* claimed a 79% response in a study of 56 patients, with radiological improvement in 22 of 25 with collapse or atelectasis, and a 50% improvement in simple tests of lung function [14]. Most centres now offering this treatment use brachytherapy with a MicroSelectron apparatus or other remote after-loading system, though it is also possible to use direct application of iridium-192 wires, passed via a mini-tracheostomy. Even in patients who have previously been treated with full doses of external beam irradiation, a dose of 40 Gy at 1 cm from the source can be given safely over a period of 48–66 hours using a 4–7 cm length of active wire. In most cases this has been preceded by at least one laser session a week beforehand.

For carcinoma of the bronchus, the earlier use of laser in combination with a radical course of external beam radiotherapy instead of using the laser later as salvage therapy, might represent a more favourable opportunity to use these two complementary techniques to better effect. This is particularly true in the large number of patients who present with malignant dyspnoea. The role of the combination of lasers and radiotherapy in the management of bronchial carcinomas has been discussed in an excellent review by Hetzel and Smith [2].

The main disadvantage of laser recanalisation for malignant dysphagia is the need for repeated treatments (typically every 4–6 weeks) as intramural and intraluminal tumour regrows. Two German groups have looked at combining laser and radiotherapy, one with both external beam and brachytherapy [15] and one with brachytherapy alone [16]. The group receiving both forms of irradiation did better, suggesting that in this situation, the external beam irradiation was complementary to the laser, whereas perhaps the laser and brachytherapy were treating the same aspect of the disease and little was to be gained from using both. Following these reports, we undertook a small pilot study involving 22 patients with advanced local disease but reasonably good general condition [17]. Initial laser recanalisation was followed by palliative external beam irradiation. This showed that there was a considerable increase in the average time interval between laser treatments. The patients in this study were selected, but it was also interesting to note that those given 30 Gy as a midline dose conventionally fractionated over 2 weeks seemed to live longer than historical controls treated by laser alone (32% 1-year survival compared with 9% in historical controls). For patients without distant metastases, this is an exciting prospect as it means that the laser has relieved the obstruction and the irradiation has controlled the growth of the main tumour bulk. However, an unanticipated observation was that this group of patients appeared surprisingly sensitive to radiotherapy. Increasing the dose above 30 Gy seemed to do more harm than good. Patients treated with a dose of 40 Gy tolerated treatment less well and did not enjoy the same increase in survival as those given 30 Gy, although the numbers involved were too small to draw any statistical conclusions. Other novel types of fractionation, possibly including hyperfractionation, have yet to be attempted and might offer more, particularly if the treatment could be offered in a shorter period than the traditional 2 weeks we currently recommend. It should be stressed that these results only come from a pilot study and need to be tested in a larger, controlled clinical trial, which is currently underway in our hospital.

Although the majority of patients with inoperable carcinomas of the bronchus or oesophagus cannot be offered long-term benefit or cure for the foreseeable future, the combined laser/radiation therapy approach offers superior palliation for many patients than was previously possible with intubation or other techniques. For a radiotherapist treating these common conditions so frequently, the ability of laser therapy to recanalise simply, safely and speedily is a highly impressive addition to the treatment we can now offer and can transform their quality of life dramatically.

J.S. Tobias
Department of Radiotherapy and Oncology

S.G. Bown
National Medical Laser Centre
University College Hospital
London WC1E 6JJ
U.K.

1. Bown SG. Palliation for malignant dysphagia—surgery, radiotherapy, laser, intubation alone or in combination. *Gut* (in press).
2. Hetzel MR, Smith SGT. Endoscopic palliation of tracheobronchial malignancies. *Thorax* 1991, **46**, 325–333.
3. Caspars RJL, Welvaart K, Verkes RJ, Hermans J, Leer JWH. The effect of radiotherapy on dysphagia and survival in patients with oesophageal cancer. *Radiother Oncol* 1988, **12**, 15–23.
4. Oliver SE, Robertson CS, Logan RFA, Sokal M, Pearson JCG, Atkinson M. What does radiotherapy add to survival over endoscopic intubation alone in inoperable squamous cell oesophageal cancer? *Gut* 1990, **31**, 750–752.
5. Fleischer D, Kessler F, Haye O. Endoscopic Nd:YAG laser therapy for carcinoma of the oesophagus: a new palliative approach. *Am J Surg* 1982, **143**, 280–283.
6. Krasner N, Barr H, Skidmore C, Morris AI. Palliative laser therapy for malignant dysphagia. *Gut* 1987, **28**, 792–798.
7. Loizou LA, Grigg D, Robertson C, Atkinson M, Bown SG. A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. *Gastroenterology* 1991, **100**, 1303–1310.
8. Rowland CG, Pagliero KM. Intracavitary irradiation in palliation of carcinoma of oesophagus and cardia. *Lancet* 1985, ii, 981–983.
9. Earlam RJ, Cunha-Melo JR. Oesophageal squamous cell carcinoma. I. A critical review of surgery. *Br J Surg* 1980, **67**, 381–390.
10. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: II. A critical review of radiotherapy. *Br J Surg* 1980, **67**, 457–461.
11. Pearson JG. The value of radiotherapy in the management of squamous oesophageal cancer. *Br J Surg* 1971, **58**, 794–798.
12. Gilmartin JJ, Veale D, Cooper BG, Keavey PM, Gibson GJ, Morritt GN. Effects of laser treatment on respiratory function in malignant narrowing of central airways. *Thorax* 1987, **286**, 12–16.
13. Hetzel MR, Nixon C, Edmonstone W, *et al.* Laser therapy in 100 tracheobronchial tumours. *Thorax* 1985, **40**, 341–345.
14. Macha HN, Coch K, Stadler M, Schumacher W, Krumahaar ED. New technique for treating occlusive and stenosing tumours of the trachea and main bronchi: endobronchial irradiation by high dose iridium 192 combined with laser utilisation. *Thorax* 1987, **42**, 511–515.
15. Bader M, Dittler HJ, Ultsch B, Ries G, Siewert JR. Palliative treatment of malignant stenoses of the upper gastrointestinal tract using a combination of laser and afterloading therapy. *Endoscopy* 1986, **18**(Suppl. 1), 27–31.
16. Hagenmuller F, Sander C, Sander R, Ries G, Classen M. Laser and afterloading irradiation with iridium-192. In: Riemann JF, Ell C, eds. *Lasers in Gastroenterology*. Stuttgart, Thieme Medical, 1989.
17. Loizou LA, Tobias J, Blackman G, Grigg D, Sargeant IR, Bown SG. Combined NdYAG laser phototherapy and external beam radiotherapy for the palliation of advanced malignant dysphagia. *Br J Cancer* 1990, **62**(Suppl. XI), 28.

Eur J Cancer, Vol. 27, No. 11, pp. 1352–1355, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Papers

*MDR*1 Gene Expression and Prognostic Factors in Primary Breast Carcinomas

Josef Wallner, Dieter Depisch, Martina Hopfner, Karin Haider, Jürgen Spona, Heinz Ludwig and Robert Pirker

To prospectively assess the role of the *MDR*1 gene in breast carcinomas, *MDR*1 RNA levels of breast carcinoma specimens were determined by slot blot analysis. In 59 evaluable patients with primary breast carcinomas, *MDR*1 RNA levels of the carcinomas were negative in 54%, low in 29% and high in 17% of the patients. No differences in age, menopause status, oestrogen and progesterone receptor levels, tumour size, lymph node involvement and c-*erb*B-2/*neu* gene expression were observed between *MDR*1 RNA negative patients and *MDR*1 RNA positive patients.
Eur J Cancer, Vol. 27, No. 11, pp. 1352–1355, 1991.

INTRODUCTION

DRUG RESISTANCE remains an important problem in the chemotherapy of breast carcinomas. Knowledge of the mechanisms involved in this resistance should help to devise ways for overcoming resistance and thus improve treatment outcome.

One mechanism of resistance, multidrug resistance (MDR1), has been extensively studied in cell lines where it is due to the expression of the *MDR*1 gene and of its 170 kD protein product, P-glycoprotein [1–4]. This transmembrane protein functions as an energy-dependent drug efflux pump for anthracyclines, vinca alkaloids and other hydrophobic natural compounds [4]. P-glycoprotein is also expressed in several normal human tissues (e.g. colon and kidney) where it most likely functions as a transport protein [1, 5, 6]. *MDR*1 gene expression was also observed in leukaemias as well as in some solid tumours, particularly in those arising from organs that normally express P-glycoprotein, and was assumed to be involved in clinical drug resistance of these malignancies [1, 6–13]. Since anthracyclines, which are among the most active single agents for the treatment of breast cancer, are affected by the *MDR*1 gene, presence of a functionally active *MDR*1 gene should affect response to anthracyclines and, therefore, might have important therapeutic consequences. This prompted us to prospectively determine both frequency and intensity of *MDR*1 gene expression in breast carcinomas and to assess its association with known prognostic factors including c-*erb*B-2/*neu* gene expression. The results of this study are reported here.