PALLIATIVE ENDOSCOPIC Nd:YAG LASER THERAPY FOR GASTROINTESTINAL CANCERS: A CLINICAL PERSPECTIVE

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Abstract

The aim of this thesis was to evaluate by means of clinical studies endoscopic Nd:YAG laser therapy (LT) for the palliation of gastrointestinal cancers in the context of alternative treatments.

A prospective comparison of LT (n=43) and endoscopic intubation (EI, n=30) for malignant dysphagia demonstrated similar long-term efficacy for thoracic oesophageal cancers (77% vs 86%); for gastric cardia tumours, EI proved superior (50% vs 92%, p<0.001). Swallowing function was better and perforation rate lower after LT, but the lifetime cost was greater and more procedures and longer hospitalisation were required. Both techniques resulted in a significant improvement in quality of life.

In a pilot study of LT plus external beam radiotherapy for malignant dysphagia, treatment was well tolerated and long-term palliation achieved in 81% (n=22). Combination therapy appeared to reduce the frequency of follow-up laser treatments (mean interval 32 weeks) and prolong survival.

LT proved safe and effective for managing dysphagia due to tumour recurrence after surgery (n=10) or endoprosthesis tumour occlusion (n=14).

A modified Celestin endoprosthesis was developed and successfully used to treat 8 patients with cervical oesophageal cancer unsuitable for other treatment.

In a prospective audit of LT for advanced rectosigmoid cancer, symptomatic palliation until death was achieved in 74% (n=42); success depended on circumferential tumour extent. Bowel perforation occurred in 5% without mortality. Macroscopic eradication of small tumours was possible in 43% (n=7).

A retrospective comparison of LT (n=35) and surgery (n=47) for incurable rectosigmoid cancer, showed similar long-term palliation rates (74% vs 85%) and survival. Morbidity and mortality were significantly greater and hospitalisation longer after surgery.
Conclusion: LT is an effective and safe palliative treatment for gastrointestinal cancers; best results are likely to be achieved if it is used in a complementary fashion with other modalities in specialist centres.
"Those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, cautery cures; and those which cautery cannot cure are reckoned to be wholly incurable."

Hippocrates 400 BC.

"To a man with a hammer, a lot of things look like a nail that needs pounding"

Mark Twain

"Medicine is an art founded on conjecture and improved by murder"

Sir Anthony Carlisle
Dedications

This thesis is dedicated to my father, Avgoustinos Loizou, physicist and academic for setting me on the path of academic achievement and for his continued encouragement to complete this work.
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# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Impressa</td>
<td>4</td>
</tr>
<tr>
<td>Dedications</td>
<td>5</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>6</td>
</tr>
<tr>
<td>List of Chapters and References</td>
<td>8</td>
</tr>
<tr>
<td>List of Tables</td>
<td>15</td>
</tr>
<tr>
<td>List of Figures</td>
<td>18</td>
</tr>
<tr>
<td>List of Appendices</td>
<td>21</td>
</tr>
</tbody>
</table>
# List of Chapters and References

**PART I: BACKGROUND**

**CHAPTER 1: OVERVIEW OF THE HISTORY OF LASER ENDOSCOPY, LASER PHYSICS AND LIGHT - TISSUE INTERACTIONS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Introduction</td>
<td>23</td>
</tr>
<tr>
<td>1.2 Historical Overview</td>
<td>23</td>
</tr>
<tr>
<td>1.2.1 History of Lasers</td>
<td>23</td>
</tr>
<tr>
<td>1.2.2 History of Laser Endoscopy</td>
<td>24</td>
</tr>
<tr>
<td>1.2.3 History of Cautery for Haemostasis and Tumour Therapy</td>
<td>25</td>
</tr>
<tr>
<td>1.3 Laser Physics</td>
<td>26</td>
</tr>
<tr>
<td>1.3.1 The Electromagnetic Theory of Light</td>
<td>26</td>
</tr>
<tr>
<td>1.3.2 Quantum Atomic Theory, Spontaneous and Stimulated Emission</td>
<td>27</td>
</tr>
<tr>
<td>1.3.3 The Components of a Laser System</td>
<td>28</td>
</tr>
<tr>
<td>1.3.4 The Nd:YAG Laser</td>
<td>28</td>
</tr>
<tr>
<td>1.3.5 The Properties of Laser Light</td>
<td>29</td>
</tr>
<tr>
<td>1.3.6 Optical Fibres</td>
<td>30</td>
</tr>
<tr>
<td>1.4 Light-Tissue Interactions</td>
<td>31</td>
</tr>
<tr>
<td>1.4.1 The Fate of Light Interacting with Biological Tissues</td>
<td>31</td>
</tr>
<tr>
<td>1.4.2 Absorption and Scattering of Light by Biological Tissues</td>
<td>31</td>
</tr>
<tr>
<td>1.4.3 Effects of Light on Biological Tissues</td>
<td>32</td>
</tr>
<tr>
<td>1.4.4 Biological Photothermal Effects</td>
<td>32</td>
</tr>
<tr>
<td>1.4.5 Morphology and Evolution of Photothermal Tissue Effects</td>
<td>33</td>
</tr>
<tr>
<td>1.5 Comments</td>
<td>34</td>
</tr>
</tbody>
</table>
CHAPTER 4: AIMS OF PRESENT STUDIES

4.1 Introduction

4.2 Palliation of Malignant Dysphagia

4.2.1 A Prospective Comparison of Nd:YAG Laser Therapy and Endoscopic Intubation for Palliation of Malignant Dysphagia (Chapter 5)

4.2.2 Nd:YAG Laser Therapy Plus Adjuvant External Beam Radiotherapy for the Palliation of Malignant Dysphagia (Chapter 6)

4.2.3 Nd:YAG Laser Therapy for Recurrent Dysphagia after Surgery or Intubation (Chapter 7)

4.2.4 Treatment of High Cervical Oesophageal Cancer by Endoscopic Intubation using Modified Endoprostheses (Chapter 8)

4.3 Palliation of Rectosigmoid Cancer

4.3.1 A Prospective Study of Nd:YAG Laser Therapy for the Palliation of Rectosigmoid Cancer (Chapter 9)

4.3.2 Surgery or Nd:YAG Laser Therapy for the Palliation of Incurable Rectosigmoid Cancer? (Chapter 10)

PART II: PALLIATION OF MALIGNANT DYSPHAGIA

CHAPTER 5: A PROSPECTIVE COMPARISON OF Nd:YAG LASER THERAPY AND ENDOSCOPIC INTUBATION FOR THE PALLIATION OF MALIGNANT DYSPHAGIA

SECTION A: EFFICACY, SAFETY AND SURVIVAL

5.1 Introduction

5.2 Patients and Methods

5.2.1 Study Design and Objectives

5.2.2 Patients

5.2.3 Instrumentation and Endoscopic Techniques

5.2.4 Patient Assessment

5.2.5 Statistics

5.3 Results

5.3.1 Functional Efficacy, Recurrent Dysphagia and Survival
6.3.1 Efficacy, Treatment Requirements and Indicators of Outcome 121
6.3.2 Quality of Palliation 123
6.3.3 Survival 126
6.3.4 Treatment Morbidity and Hospitalisation 126
6.4 Discussion 129

CHAPTER 7: Nd:YAG LASER THERAPY FOR RECURRENT DYSPHAGIA AFTER SURGERY OR INTUBATION 134

SECTION A: ANASTOMOTIC TUMOUR RECURRENCE
7.1 Introduction 134
7.2 Patients and Methods 135
7.2.1 Patients 135
7.2.2 Treatment Techniques and Patient Assessment 135
7.2.3 Statistics 135
7.3 Results 136
7.4 Discussion 136

SECTION B: PROSTHESIS TUMOUR OBSTRUCTION
7.5 Introduction 139
7.6 Patients and Methods 139
7.6.1 Patients 139
7.6.2 Treatment Techniques and Patient Assessment 140
7.6.3 Statistics 141
7.7 Results 141
7.8 Discussion 145

CHAPTER 8: ENDOSCOPIC INTUBATION USING MODIFIED ENDOPROSTHESES FOR THE PALLIATION OF HIGH CERVICAL OESOPHAGEAL CANCER 147
8.1 Introduction 147
8.2 Patients and Methods 148
8.2.1 Patients 148
8.2.2 Endoprostheses 148
## List of Tables

### CHAPTER 5

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 5.1</td>
<td>Details of patients with malignant dysphagia treated by laser therapy or endoscopic intubation.</td>
<td>74</td>
</tr>
<tr>
<td>Table 5.2</td>
<td>Tumour details in patients treated by laser therapy or endoscopic intubation.</td>
<td>75</td>
</tr>
<tr>
<td>Table 5.3</td>
<td>Palliation of malignant dysphagia with laser therapy or endoscopic intubation: Success rates, survival and treatment requirements.</td>
<td>79</td>
</tr>
<tr>
<td>Table 5.4</td>
<td>Palliation of malignant dysphagia with laser therapy or endoscopic intubation: Treatment failures and further management.</td>
<td>81</td>
</tr>
<tr>
<td>Table 5.5</td>
<td>Spearman correlation coefficients between paired scores of quality of life measurements of patients with malignant dysphagia treated by laser therapy or endoscopic intubation.</td>
<td>94</td>
</tr>
<tr>
<td>Table 5.6</td>
<td>Unit cost estimates of procedures used for endoscopic palliation of dysphagia.</td>
<td>108</td>
</tr>
<tr>
<td>Table 5.7</td>
<td>Patient traffic and number of procedures performed according to pathway.</td>
<td>109</td>
</tr>
<tr>
<td>Table 5.8</td>
<td>Probability of patient traffic and estimated cost per patient for each pathway for the base-case analysis.</td>
<td>110</td>
</tr>
</tbody>
</table>
Table 5.9  Survival and total expected cost per patient for the base-case and sensitivity analysis. 112
Table 5.10 Estimated costs of procedure related complications used in resource intensive analysis. 113

CHAPTER 6
Table 6.1  Patient and tumour details. 119
Table 6.2  Long-term palliation of dysphagia with laser therapy plus external beam radiotherapy or laser therapy alone. 122
Table 6.3  Treatment requirements in patients palliated until death. 124
Table 6.4  Survival data according to treatment given. 127

CHAPTER 8
Table 8.1  Patient and tumour details. 149
Table 8.2  Treatment results and survival after intubation with modified endoprostheses. 157

CHAPTER 9
Table 9.1  Patient details, symptomatic presentation and indications for laser therapy. 165
Table 9.2  Tumour details. 166
Table 9.3  Functional outcome after laser therapy according to circumferential tumour extent in patients with advanced rectosigmoid cancer. 171
Table 9.4  Functional outcome after laser therapy according to main presenting symptoms and management of treatment failures in patients with advanced rectosigmoid cancer.  172

CHAPTER 10

Table 10.1  Patient details, tumour characteristics and extent of disease.  181
Table 10.2  Long-term palliation rates.  183
Table 10.3  Morbidity, mortality and hospitalisation time.  184
Table 10.4  Survival according to extent of disease and treatment.  188
### List of Figures

#### CHAPTER 5

| Figure 5.1 | Survival and dysphagia palliation (DP) distributions (life table method) for patients treated by laser therapy or endoscopic intubation. | 80 |
| Figure 5.2 | Mean lifetime consistency of diet in patients palliated until death by laser therapy or endoscopic intubation. | 83 |
| Figure 5.3 | Long-term functional outcome of all patients managed by laser therapy with intubation for treatment failures when indicated or by endoscopic intubation alone. | 84 |
| Figure 5.4 | Scatter diagrams of relation between dysphagia grade and LASA and dysphagia grade and QLI in patients with malignant dysphagia treated by laser therapy or endoscopic intubation. | 95 |
| Figure 5.5 | Mean QLI and LASA scores of patients palliated until death by laser therapy. | 96 |
| Figure 5.6 | Mean QLI and LASA scores of patients palliated until death by endoscopic intubation. | 97 |
| Figure 5.7 | Decision tree showing structure of model for costing laser therapy and endoscopic intubation as palliative treatments for malignant dysphagia and the probability, patient traffic and cost for each pathway. | 103 |
CHAPTER 6

Figure 6.1  Bar chart plots of mean dysphagia grade of patients treated by laser therapy plus external beam radiotherapy. 125

Figure 6.2  Survival curves (life table method) for patients treated by laser therapy plus external beam radiotherapy and historical laser only controls. 128

CHAPTER 7

Figure 7.1  A typical prosthesis tumour overgrowth before and after treatment. 142

Figure 7.2  A less typical example of prosthesis tumour overgrowth. 143

Figure 7.3  A further example of prosthesis tumour overgrowth before and after treatment. 144

CHAPTER 8

Figure 8.1  A standard and a modified Celestin endoprosthesis. 150

Figure 8.2  Endoscopic views of the modified endoprosthesis in the hypopharynx. 152

Figure 8.3  Gastrograffin swallow in a patient with carcinoma of the cervical oesophagus before and after intubation with a modified Celestin endoprosthesis. 154
CHAPTER 9

Figure 9.1  Survival and symptom palliation distributions for patients with advanced rectosigmoid cancer. 170

CHAPTER 10

Figure 10.1  Survival curves of patients with advanced rectosigmoid cancer managed by palliative surgery or laser therapy. 186

Figure 10.2  A, Survival curves of patients with rectosigmoid cancer and hepatic metastases managed by palliative surgery or laser therapy. 187
    B, Survival curves of patients with locally advanced rectosigmoid cancer managed by palliative surgery or laser therapy. 187
# List of Appendices

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPENDIX 1</td>
<td>PUBLICATIONS ARISING FROM THIS WORK</td>
<td>233</td>
</tr>
<tr>
<td>APPENDIX 2</td>
<td>STATEMENT OF INDIVIDUAL CONTRIBUTION TO STUDIES</td>
<td>234</td>
</tr>
</tbody>
</table>
Part I: Background
1.1 Introduction

The word LASER is an acronym for the description of the physical process of Light Amplification by Stimulated Emission of Radiation. Lasers are machines which amplify stimulated electromagnetic waves, producing laser "light" or radiation with precise and unique characteristics. These unique properties of lasers have been increasingly exploited over the last twenty years for the development of new diagnostic and therapeutic applications in medicine. This chapter will provide an overview of the history of lasers and laser endoscopy, the basic physics necessary to develop a conceptual understanding of the construction and working of a laser and the complex process of interaction of laser radiation with living tissues.

1.2 Historical Overview

1.2.1 History of Lasers

The theoretical principles on which the functioning of a laser are based, were first proposed by Einstein (1917) with the description of the concept of stimulated emission. Inherent in this concept is the achievement and maintenance of a state of population inversion in the atoms of the lasing medium which was described independently and almost synchronously by the American Charles H Townes (Gordon et al 1954) of Columbia University and the Russians Basov and Prokhorov (1954) of the Lebedev Institute while working on methods to amplify microwave signals used for radar detection systems. This research culminated in the construction by Townes (Gordon et al 1955) of a MASER (an acronym for Microwave Amplification by Stimulated Emission of Radiation), the forerunner of the laser. In recognition of their work, Townes, Basov and Prokhorov were awarded the Nobel Prize for Physics in 1964.
All the aforementioned work came to practical fruition in 1960 when Theodore H Maiman, while working for the Howard Hughes Aircraft Corporation in California, constructed the first laser. This was a pulsed ruby laser producing radiation in the red part of the visible spectrum. Subsequently, several other lasers were constructed in rapid succession. The Helium-Neon laser developed by Javan and colleagues in 1961 was both the first gas laser and the first continuous wave laser. In 1964, three lasers which have found multiple medical applications were developed: the argon ion laser by Bridges, the Neodymium: Yttrium-Aluminium-Garnet (Nd:YAG) laser by Geusic and colleagues and the carbon dioxide laser by Patel and coworkers.

1.2.2 History of Laser Endoscopy

The construction of workable flexible fibreoptic endoscopes in the late 1960s made possible the direct inspection of the proximal upper gastrointestinal tract and the large bowel. Since the early 1970s gastrointestinal endoscopy has been given tremendous impetus with the development of a multitude of endoscopic therapeutic techniques which have revolutionized the practice of gastroenterology. Laser endoscopy has evolved as a separate discipline of therapeutic endoscopy, as scientists and gastroenterologists sought to exploit the unique properties of laser light for the treatment of gastrointestinal diseases. The first application of lasers was in the control of gastrointestinal haemorrhage. As early as 1967, Ketchum and coworkers showed that laser energy could produce small vessel thrombosis. In 1970 Goodale and colleagues demonstrated the ability of an unfocused carbon dioxide laser beam delivered via a rigid endoscope to control bleeding from experimentally produced gastric erosions in the dog stomach. Clinical application of laser haemostasis was hampered by the lack of flexible fibres capable of transmitting laser radiation safely and efficiently. The first flexible transmission system was developed by Nath and colleagues in 1973 and was capable of transmitting argon laser light. The first endoscopic laser treatments in man were performed by Fruhmorgen and coworkers in 1975; using the Argon laser and a flexible fibre attached to the outside of a fibrescope, they successfully terminated active haemorrhage from erosive gastritis and photocoagulated colonic haemangiomas (Fruhmorgen et al 1976). A flexible delivery system for the Nd:YAG laser was developed by Kiefhaber's group in Munich and in 1977 they reported the use of this laser for the endoscopic control of gastrointestinal haemorrhage in man (Kiefhaber et al 1977). The
Nd:YAG laser soon became preferred over the Argon laser for endoscopic haemostasis because of its greater clinical efficacy, later confirmed by randomised trials, and its greater operational reliability. Although initially developed for endoscopic haemostasis, laser therapy has found much greater application in the treatment of gastrointestinal tumours. Both the Argon and especially the high power Nd:YAG laser have been employed endoscopically to photoablate advanced tumours of the oesophagus and cardia (Fleischer et al 1982), stomach (Bown 1983) and colon (Lambert and Sabben 1983) in an attempt to provide symptomatic palliation in terminally ill patients. More recently, the increased accuracy of tumour extent assessment provided by endoscopic ultrasonography (Tio and Tytgat 1986) and the development of photodynamic therapy with the potential for "selective" tumour destruction, have enabled endoscopic laser therapy to be used with curative intent in cases of early gastrointestinal cancer (Kato et al 1986). The late 1980s have witnessed the development of another endoscopic application of lasers in gastroenterology, that of lithotripsy for biliary and pancreatic calculi using shockwaves generated by pulsed lasers (Nishioka et al 1987).

1.2.3 History of Cautery for Haemostasis and Tumour Therapy

Quite frequently, what appears to be new turns out not to be new at all. This is the case with the use of heat, or cautery, to secure haemostasis and destroy tumours. The first clear description of cautery appears in the Edwin Smith Surgical Papyrus (original text 3000-2500 BC.) and refers to treatment of unspecific breast tumours (Breasted 1930). Cautery was extensively used by ancient Greek and Roman physicians. Cautery instruments were usually made of iron ("the irons" referred to in the Hippocratic writings) but other metal cauteries and boxwood spindles dipped in boiling oil were also used (Hippocrates, translation by F Adams 1884). Cauteries of several shapes were constructed for different therapeutic applications. For internal treatment in the anal canal or in the nasal cavity, Hippocrates describes the use of cauteries with a protective outer tube, the forerunner of the modern endoscopic overtube.

The first documented use of cautery for tumour destruction appears in the writings of Aetius (4th century AD) who describes the treatment of a woman with breast cancer: "... I incise the sound part of the breast outside the cancer and burn the incision with cauteries. By and by I incise again and dissect the depth of the breast ... and after the amputation is completed I again burn all
the parts to desiccation. The first cauterization is for the sake of stopping the haemorrhage, the second for eradicating all traces of the disease" (Milne 1907).

The earliest description of the use of cautery to control haemorrhage from the gastrointestinal tract appears in the works of Hippocrates who treated bleeding haemorrhoids using an obol shaped cautery with a protective overtube (Hippocrates, translation by F Adams 1884). Cautery was first employed to terminate peptic ulcer haemorrhage by Mikulicz and Kuster in the late 19th century during their early surgical attempts to control gastrointestinal haemorrhage (Dieulafoy 1889). No further significant advance occurred until the 1920s and 1930s when the development of high frequency diathermy paved the way for electrocoagulation as a haemostatic and tumour destroying tool (Bovie and Cushing 1928). Although electrocoagulation had been used occasionally in conjunction with rigid gastrointestinal endoscopes since the 1920s, it was not until the advent of fibreoptic endoscopy and the development of flexible probes in the 1970s that this endoscopic treatment became a practical reality (Blackwood and Silvis 1971).

1.3 Laser Physics

1.3.1 The Electromagnetic Theory of Light

According to the wave theory of Huygens and Maxwell, light is an electromagnetic wave with electrical and magnetic field components. The speed of light and other electromagnetic radiation, approximately 300,000 km/sec, is the product of the wavelength and the frequency of oscillation of the radiation. The electric and magnetic field vectors are self-sustaining thus accounting for the self-propagating nature of light and phenomena such as diffraction, refraction and polarization. On the basis of the electromagnetic wave theory, Max Planck proposed that light waves could be regarded as discrete "packets" of energy or "photons", the energy of each photon being inversely proportional to the wavelength of the radiation.
1.3.2 Quantum Atomic Theory, Spontaneous and Stimulated Emission

According to the theory of atomic structure proposed by Rutherford and developed by Niels Bohr, the atom consists of a positively charged nucleus and a balancing number of electrons inhabiting one of several orbits around the nucleus. The energy of an electron is smallest when it is in the orbit with the smallest radius; as electrons increase their energy they occupy orbits of progressively greater radius. As the electron orbits of a given atom are fixed, electron jumps from one orbit to another are associated with energy changes, or quanta, which are unique for the particular atom. The energy generated by an electron transition from a higher to a lower energy orbit is dissipated in the form of radiation, the wavelength of which is inversely proportional to the energy change. Conversely, for an electron to move from a lower to a higher energy orbit, it must absorb an amount of energy equal to the difference between the two orbits in the form of heat or a photon of light with a wavelength inversely proportional to the energy transition. Thus, the energies and hence the wavelength of the photons which a particular atom can absorb or emit are specified by its quantum levels.

Because of the law of entropy, excited atoms have a tendency to return spontaneously to a lower energy state in doing so emitting radiation, a process termed spontaneous emission. Photons of spontaneously emitted radiation are random in phase, polarity and direction. An excited atom can decay to a lower energy level with the release of a photon either spontaneously or, as predicted theoretically by Einstein, after being stimulated by another photon of the same energy. The photon released as a result of this interaction is identical to the stimulating photon which remains totally unchanged. It is obvious therefore, that stimulated emission has the potential to amplify a flux of photons. For the process of stimulated emission to occur, more atoms need to exist in the excited state rather than in ground state; under normal circumstances the converse is true. The population inversion required in order to favour stimulated emission can be achieved in solids, liquids and gases by pumping in large quantities of energy, usually in the form of light or electricity. Most lasers employ lasing media with a three or four level atomic system which allow population inversion to be achieved and maintained more efficiently. The Nd:YAG laser is an example of a four level system.
1.3.3 The Components of a Laser System

All laser systems consist of three basic components:

1. **The active or laser medium**: this can be a solid, liquid or gas capable of stimulated emission.

2. **The source of excitation energy**: the power source provides the energy to produce population inversion. The pump may be a source of thermal, electrical or optical (e.g. Xenon or Krypton flash lamp, laser radiation) energy.

3. **An optical resonator**: this consists of two parallel mirrors facing each other placed at each end of the active medium, so that multiple reflections can take place between them. One of the mirrors is a total and the other a partial reflector. The separation of the mirrors is such so that constructive interference can occur.

The majority of the spontaneously emitted radiation will escape from the sides of the resonator and will be dissipated as heat. A small percentage of spontaneous radiation will travel along the axis of the resonator and these photons will collide with atoms which have been excited by pumping, resulting in stimulated emission of radiation. As further collisions of photons and excited atoms occur, the intensity of the laser beam increases. Reflections of the laser beam between the two mirrors allow repeated passes through the active medium resulting in progressive amplification; the process will continue for as long as the laser medium is sufficiently pumped. At the partially reflecting mirror, a proportion of the energy (approximately 5%) is allowed to escape from the resonator as an intense beam of coherent light.

1.3.4 The Nd:YAG Laser

The advantages of the trivalent ion of neodymium as a lasing medium stem from its atomic structure. Of the one hundred and fifty or so different host crystals into which neodymium atoms have been doped, yttrium aluminium garnet (YAG), a man made crystal, has emerged as the best for continuous wave operation of the laser. The first Nd:YAG laser operated at the Bell Laboratories in 1964 (Geusic et al 1964). The laser rod is enclosed in an optical resonator as discussed above and pumping is performed by light from a
krypton flash lamp focused onto the laser rod. Lasing results in the emission of near infra-red radiation with a wavelength of 1064nm. The 100W continuous wave Nd:YAG laser employed in the present studies has an overall operating efficiency of 1-2%, requires a three phase electrical supply and high flow water cooling. In order to enable targeting of the invisible 1064nm laser beam, the red beam of a 5mW Helium-Neon laser is passed coaxially through the optical fibre.

1.3.5 The Properties of Laser Light

Laser light is unique in that it is the only type of radiation that possesses all three properties described below:

1. Monochromaticity
Monochromaticity implies that the light is of a single wavelength and hence frequency. Lasers emit a single wavelength or a very narrow band of wavelengths, producing light of very pure colour, in contrast to conventional light sources which emit over a much broader band of wavelengths.

2. Coherence
Coherence implies that all waves are in phase with another. Laser light is coherent both in time (temporal coherence) and in space (spatial coherence).

3. Collimation
Collimation implies a low degree of divergence of the laser beam. The diameter of a laser beam, and hence its power density, remains fairly constant even over large distances.

What are the practical advantages resulting from these unique properties of laser light? The strong collimation of a laser beam allows it be focused with a lens onto a very small spot and coupled to small diameter (down to 200μm) flexible optical fibres which can be used for endoscopic therapy. The ability to focus a laser beam to a very small spot size increases the irradiance (power per unit area) of the beam enormously. The practical importance of the monochromaticity of laser light is that, as particular components of human tissues absorb and scatter one wavelength more than others, a specific laser is chosen according to the tissue effects required. For example, the blue-green light of the argon laser is strongly absorbed by oxyhaemoglobin leading to coagulation of blood vessels but as it is scattered superficially, its penetration
is limited to about 1mm thus avoiding thermal damage to deeper tissue layers. In contrast, the near infra-red radiation (1064nm) emitted by the Nd:YAG laser is four to five times more penetrating and can be used to coagulate deeper lying blood vessels and ablate gastrointestinal tumours; however, the thermal damage to deeper tissue layers carries an increased risk of perforation of a hollow viscus.

1.3.6 Optical Fibres

With the development of interest in the application of lasers for therapeutic endoscopic work in the gastrointestinal tract, optical fibres which had been used previously for the transmission of visual images and the construction of flexible endoscopes, were recognised as a convenient delivery system.

Optical fibres are essentially long cylinders made of high silica content glass or quartz. Transmission of light along an optical glass fibre depends upon the principle of total internal reflection. The problem with such fibres is their tendency to lose light energy as a result of scattering by impurities or extraneous matter which accumulates on the fibre surface; in addition, absorption of laser energy by the impurities leads to overheating and ultimate destruction of the fibre. In order to overcome these problems and provide consistent total internal reflection, the outer surface of the fibre is coated with a low refractive index polymer (cladding). Laser light is coupled to the fibre, by exactly focusing it using a lens system onto the proximal end of the fibre. Although laser light entering the fibre is collimated and coherent, it leaves the fibre as an incoherent diverging beam with an angle of usually about 10° (which depends on the angle of entry into the fibre). The irradiance at the tissue surface therefore, depends on the divergence angle of the laser beam and the distance between the fibre tip and tissue.

The flexibility of an optical fibre depends on the characteristics of the fibre material and its diameter. For laser endoscopy, a 200-600μm diameter quartz fibre housed in a Teflon catheter approximately 2mm in diameter is used. These fibres combine a large enough diameter to allow easy coupling of the laser output with sufficient flexibility. The Teflon catheter gives the delivery system mechanical strength and also allows the passage of a coaxial stream of CO₂ which helps to reduce contamination and overheating of the tip of the fibre and to clear the target of blood and debris.
1.4 Light - Tissue Interactions

1.4.1 The Fate of Light Interacting with Biological Tissues

Light striking biological tissue may be reflected, scattered, absorbed or transmitted. Scattered light may be absorbed, leave the tissue through the entry interface (back scattering or indirect reflectance) or be transmitted (forward scattering); laser light which has been scattered loses both its collimation and coherence. Experiments with Nd:YAG laser irradiation of the dog stomach have shown that 30-40% of the incident light is back scattered and 25-30% transmitted (Hallodorsson et al 1981).

1.4.2 Absorption and Scattering of Light by Biological Tissues

In the visible and near infra-red part of the spectrum, absorption occurs predominantly by haemoglobin and melanin. Haemoglobin absorbs visible light maximally in the yellow part of the spectrum with a tenfold reduction towards the infra-red and a fivefold reduction towards the violet part, although there is also a peak of absorption in the ultra-violet region (Boulnois 1986). The absorption of melanin falls progressively by a factor of ten from the violet to the near infra-red region. Water does not absorb light in the visible and near infra-red region to any significant extent but absorption increases by a factor of ten between 1060 - 1320nm; water absorption completely dominates light-tissue interactions for wavelengths greater than 2μm.

Scattering is dependent on the wavelength of the radiation and the composition of the target tissue. With increasing tissue penetration, progressive scattering of light occurs. As a result, the energy density is maximum not at the tissue surface but at a deeper point; if enough heating occurs at this point to cause vaporisation, steam escapes leaving a small crater at the tissue surface. An additional effect of light scattering is beam broadening resulting in an increase in the volume of tissue irradiated.

The depth to which light of a specific wavelength penetrates a given tissue is dependent on its absorption and scattering. If scattering is slight, tissue penetration is almost entirely dependent on absorption. In contrast, if scattering is marked, penetration depth is small and largely independent of the absorption properties of the tissue.
1.4.3 Effects of Light on Biological Tissues

The absorption of laser light by biological tissues can result in several different tissue effects. The type of tissue effect depends mainly on the power density of the radiation and the interaction time. Based on these two parameters, three distinct tissue effects are recognised (Boulnois 1986):

1. **Photochemical**
   These effects are observed with long interaction times of 10-1000 sec and power densities of $10^{-3} - 1 \text{ W/cm}^2$. No primary heating of the target tissue occurs. Photodynamic therapy and biostimulation are the two main examples of photochemical reactions.

2. **Photothermal**
   With shorter interaction times (1msec-100sec) and higher power densities (1-$10^6 \text{ W/cm}^2$) photothermal effects are noted. The conversion of optical energy to heat results in an increase in temperature of the irradiated tissue and a series of sequential tissue effects which are discussed below. The main applications of lasers in gastroenterology - haemostasis and tumour ablation - are based on photothermal effects.

3. **Photoionising**
   Photoionising or non-linear effects are observed with lasers which produce pulses of $10^{-6} - 10^{-12} \text{ sec duration and peak powers exceeding } 10^7 \text{ W/cm}^2$. Non-linear effects are dependent on the conversion of optical to kinetic or mechanical energy. Photoablation has been exploited to produce precise (<50µm) non-necrotic cuts using excimer lasers and photofragmentation to perform lithotripsy using pulsed dye lasers or the Q-switched Nd:YAG laser.

1.4.4 Biological Photothermal Effects

With increasing tissue temperature, four distinct effects are recognised:

1. **Photohyperthermia: 37 - 60° C**
   At temperatures between 37-60° C no irreversible tissue changes occur, provided that the duration of the temperature elevation is relatively short. The rate of temperature dependent enzymatic reactions is speeded up and the permeability of cellular membranes increased resulting in tissue oedema.
2. Photocoagulation: 60 - 100°C
At temperatures between 60-65°C irreversible denaturation and conformational change of chromosomes, enzymes and structural proteins such as collagen occurs resulting in coagulative tissue necrosis. As tissue coagulates it changes to a white-grey colouration with a consequent increase in its scattering coefficient; as a result penetration depth decreases and the laser light is absorbed by the more superficial tissue layers. Denaturation of connective tissue proteins and to a lesser extent dehydration, causes contraction of the treated tissue.

3. Photocarbonisation: 100 - 300°C
As the temperature exceeds 100°C, water is lost as superficial cells swell and eventually explode with the release of steam. As haemoglobin and other chromophores are oxidised, the tissue changes to a black colouration resulting in increased absorption of laser light, a further rise in temperature and charring and carbonisation of tissue. The dehydrated, carbonised tissue loses its mechanical strength and becomes brittle.

4. Photovaporisation: greater than 300°C
With further rise in temperature above 300°C, the charred tissue catches fire (pyrolysis) and vaporises with the formation of laser smoke or plume resulting in the removal of solid tissue material. This has been used to therapeutic advantage in the recanalisation of obstructing gastrointestinal tumours.

1.4.5 Morphology and Evolution of Photothermal Tissue Effects

Depending on the power density of the laser beam and the interaction time, all four tissue effects described above may be observed within the irradiated volume. From the centre of the tissue lesion towards the periphery, five distinct zones are recognised:

1. Central cavity - this develops as a result of photovaporisation of tissue.

2. Carbonisation zone - measures less than 0.2mm in width and is composed of amorphous eosinophilic and carbonised material.
3. **Peripheral cavitation zone** - measures 0.2 - 0.5mm in width and consists of cavities of various sizes, produced by cell bursting as a result of evaporation of cellular water, surrounded by coagulated cellular debris.

4. **Coagulation zone** - measures 1.5 - 4.5mm in width and consists of coagulated tissue stroma and necrotic cells with eosinophilic cytoplasm and pyknotic nuclei. The width of the coagulation zone increases with the power of the laser beam and with treatment time.

5. **Transitional and hyperaemic zone** - this zone is characterised by cells with lesser and reversible thermal damage, interstitial oedema and marked hyperaemia.

Survival animal studies have shown that within 24 hours, the acute lesion produced by Nd:YAG laser treatment of the stomach is characterised by superficial ulceration, mucosal and submucosal oedema, coagulation necrosis of the submucosa and part of the muscularis propria, fibrinoid necrosis of submucosal arterioles and venules and thrombosis of capillaries (Kelly et al 1983, Zimmermann et al 1987). Within a few days of treatment, the tissue damage is significantly more extensive as a result of scattering of laser radiation and heat conduction during treatment and ischaemia secondary to vessel thrombosis. Tissue repair processes are histologically evident 3-4 days after the initial injury. Re-epithelialisation of the ulcerated surface commences, the zone of coagulation necrosis is gradually resorbed with ingrowth of granulation tissue from viable neighbouring tissue and some renewal of the smooth muscle layer occurs. By about five weeks after photocoagulation the ulceration has healed completely and microscopically a connective tissue scar can be recognised in the submucosa and muscularis propria. Laser induced fibrosis has also been noted in oesophageal carcinomas after multiple treatments with the Nd:YAG laser (Bown 1983).

**1.5 Comments**

The marriage of flexible endoscopy and laser and fibre technology has enabled gastroenterologists to exploit the unique properties of laser light for the treatment of gastrointestinal diseases. As the interaction of laser light with biological tissues has become better understood, both qualitatively and quantitatively, the range of ways in which different lasers can be used to treat
gastrointestinal diseases has increased. Used initially for haemostasis, laser therapy has found much greater application in the ablation of tumours; recently it has also been used for lithotripsy of difficult biliary calculi. The Argon laser, which was the first laser to be used clinically twenty years ago, has been more or less replaced in gastroenterological practice both for haemostasis and tumour ablation by the continuous wave Nd:YAG laser. With the development of the technique of photodynamic therapy, lasers operating at longer visible wavelengths such as the gold vapour laser and tunable dye lasers have been increasingly used. Technological modifications such Q switching and pulsing of the Nd:YAG laser or pulsing of dye lasers, have enabled these systems to be used for lithotripsy. New lasers, for example the holmium and erbium YAG systems or excimer lasers, are being developed in an attempt to extend the therapeutic potential of existing systems and effect the desired type of tissue response. Such technological developments, which will ultimately benefit the patient, are a challenge not only for engineers and scientists but also for gastroenterologists who should collaborate closely in order to achieve the best possible results.
Chapter 2

Oesophageal and gastric cardia cancer: Need for palliation and overview of therapeutic options

2.1 Epidemiology and Time Trends

The occurrence of oesophageal cancer varies dramatically in different parts of the world, within discrete geographic areas, among different ethnic groups and between males and females. Squamous cell carcinomas occur most frequently in blacks and the lower socio-economic groups. The incidence rate per 100,000 of the population is around 3 for white men, 1 for white women, 17 for black men and 4.5 for black women; the male to female ratio increases with age. In high incidence areas like South Africa, northern China, Iran and the Caspian Sea area, the frequency exceeds 100 cases per 100,000 (Durham and Bailar 1968, Blot et al 1991, Munoz 1993).

Oesophageal adenocarcinomas are almost exclusively confined to the lower third of the oesophagus. It is difficult to determine their true incidence as many lesions arising in the gastric cardia invade the lower oesophagus, but from a clinical point of view this is of no practical importance as the two tumours behave in a similar fashion. In contrast to squamous cell tumours, adenocarcinomas occur predominantly in white males and social classes I and II. Incidence rates of oesophageal adenocarcinoma per 100,000 of the population are around 1.3 for white men, 0.2 for white women, 0.4 for black men and 0.05 for black women. The corresponding figures for gastric cardia adenocarcinoma are around 2.8, 0.5, 1.4 and 0.4 respectively (Durham and Bailar 1968, Blot et al 1991, Powell and McConkey 1992, Munoz 1993). Except for the increased risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus, little is known about the origin of these tumours (Cameron et al 1985, Li et al 1989) The much higher rates among whites than blacks, suggest that alcohol intake and cigarette smoking are not major risk factors as is the case for squamous cell carcinoma (Day and Munoz 1982).

Time trends in the incidence of squamous cell oesophageal carcinoma over the last 30 years show only limited variations, with an overall tendency to decrease. In contrast, oesophageal and gastric cardia adenocarcinomas have
been increasing in incidence since the early 1970s by 4-10% per annum despite an overall decrease in the frequency of gastric cancer (Lund et al 1989, Blot et al 1991, Powell and McConkey 1992, Munoz 1993) and presently account for 30%-40% of all oesophageal and gastroesophageal junction cancers (Wang et al 1986, Reed and Johnston 1993). In Britain between 1966 and 1981, the incidence of oesophageal adenocarcinoma increased nearly fivefold and that of gastric cardia adenocarcinoma threelfold (Powell and McConkey 1992). In parallel with this increasing incidence, there has been an increase in the proportion of poorly differentiated and advanced stage tumours, factors with a pronounced influence on prognosis (Lund et al 1989). These data account for the disturbing increase in oesophageal cancer mortality in Britain over the last 30 years by 60% in men and 35% in women (Cheng and Day 1992); a total of about 10 deaths per 100,000 of the population are reported annually (WHO 1988).

2.2 Presentation and Staging

The symptoms of carcinoma of the oesophagus and gastric cardia include anorexia, dysphagia and odynophagia, weight loss, pain, hoarseness, cough, stridor, bleeding and neck swelling. Progressive dysphagia is the commonest presenting complaint occurring in over 90% of patients and is accompanied by odynophagia in up to 50% of cases (McKeown 1986). Presentation with dysphagia usually occurs late in the natural history of the disease. The oesophagus exhibits receptive relaxation which is facilitated further by the lack of a serosal layer. As a result, the patient will experience significant dysphagia only when the tumour has infiltrated at least 60% of the oesophageal circumference and the luminal diameter is reduced to less than 12mm (Edwards 1974). Following the development of dysphagia, the diagnosis is not usually established for an additional 3-6 months as patients often delay seeking medical advice; during this time, their general and nutritional status deteriorates significantly with losses in body weight of up to 10kg (McKeown 1986, DeMeester and Barlow 1988). As a consequence, the disease is usually far advanced at presentation.

Oesophageal and gastric cardia cancer presents late not only in its own natural history but also that of the patient as well. Average age at presentation is 70 years; some 70% of patients are older than 65 years and 40% older than 75 years (DeMeester and Barlow 1988, Oliver et al 1992). Such elderly patients
frequently have additional major medical problems, especially cardiovascular and respiratory diseases, which increase the risk of major surgery significantly and influence seriously therapeutic decision making.

Autopsy studies have shown that only about 10% of squamous oesophageal cancers are early and limited to the mucosa and submucosa (pT1 using the TNM classification); roughly 15% involve the muscularis propria (pT2), 45% the adventitia (pT3) and 30% extend into adjacent para-oesophageal structures (pT4). The overall frequency of lymph node metastases is 70-85% and their incidence increases with progressive depth of tumour infiltration: pT1 36%, pT2 54%, pT3 75% and pT4 90% carcinomas. Intramural metastases as a result of spread along the extensive submucosal oesophageal lymphatic system, are found frequently in advanced oesophageal cancer. Distant metastases to the liver, lungs, pleura, adrenal glands and supraclavicular and coeliac axis lymph nodes are reported on average in 30% of cases (Anderson and Lad 1982, Tio et al 1990, Kato et al 1992). Tumour length has been found to correlate roughly with the depth of wall penetration and risk of distant spread. Of tumours with a length greater than 5cm, only 10% are localised to the oesophageal wall and 75-90% have developed lymph node metastases (Rubin 1974, Rosenberg et al 1981).

Using the above data, classification according to the TNM system shows that approximately 5% of oesophageal carcinomas are stage I, 25% stage II, 40% stage III and 30% stage IV. Thus at the time of presentation, the disease is practically incurable by surgery in 70% of patients either because of limitations in performing radical tumour resection (stage III) or systemic spread (stage IV).

### 2.3 Surgical Treatment and Need for Palliation

The feasibility of surgical treatment for cancer of the oesophagus and gastric cardia and its potential to achieve cure are limited because of the following reasons. Firstly, as the majority of patients are elderly with serious comorbid conditions and poor general and nutritional status at the time of presentation, the surgical option is often rejected because of the high operative risk involved. Secondly, in view of the late symptomatic presentation in the natural history of the disease, the tumours are usually advanced limiting the potential for radical resection because of local invasion.
or distant metastasis. Thirdly, there are inherent difficulties in performing curative resection which are only partly related to the relative inaccessibility of the oesophagus. En block resection of the tumour and its metastases according to basic surgical oncological principles, is impossible for lesions located in the upper and middle thirds of the oesophagus because of the close anatomical relationship to vital structures such as the trachea, aorta and pericardium. In contrast, en block resection is feasible for tumours of the lower third of the oesophagus and gastric cardia. In addition as lymphatic spread occurs in a non-segmental fashion, a curative resection should include all nodes from the level of the mid-trachea down to the coeliac axis which is virtually impossible. As a result, the majority of oesophageal resections are only palliative.

The following data from the published literature help to provide an overall picture of the situation. In a review of 122 papers published between 1954-1979, Earlam and Cuhna-Melo (1980a) presented the results of surgical treatment and outcome of oesophageal carcinoma in 83,783 patients; adenocarcinomas of the cardia and lower oesophagus were excluded as far as possible. After standardisation of the data, it appeared that of 100 patients, 42 were considered unsuitable for surgery because of high anaesthetic risk or advanced disease on pre-operative staging. Of the 58 patients explored, tumour resection was possible in only 39 and 13 (33%) of these died. Of the 26 patients discharged from hospital following tumour resection, 18 (70%) survived for 1 year, 9 (29%) for 2 years and 4 (18%) for 5 years.

As a follow-up to Earlam and Cunha-Melo's study, Muller and colleagues (1990) published a review of the literature (130 papers) during the period 1980-1988 presenting the results of surgical treatment of oesophageal carcinoma in 76,911 patients; adenocarcinomas were again excluded as far as possible. Of 100 patients with oesophageal cancer presenting to a surgeon, 56 underwent tumour resection and 7 (13%) died of post-operative complications, the latter representing a greater than 50% reduction in operative mortality during the 1980s compared to Earlam and Cuhna-Melo's study. Of the 49 patients discharged from hospital, 27 (55%) survived for 1 year, 12 (24%) for 2 years and 10 (18%) for 5 years.

In a retrospective population based study in the Nottingham area, of the 268 patients with oesophageal and gastric cardia cancers diagnosed between 1982-
1985 only 92 (34%) were considered suitable for surgery and 22 of these proved to have unresectable tumours (Oliver et al 1992). Thus, overall 74% of patients required non-surgical treatment. Hospital mortality following resection was 9% and survival at 1, 2 and 4 years was 41%, 19% and 4% respectively. The survival of patients with squamous tumours and adenocarcinomas was similar (median 364 and 263 days respectively).

From these data, it can be concluded that despite the significant variation in operability and resectability rates in different studies which reflect patient selection, local expertise and the aggressiveness of the surgeon, on average only 25%-50% of patients with oesophageal and gastric cardia cancer are suitable for surgery. The poor long-term prognosis following surgery has remained unchanged for the last 30 years despite a significant reduction in operative mortality and reflects the fact that the majority of resections are only palliative. However, patients who are deemed operable should not be denied surgery as it achieves a quality of palliation (normal swallowing in more than 90% of cases) and survival unparalleled by any other treatment (Watson 1982). For the majority of patients who are unsuitable for resection, alternative palliative treatments are employed.

2.4 Review of Palliative Treatments for Malignant Dysphagia

Palliative surgical procedures by-passing the tumour using the stomach or intestine, have been abandoned because of the high associated morbidity (up to 71%) and mortality (24%), long hospitalisation required (4-6 weeks) and failure to prevent local complications such as haemorrhage, sepsis or fistulation (Muller et al 1990). Chemotherapy as single modality treatment has been disappointing, characterised by significant toxicity, poor response rates and no predictable or proven effect on survival or palliation. There is no justification for its use outside the context of controlled clinical trials (Kelsen 1983). The value of bougie or balloon dilatation as monotherapy for the palliation of dysphagia is limited as the symptomatic benefit is almost invariably short lived; such treatment may be worthwhile in patients with a very limited life expectancy (Moses et al 1985). The basic principle of all palliative treatments is to provide a lumen through the obstructing cancer of sufficient diameter to enable the patient to eat and drink and in extreme cases to swallow his/her saliva. Luminal patency can be achieved by placement of a stent through the tumour or destruction of intraluminal tumour using
radiotherapy, thermal or chemical methods. It is important however, that this aim should be achieved with minimum morbidity resulting ultimately in an improvement in the quality of remaining life.

2.4.1 Radiotherapy

2.4.1.1 External Beam Radiotherapy

The modern era of radiotherapy for oesophageal cancer was ushered in during the mid 1950s with the introduction of linear accelerators producing megavoltage radiation and tissue effects at a significant depth below the skin surface. Of the early work in the field, Pearson’s was most prominent; he reported exceptional results, including survival rates of 44% at 1 year and 22% at 5 years, which have not been duplicated by other radiotherapists (Pearson 1966). The majority of patients included in studies of radiotherapy are considered inoperable because of advanced disease or poor general condition. Despite this negative bias, Earlam and Cuhna-Melo (1980b) in their review of radiotherapy in more than 8,000 patients found an equivalent survival (18% at 1 year, and 6% at 5 years) and a lower complication rate compared to surgery. To date, a randomised comparative study of surgery and radiotherapy for operable squamous oesophageal cancer has not completed. In a prospective study of 22 patients with such lesions treated by radical radiotherapy, Earlam and Johnson (1990) reported survival results equal to or better than in most surgical series.

Apart from a few exceptions, published studies have focused on "cure" and 5 year survival rates without examining the quality of palliation achieved. Palliative treatment is given at lower than full dosage; the median dose is 30Gy and is delivered in ten fractions over 2 weeks (Earlam and Johnson 1990, O’Rourke et al 1992). Up to 30% of patients deteriorate during treatment and are unable to complete the planned course; the ability to tolerate treatment is dependent upon the severity of the dysphagia and the general condition of the patient (Wara et al 1976, Caspers et al 1988). The side-effects of treatment, which include weakness, malaise, anorexia and radiation oesophagitis, and their influence on quality of life are poorly documented in the literature. Treatment related mortality is low, usually less than 3%, because radiotherapy is stopped if a patient's condition deteriorates. Median survival after palliative radiotherapy is only 6 to 7 months (Wara et al 1976, Earlam and Cuhna-Melo 1980b, Caspers et al 1988, O'Rourke 1992).
Initial improvement in dysphagia after palliative radiotherapy occurs in around 70% of patients; of these, 60% are able to eat solid food, 30% semi-solids and 10% are restricted to taking liquids. The proportion deriving long-term palliation varies from 40-70%; persistent or recurrent dysphagia is invariably due to local treatment failure as symptomatic fibrous strictures occur very rarely with doses less than 40Gy (Wara et al 1976, Caspers et al 1988, O'Rourke et al 1992). A regimen of concurrent radiation and chemotherapy may provide superior results to radiotherapy alone without significantly increasing morbidity. In one study using 5-fluorouracil, mitomycin C and a median radiation dose of 50Gy, 91% of 48 patients with advanced disease treated with palliative intent, had an initial improvement in swallowing function and 67% derived palliation until death (median survival 8 months). 84% of palliated patients could swallow most or all solids and the rest pureed foods and liquids (Coia et al 1992). Very few studies have compared radiotherapy with other treatments in terms of quality of palliation; in a small study, swallowing function after radiotherapy or endoscopic intubation was equivalent (O'Rourke et al 1992).

The most significant prognostic factor of outcome following radiotherapy is the initial severity of dysphagia. In the study by Caspers et al (1988), only 40% of patients who at best were able to swallow liquids at the start of treatment derived long-term improvement compared to 64% for those able to swallow at least semi-solids initially. For the former group of patients endoscopic palliation would be more appropriate; for the latter high dose radiotherapy should be considered as this may prolong survival without compromising palliation.

The time scale of the response to radiotherapy is clearly important but poorly documented in most studies. An initial worsening of swallowing during the first week of treatment is not uncommon. The improvement in dysphagia is gradual, the median time to initial and maximal improvement being 2 and 4 weeks respectively with a range of 1-21 weeks (Wara et al 1976, Pearson 1978, Coia et al 1992). Patients with exophytic, well vascularised tumours tend to respond more rapidly than those with ulcerated tumours (Earlam and Cuhna-Melo 1980b). Another important issue is the radiosensitivity of adenocarcinomas. Although it is generally believed that they respond poorly and should not be treated by radiotherapy, the few studies which have compared the outcome of squamous cell carcinomas and adenocarcinomas
did not show a significant difference in symptomatic response or survival (Cederqvist et al 1978, Caspers et al 1988, Coia et al 1992).

Although the data on a number of important issues is incomplete, the available information indicates that palliative external beam radiotherapy provides relatively slow relief of malignant dysphagia, has a moderate morbidity and is most suitable for patients with mild to moderate dysphagia and good general condition. Given as an adjuvant to methods producing intraluminal debulking, including brachytherapy, it may allow prolonged palliation and perhaps survival.

2.4.1.2 Brachytherapy

Following the disastrous attempts of Einhorn and Exner in 1904, Guisez in 1921 and Souttar in 1937 using various forms of radium, intracavitary irradiation or brachytherapy fell into disrepute. Interest in brachytherapy has been revived recently with the development of remote controlled afterloading machines such as the Selectron, which make the procedure simpler, quicker and safer (Rowland and Pagliero 1985). Using this technique very high doses can be delivered to the intraluminal part of the tumour on a day-case basis. Compared to laser therapy and other methods of intraluminal tumour debulking which can be performed under direct visual control, brachytherapy may be less appropriate for asymmetric oesophageal tumours as the circumferential effect produced exposes normal tissues to radiation leading to persistent oesophagitis. An added disadvantage of brachytherapy is that repeat treatments are limited by the problem of cumulative toxicity. The published data regarding the use of brachytherapy as monotherapy for the palliation of malignant dysphagia is limited. In a pilot study of 40 patients treated with a single 15Gy fraction, dysphagia improved in 70% of patients with squamous carcinoma and 60% with adenocarcinomas over a median period of 15 and 12 weeks respectively; two patients were successfully retreated at 30 weeks (Rowland and Pagliero 1985). The quality of swallowing, survival and efficacy in providing long-term palliation were not stated. The morbidity of the procedure was low (13% reported transient symptoms of oesophagitis) and there was no mortality. In a subsequent report from the same unit, long-term palliation with brachytherapy was reported in 66% of 58 patients over a mean survival period of 7 months (1 year survival 17%); the treatment failures were managed by endoscopic intubation (Kaul et al 1989). The relief of dysphagia with brachytherapy is much faster than after external
radiotherapy. In a randomised study of 23 patients (Low and Pagliero 1992), Nd:YAG laser therapy and brachytherapy proved equally efficacious in palliating dysphagia both initially (91% vs 83%) and at 2 months (81% vs 75%); in the laser group dysphagia was relieved more rapidly but retreatments were three times more frequent. The only serious complication reported was a laser induced oesophageal perforation.

The combination of brachytherapy and external beam radiotherapy is conceptually very attractive as it has the potential to improve the therapeutic ratio of radiation treatment, the former delivering high doses to the intraluminal component of the tumour while relatively sparing adjacent normal tissues while lower doses of the latter are targeted onto the peripheral tumour and the lymph nodes. Flores (1989) treated 112 patients with advanced oesophageal and gastric cardia carcinomas with a single 15Gy fraction of brachytherapy followed by 40Gy of external radiotherapy over 3 weeks. Dysphagia improved initially in 90% of patients and of these, 57% could swallow solids, 29% semi-solids and the rest liquids only. Subsequently however, one third of patients required repeated dilatations to maintain palliation long-term. There was no treatment related mortality and survival at 1 and 2 years was 32% and 22% respectively. Severe, persistent radiation oesophagitis was noted in 14% of patients. Frequent serious complications after brachytherapy plus external beam radiotherapy have also been reported by Hishikawa and colleagues (1984). The experience of Agrawal and coworkers (1992) is similar; after combination radiotherapy about 50% of their patients required dilatations for recurrent dysphagia, 9% developed serious complications and 42% survived for 1 year.

2.4.2 Endoscopic Intubation

The most widely used treatment for the palliation of malignant dysphagia is insertion of an endoprosthesis. Surgical intubation which carries a mortality up to 40% (Watson 1982, Muller et al 1990), has been superseded since the late 1970s by the endoscopic technique (Atkinson et al 1978). Intubation is indicated for both intraluminal and extrinsic tumours and is the treatment of choice when oesophageal perforation or fistulation into the tracheo-bronchial tree has occurred. Traditionally it has been contraindicated for tumours of the cervical oesophagus because of troublesome foreign body sensation and for polypoid non-circumferential tumours which cannot securely anchor an endoprosthesis. Rigid plastic prostheses are most commonly used; placement
is usually performed under conscious sedation and patients are hospitalised for only 2 to 3 days unless there are additional medical problems.

Review of the literature on endoscopic intubation with plastic prostheses shows that successful placement is possible in 85-95% of patients; failures occur when the tumour does not admit a guide-wire or cannot be adequately dilated. The procedure related mortality is of the order of 3-12% and is accounted for mainly by perforation of the tumour or pharynx which occurs in 6-12% of cases as a result of the aggressive dilatation which is necessary prior to stent insertion (Jones et al 1981, Ogilvie et al 1982, Tytgat et al 1986, Buset et al 1987). An additional significant disadvantage of the technique is that all food must pass through a rigid tube and consequently the quality of swallowing is limited by the luminal size of the prosthesis. Using commercially available tubes with an internal diameter of 10-12mm, only approximately 10% of patients can swallow a near normal diet and 50-60% are able to eat semi-solids and some solid food (Ogilvie et al 1982, Gaspari et al 1987). In one series using home-made prostheses with a luminal diameter of 14mm, all patients were able to eat a normal diet (Buset et al 1987). Several problems may be encountered after intubation: late oesophageal pressure necrosis and perforation, food bolus obstruction (6-20%), prosthesis tumour obstruction (8-14%), tube displacement or disintegration (8-18%), severe reflux oesophagitis with prostheses crossing the cardia and continuous discomfort with tubes located close to the cricopharyngeous which often necessitates their removal. The majority of these complications can be managed endoscopically (Jones et al 1981, Ogilvie et al 1982, Tytgat et al 1986, Gaspari et al 1987). The reported average survival after endoscopic intubation is only 3 to 6 months (Earlam and Cuhna-Melo 1982a, Bown 1991).

Self expanding metal stents which were introduced into clinical practice in the late 1980s, possess a number of advantages compared to their plastic counterparts. Firstly their deployment system is much more "user friendly" increasing the success of prosthesis placement. Secondly, the relatively slim delivery catheter (diameter 8-11mm) enables placement even in tight strictures after dilatation to only 30Fr, in contrast to the forceful dilatation to 45-54Fr required for insertion of plastic stents; the largely atraumatic nature of the procedure is expected to contribute to patient safety and comfort. Thirdly, their luminal diameter when fully expanded is significantly greater than that of plastic stents (14-20mm compared to 10-12mm) and should provide a better
The published experience with uncovered metal stents (14-20mm diameter) shows that although successful placement was possible in virtually all patients with oesophageal and gastric cardia carcinomas, stent expansion was incomplete in up to one third of cases necessitating balloon dilatation. 85-100% of patients were able to consume solid or semi-solid food (median dysphagia grade 1 on a standard scale) after intubation. Major complications occurred in up to 30% of patients: recurrent dysphagia due to tumour ingrowth in 19%, oesophageal perforation in 4%, delayed oesophageal pressure necrosis in 3%, food bolus obstruction in 8%, tumour overgrowth in 4%, stent migration in 4% and gastrooesophageal reflux in 15%. Most complications were managed endoscopically by clearing food boluses, placement of additional stents or laser therapy. Procedure related deaths occurred in up to 5% of patients (Domschke et al 1990, Kozarek et al 1992, Neuhaus et al 1992, Rajiman et al 1994). In clinical studies employing silicone covered metal stents, successful occlusion of oesophago-respiratory fistulae was possible in 70% of patients. Covered stents largely abolish tumour ingrowth albeit at the cost of an increased rate of migration (up to 9%), a problem which can be overcome by future modifications in stent design (Kozarek et al 1992, Wu et al 1994).

In a randomised comparison of uncovered Wallstents and plastic stents for the palliation of malignant dysphagia, treatment success, recurrent dysphagia rate and need for re-intervention and overall survival were similar in the two groups (Knyrim et al 1993). Dysphagia scores improved significantly and to a similar degree with both stent types despite the greater diameter of the Wallstent (16mm vs 12mm), perhaps as a result of incomplete stent expansion in some patients. Complications (0% vs 43%, p<0.001), mortality (0% vs 14%, not significant) and hospitalisation (mean 5.4 vs 12.5 days, p<0.005) were less with metal stents, resulting in a greater cost-effectiveness despite their twelve-fold higher cost.
Endoscopic intubation provides immediate relief of dysphagia and is the treatment of choice for cases complicated by perforation or fistulation. Using plastic tubes, the treatment related morbidity and mortality is not insignificant and the quality of swallowing is limited by the diameter of the prosthesis so that only a minority of patients can eat a near normal diet. Current evidence suggests that these disadvantages will be overcome to a great extent with the use of self expanding metal stents, but additional clinical studies are needed in order to establish their proper clinical role.

2.4.3 Endoscopic Nd:YAG Laser Therapy

Nd:YAG laser therapy for the palliation of malignant dysphagia was introduced by Fleisher and colleagues in 1982 in the hope of improving on the results of endoscopic intubation. Since then a considerable worldwide experience has been published defining indications, treatment parameters and techniques, efficacy and complication rates (Mellow and Pinkas 1985, Mathus-Vliegen and Tytgat 1986a, Pietrafitta 1987, Bown et al 1987, Krasner et al 1987). Laser therapy is indicated for tumours with a significant intraluminal (exophytic) component; submucosal and extrinsic tumours are not suitable. For cervical oesophageal tumours and malignant strictures impassable with a guidewire, laser recanalisation is the treatment of choice as intubation is either poorly tolerated or technically impossible. Tumour perforation or fistulation into the tracheo-bronchial tree constitute absolute contraindications for laser therapy and should be managed by endoscopic intubation.

An international inquiry published in 1986 reported results from twenty centres in 1184 patients with malignant dysphagia treated by laser therapy (Ell et al 1986). 80% of participants employed a combination of dilatation and laser treatment. Initial tumour recanalisation required an average of three sessions and a total average energy of 11,000J. After treatment 83% of patients were able to eat a virtually normal diet. Major complications occurred in 4.1% (perforation: 2.1% [risk increased nine fold in those who had received radiotherapy], fistulation: 0.8%, haemorrhage: 0.7% and sepsis, including bacteraemia and fever: 0.5%) with an overall procedure related mortality of 1%. The most frequently reported minor complications were retrosternal pain and gaseous abdominal distention. After a successful initial laser course, recurrent dysphagia due to regrowth of intraluminal tumour occurs in up to 70% of patients within 4 to 6 weeks (Buset et al 1983, Mellow and Pinkas 1985,
Krasner et al 1987, Bown et al 1987) and in most units procedures are repeated electively regardless of symptoms when laser treatment is used as monotherapy (Bown et al 1987, Barr et al 1990a). Later in the course of the disease, 10-15% of patients may develop dysphagia because of extrinsic tumour compression or the development of a fibrous stricture induced by repeated laser treatments; in these situations endoscopic intubation is indicated (Bown et al 1987). The average survival of patients treated with laser therapy is only 4 to 6 months (Mellow and Pinkas 1985, Krasner et al 1987, Bown et al 1987, Buset et al 1987).

The success of any palliative treatment for malignant dysphagia depends both on the duration and degree of symptomatic improvement. Information from published studies indicates that after successful initial treatment, palliation can be maintained until death in 61-81% of patients by elective laser treatments and/or dilatation at intervals of 4 to 6 weeks, the remaining patients requiring alternative palliative treatments (Krasner et al 1987, Bown et al 1987, Buset et al 1987, Naveau et al 1990). Although elective re-treatment is generally well tolerated and can be performed on an out-patient basis, it represents a significant burden for elderly, terminally ill patients with a limited life expectancy. Attempts to prolong the dysphagia free interval after laser therapy with adjuvant radiotherapy may prove extremely useful in this respect (Bader et al 1986). Regarding the quality of swallowing after successful treatment, the evidence from the literature shows that approximately one third of patients can eat a normal diet, one half semi-solids and some solid food and the remaining small minority liquids only (Krasner et al 1987, Bown et al 1987, Buset et al 1987, Naveau et al 1990, Barr et al 1990a).

In order to help aid patient selection, various studies have attempted to define parameters affecting outcome after Nd:YAG laser therapy. Poor patient performance status and severe anorexia at the start of therapy has been shown to correlate with inadequate relief of dysphagia and a higher rate of treatment related complications (Mellow and Pinkas 1985, Alexander et al 1994). Fleischer and Sivak (1985) found that the initial outcome of patients with squamous cell carcinomas and adenocarcinomas was similar; exophytic tumours of the mid and distal oesophagus less than 5cm in length responded best, while results were least good with tumours of the cervical oesophagus (despite adequate tumour recanalisation) and with horizontally angulated tumours of the cardia. A regression analysis by Naveau and coworkers(1990)
demonstrated that patients able to swallow solids after initial treatment and those with adenocarcinomas and tumours less than 6cm in length had the best long-term outcome. In contrast, in a study by Mason and colleagues (1991) no prognostic factors could be identified and their policy, as in our unit, has been to treat all patients whose general condition is reasonably good with laser therapy initially and resort to intubation in those with a poor result.

The technical feasibility, safety, efficacy, indications and contraindications for laser treatment of oesophageal and gastric cardia carcinomas have been defined. Its role in an overall treatment plan can only be established through well designed comparative trials with other modalities.

### 2.4.4 BICAP Therapy

Bipolar electrocoagulation tumour probes (BICAP) which provide controlled tissue heating were developed in the early 1980s (Johnston et al 1985). Tumour ablation is achieved by performing overlapping burns throughout its length which result in necrosis and subsequent sloughing of tumour tissue.

In comparison with laser treatment which is indicated only for exophytic cancers, BICAP therapy can be used both for exophytic and submucosal tumours. As treatment is performed without visual control, it is most suitable for circumferential lesions despite the development of probes producing partial burns. Smoke generation and tumour bleeding which may impair laser therapy are not troublesome during BICAP treatment. For tumours of the cervical oesophagus, BICAP treatment is probably technically easier than laser therapy as there is no difficulty in maintaining a stable treatment position. Unlike laser therapy, the symptomatic response after BICAP therapy is often delayed for 2-4 days during which dysphagia may even worsen. Although the BICAP generator and tumour probe are significantly less expensive than the laser, they are much less versatile.

In a pilot study of BICAP therapy, initial recanalisation (mean 1.7 treatments) of oesophageal and gastric cardia carcinomas was possible in all 20 patients who were able to swallow most solids after treatment (Johnston et al 1987). Treatment was repeated for recurrent dysphagia at average intervals of 8 weeks and long-term it proved functionally successful in 14 (70%). Worryingly 4 patients developed major complications (2 delayed haemorrhage, 2
oesophago-respiratory fistulae), two of whom died. Although treatment was found to be quick and technically easy, the number of instrument passages during each procedure proved a significant disadvantage.

Subsequent studies have compared BICAP therapy with other endoscopic treatments. Jensen and colleagues (1988) in a study comprising 28 patients, found that low-power Nd:YAG laser therapy and BICAP treatment were equally effective in palliating dysphagia, 86% of patients in both groups managing a soft or solid diet. Repeat treatment intervals with the two techniques were similar. One patient (7%) in the BICAP group developed a tracheo-oesophageal fistula, while no complications occurred with laser treatment. A small study comparing BICAP treatment and endoscopic intubation in 30 patients showed equal efficacy in palliating dysphagia, 85% managing a semi-solid or solid diet (McIntyre et al 1989). Re-treatment with the tumour probe was required at intervals of 28 days in 75% of patients. Complications were more frequent in the intubation group (43% vs 6%); the only complication after BICAP treatment was a tracheo-oesophageal fistula.

Although encouraging, these results should be regarded only as preliminary as the number of patients treated has been small and the rate of serious complications variable. More extensive clinical experience is required before BICAP therapy can be considered a useful addition to the armamentarium of the therapeutic endoscopist.

2.4.5 Endoscopic Injection Chemical Tumour Necrolysis

The potential of absolute alcohol and sclerosing agents to induce necrosis when injected into malignant tumours has been recognised for some time (Spiller and Misiewicz 1987). Endoscopic injection treatment is a promising new technique for the palliation of malignant dysphagia which involves the multiple injection of small aliquots of absolute alcohol or sclerosant using a standard variceal sclerotherapy needle into protruberant tumour tissue in order to induce its necrosis and sloughing.

Compared with other endoscopic treatments, injection therapy is inexpensive, does not require special equipment and is technically simple and could therefore be performed in most gastroenterology units. It can be applied to exophytic tumours of the whole oesophagus and gastric cardia irrespective of their circumferential extent or severity of luminal obstruction. One of the
significant problems of the technique is judging the adequacy of treatment. Unlike laser or BICAP therapy, there is no immediate visual feedback of the extent of tissue damage induced leading to over or underinjection, which may result in complications or an inadequate symptomatic response.

Three recent prospective uncontrolled studies of alcohol injection therapy for the palliation of malignant dysphagia using similar methodology and comprising 105 patients, report consistent results (Fiorini et al 1993, Nkwokolo et al 1994, Chung et al 1994). The initial functional success rate for squamous cell carcinomas and adenocarcinomas was 81-95% and symptomatic improvement was noted after one to two treatments. On average, patients improved from being able to swallow liquids only prior to treatment to eating at least some solid food. More than 80% of patients developed recurrent dysphagia after a mean of 35 days and required repeat treatment. As no detailed follow-up was provided, the long-term efficacy of the technique could not be evaluated. Treatment was well tolerated, most patients reporting only mild retrosternal discomfort. No complications occurred in the study of Nkwokolo and colleagues (1994), whereas Chung and coworkers (1994) reported the development of oesophago-respiratory fistulae and mediastinitis in 9% of patients who were subsequently successfully managed by endoscopic intubation.

In a randomised study of Nd:YAG laser and injection therapy with 3% polidocanol in 34 patients with malignant dysphagia, approximately 80% in both groups could swallow most solids after an average of three treatments (Angelini et al 1991). Successful long-term palliation with repeated treatments was possible in a similar proportion of patients in both groups but those treated with the laser required significantly more procedures. Both treatments were well tolerated. Injection treatment resulted in oesophageal perforation in 7% of patients who were successfully managed by endoscopic intubation; no complications occurred after laser therapy.

Injection therapy may also have a role as an adjuvant to other endoscopic therapies. In a pilot study, alcohol injection given in combination with Nd:YAG laser therapy, reduced the amount laser energy required to complete recanalisation by 40% without an increase in complications (Banerjee et al 1993).
2.5 Comments

For the majority of patients with cancer of the oesophagus and gastric cardia considered unsuitable for surgery, the main aim of treatment is to palliate the progressive dysphagia, improve the quality of remaining life and prevent an unpleasant death. This aim needs to be achieved with minimum morbidity and inconvenience for the patient both during and after treatment. From an ethical point of view, the quality rather than the length of survival is more important especially if the latter is achieved at the cost of disabling side-effects. However, survival may well be prolonged by purely palliative treatments because of improved nutritional intake.

The increasing number of non-surgical palliative methods used in recent years fall into two broad categories: endoscopic techniques that maintain patency of the oesophageal lumen and radiotherapy or chemotherapy that in addition to relieving obstruction have the potential to alter the natural history of the disease. A critical assessment of their use is necessary in order to recommend the best method or combination of methods for individual patients. The important questions to be addressed are: What are the indications for treatment? What is the initial and long-term efficacy of treatment and what is the time-scale of the response, that is how quickly will symptoms be relieved? Can treatment be repeated if dysphagia recurs? What is the treatment related morbidity and mortality? Does treatment improve quality of life? and lastly in an era of limited health budgets, Is the treatment cost-effective? The review of the literature presented in this chapter has attempted to answer these questions, define relative indications and advantages and identify problems for the various palliative treatments in current use. For some of the better studied treatments such as endoscopic intubation, laser therapy and external beam radiotherapy answers have been provided to most of these questions, although these are often incomplete and contradictory. For newer and promising treatments such as injection therapy, expanding metal stents and brachytherapy much more information is required in order to establish their proper clinical role. Direct comparison between studies, is difficult because of patient selection, incomplete documentation, different treatment end-points and variable assessment and analysis of results.
What is clear is that there is no ideal single palliative therapy and that treatment must be individualised, exploiting specific advantages of various techniques in different clinical situations. Best results will probably be achieved by combinations of treatments, especially methods of intraluminal tumour debulking and external beam radiotherapy with or without chemotherapy which may allow prolonged palliation and perhaps survival. Which treatment or combination of treatments is best for individual patients will be determined by well designed comparative trials detailing long-term outcome. In order to establish benefits and provide clinically meaningful answers, future studies must carefully and systematically gather data on quality of palliation using a clearly defined grading system for dysphagia, quality of life, survival and cost. The work in this thesis was designed to tackle some of these challenges and provide clinically relevant answers.
Chapter 3

Palliative management of rectosigmoid cancer: Review of therapeutic options

3.1 Epidemiology and Challenges in Management of Rectosigmoid Cancer

Colorectal cancer is one of the leading causes of death from malignant disease in Britain. It is responsible for over 20,000 deaths annually and its incidence is estimated at around 30 cases per 100,000 of the population per year. Rectal cancer accounts for approximately half of all cases and exhibits a male predisposition (male to female ratio: 1.3-2.0) which is apparent at all ages (King’s Fund Forum 1990).

The incidence of colorectal cancer rises with age and the increasing longevity in the general population has resulted in a greater proportion of elderly patients. In a population based study from Scotland, 56% of the patients were more than 70 years old (Gordon et al 1993). Symptoms present late in the natural history of the disease (Finlay et al 1988) and in addition there is often a delay of 6-7 months between the onset of symptoms and diagnosis and treatment (Wobbes 1985). As a consequence, at presentation 20-40% of patients are incurable by surgical resection either because of advanced loco-regional disease or distant metastases (Bordos et al 1974, Wanebo et al 1978, Johnson et al 1981, Goligher 1984, Moran et al 1987, Longo et al 1988, Gordon et al 1993).

The aims of treatment in patients with incurable disease are to palliate symptoms due to intraluminal tumour (obstruction, bleeding, discharge, incontinence, diarrhoea and tenesmus) and prevent local complications as a result of growth of the tumour in the pelvis (pain, sepsis, ureteral and intestinal obstruction) thus ultimately improving the quality of remaining life. Absolute survival should be considered of secondary importance, although unfortunately until recently this has been the major endpoint in several studies. The ideal palliative treatment should achieve these aims with minimum morbidity and mortality and require only limited hospitalisation.
It is widely believed by many surgeons that surgery offers good, if not the best, palliation for advanced rectosigmoid cancer because, as Alexander-Williams (1990) puts it in an editorial, "resection is the only method of palliation they know". Careful audit of published results suggests that this may not be so. Although palliative tumour resection provides the best control of local symptoms, it is a formidable procedure with several disadvantages. Firstly it carries a significant morbidity and mortality as a result of having to operate on frail, elderly patients. Although curative radical resections in patients over 70 years can now be performed with a low mortality of 2-8% as a result of advances in intensive care and anaesthesia, improved surgical techniques and better peri-operative care, palliative resections carry a significantly higher mortality ranging from 16-38%. The morbidity of both radical and palliative resections is very high; 30-50% of patients experience complications, approximately two thirds of which are major (Wobbes et al 1985, Lewis and Khoury 1988, Gordon et al 1993). Older patients and those with extensive disease are less able to tolerate major surgery or subsequent complications accounting for the higher mortality in these groups. Secondly, prognosis after palliative resection is dismal with a median survival of only 8 to 16 months, patients with distant metastases faring worst (Bordos et al 1974, Wanebo et al 1978, Moran et al 1987, Longo et al 1988). Thirdly, palliative resections require prolonged hospitalisation (median 20-50 days) and a long recovery period of several months which represents a significant, and in terms of quality probably the best, portion of remaining life (Bordos et al 1974, Moran et al 1987, Longo et al 1988, Lewis and Khoury 1988). Fourthly, on average one third of patients undergoing palliative resection (abdominoperineal or anterior) require the formation of a permanent or temporary colostomy (Moran et al 1987, Lewis and Khoury 1988). This constitutes a great disadvantage for elderly patients as it prolongs their hospitalisation in order to receive training in the care of their stoma, but more importantly because many are unable to adjust to a colostomy and lead an independent life. For patients with unresectable tumours a proximal defunctioning colostomy, which carries a mortality around 6% and a significant morbidity, will relieve obstruction but is of little value in controlling rectal bleeding, discharge and tenesmus (Bordos et al 1974, Moran et al 1987, Longo et al 1988).

Clearly for patients with advanced incurable disease and those who have a high operative risk or refuse surgery (usually because of unwillingness to accept a permanent colostomy) alternative, less aggressive, low morbidity
treatments are required. In view of the easy accessibility of rectosigmoid cancers, several such palliative local forms of treatment have been developed over the past 50 years and are reviewed below.

3.2 Review of Palliative Therapeutic Options

3.2.1 Endoscopic Nd:YAG Laser Therapy

The high power Nd:YAG laser has been used extensively for the treatment of rectal and colonic cancers since the early 1980s. The majority of patients are treated with a palliative intent although in a minority with small, early tumours the aim is complete tumour eradication and cure. Lesions anywhere in the large bowel are potentially treatable as the procedure is performed using flexible endoscopes. Nearly all investigators use a high power non-contact technique; low-power contact treatment using sapphire tips is hardly used as it has no real advantages over conventional treatment and is dearer (Rutgeerts et al 1987). For tumours close to the anal canal the argon laser is occasionally used as Nd:YAG laser treatment can be painful in this region (Brunetaud et al 1987).

Before reviewing the published results certain points need to be emphasised. Firstly, some reports include both small or early and advanced tumours without clearly separating the two groups, making evaluation of results difficult if not misleading. Secondly, maintenance treatment protocols after completion of initial treatment vary between studies; some endoscopists electively re-endoscope their patients at intervals of 4-8 weeks whereas others repeat treatment only if symptoms recur, resulting in significant differences in the number of treatment sessions but more importantly long-term outcome. Thirdly, an important shortcoming of most studies is that the long-term efficacy of treatment is not documented as a significant proportion of patients are not followed-up until death. Additionally, the causes of treatment failure and the subsequent patient management are not described. Fourthly, the nature of the symptoms assessed, their evaluation individually or in groups and the definition of treatment success vary between studies often making comparison of results difficult. Some studies lump all symptoms together and report an overall success rate; others analyse the response of each symptom individually. In most papers, patients presenting with diarrhoea, bleeding, incontinence, rectal discharge and pain or tenesmus
are grouped together (referred to in the French literature as the "rectal syndrome") and evaluated as a whole separate from those presenting with predominantly obstructive symptoms. Clinically meaningful differences in response rates to laser therapy can only be discerned using such an analysis. Evaluation of the effect of treatment is difficult and to a great extent subjective especially in patients presenting with non-obstructive symptoms. Some authors have employed rigid and often impractical criteria of treatment success in an attempt to provide a "quantitative" assessment whereas others have used a more subjective, pragmatic approach. In patients with obstructive symptoms, the avoidance of a defunctioning colostomy is the most commonly employed definition of treatment success.

Several detailed series which allow analysis of the results of laser therapy have been published (Escourou et al 1986, Naveau et al 1986, Bown et al 1986, Mathus-Vliegen 1986b, 1986c, Brunetaud et al 1987, Krasner 1989). These studies include around 500 patients with a mean age 70-79 years, treated for palliation of advanced rectosigmoid cancer. Approximately two thirds of tumours were located in the distal and mid-rectum and the remainder in the upper rectum and distal sigmoid; 42-75% involved more than two thirds of the bowel wall circumference. In order to facilitate comparison of results, presenting symptoms were classified as far as possible into two groups: predominantly obstructive or rectal discharge (including diarrhoea and incontinence) bleeding and tenesmus. The overall success rate was strikingly similar in different series, 80-90% of patients achieving worthwhile palliation over a follow-up of up to 50 weeks. Importantly initial symptomatic improvement was achieved early, most authors requiring two to four treatment sessions over 1-2 weeks. When the success rate was analysed according to presenting symptoms there was again significant accord in the studies reviewed, patients with obstruction responding less favourably.

Palliation of rectal discharge, bleeding and tenesmus was reported in 71-95% (average 90%) of patients and of obstructive symptoms in 47-87% (average 75%). Treatment was usually performed after simple bowel preparation and with minimal sedation and was generally well tolerated, although not uncommonly patients experienced a burning discomfort in the rectum. Some patients had increased rectal discharge for the first 48 hours after treatment due to sloughing of necrosed tumour. In most studies patients were hospitalised for completion of initial treatment and follow-up sessions were performed on an out-patient basis. The average total number of treatment
sessions per patient was 3 to 4, with a wide range of up to 40 procedures; average total hospitalisation time in these series was approximately 6 days. Complications occurred in 0-13.1% (average 7.6%) of patients and the procedure-related mortality varied from 0-3.6% (average 1%). The most frequent complications were perforation (approximately 50% of the total), haemorrhage, fistulation with pelvic sepsis and stenosis although the last two are probably complications of the disease rather than of the treatment itself. Average survival in these studies ranged from 9-30 weeks, although individual patients survived for periods up to 53 weeks.

The series of Brunetaud and colleagues (1987) provides the most detailed documentation of long-term outcome after Nd:YAG laser treatment. In 85 patients with advanced rectosigmoid tumours, the overall initial success rate of treatment was 85%; improvement was noted in 88% of patients presenting with diarrhoea, bleeding and tenesmus compared to 47% in those with obstructive symptoms. Although patient survival decreased rapidly with time (61%, 39% and 19% at 6, 12 and 24 months respectively), the proportion of patients dying palliated remained high within the first year (90% at 6 months and 82% at 12 months) and fell slightly by 24 months (68%). In contrast, two other groups have reported poor long-term results with laser therapy. In a study by Van Custem and coworkers (1989) although the initial symptomatic improvement rate (82%) was comparable to that reported in most series, the proportion of patients dying palliated over the next 2 years was significantly lower - 51%, 41% and 25% at 6, 12 and 18 months respectively. The rather poor long-term outlook was attributed by the authors to progressive extrinsic tumour growth, which is not amenable to laser treatment. However, their policy to repeat laser therapy only if patients developed further symptoms may well have contributed, as tumours re-grow to a large size if the interval between procedures is long (mean 4.7 months in this study) constituting treatment technically difficult. In another study by Bright and colleagues (1992) only 8 of 25 patients (32%) with advanced rectal cancers were successfully palliated until death and eleven patients required colostomy formation. Results were equally poor for patients with obstruction and those with tenesmus, rectal bleeding or discharge. Treatment failure was attributed to the extensive nature of the tumours or to impaired continence as a result of tumour involvement of the sphincters and loss of rectal compliance. The authors recommended that such tumours are better palliated by surgical techniques.
Various groups have attempted to identify prognostic indicators of symptomatic response to laser therapy. Brunetaud and colleagues (1987) have found that in addition to the predominant presenting symptoms (obstructive as opposed to discharge, bleeding or tenesmus), the circumferential extent of the tumour significantly predicted treatment outcome, smaller tumours responding best. In contrast, Naveau and coworkers (1986) and Van Custem and coworkers (1989) have not found circumferential tumour extent to be a significant indicator of outcome. In these studies, long-term outcome was significantly worse in patients with locally advanced or recurrent carcinomas, presumably because such tumours have a significant extrinsic component, and carcinomas with an axial length greater than 4cm.

The ultimate aim of any palliative treatment is to improve the quality of remaining life. In a study of laser therapy for the palliation of inoperable rectal cancer, treatment provided a significant improvement of quality of life in patients with symptoms due to intraluminal tumour but was of little benefit in those with malignant cachexia and deep pelvic pain, underscoring the importance of appropriate patient selection (McGowan et al 1989).

Some of the series reviewed above (Lambert et al 1986, Escourou et al 1986, Brunetaud et al 1987, Bright et al 1992), include a limited number of patients with small (and possibly early) rectosigmoid cancers (maximum diameter less than 3cm and less than 25% circumferential) who were treated with the Nd:YAG laser, as they either had refused surgery or been considered inoperable because of age or associated medical problems, with excellent results. In the series of Brunetaud and colleagues (1987) which is the best documented, complete macroscopic and microscopic tumour eradication was achieved without complications in all 10 patients treated. Importantly, local tumour recurrence did not occur after laser therapy; one patient had died of metastatic disease and two of unrelated causes, while the remaining patients were still alive and tumour free after a mean follow-up of 18 months.

3.2.2 Radiotherapy

3.2.2.1 External Beam Radiotherapy

External beam radiotherapy is frequently employed as an adjuvant to surgery for rectal cancer, either pre-operatively in an attempt to render previously inoperable tumours resectable (James and Schofield 1985) or post-operatively
in Duke's B and C cancers to achieve a prolongation of survival (Gastrointestinal Tumor Study Group 1985). It has also been advocated as an effective treatment for patients with unresectable, locally invasive tumours or those who are considered inoperable because of associated medical problems.

The early experience using high doses of supervoltage radiotherapy (60Gy over 6 to 8 weeks) in 189 patients considered unsuitable for surgery either because of advanced disease (82%) or high anaesthetic risk (18%), showed that complete symptomatic relief was possible in 76% of patients with rectal bleeding, 55% with tenesmus, 48% with pain and 47% with mucous discharge per rectum (Williams and Horwitz 1956). 55% of patients required a colostomy either because of significant obstructive symptoms prior to radiotherapy or the development of a radiation stricture. The morbidity of treatment was significant. In 55% of patients, treatment was interrupted or modified because of acute bladder and gut radiation damage; late complications - fistulae, "chronic radiation necrosis" and strictures - developed in 28% of patients. Overall survival was 33% at 2 years, 14% at 3 years and 5% at 5 years; as expected, patients with smaller tumours had the best survival.

Subsequent studies of supervoltage (Wang and Schultz 1962, Soleimani et al 1972, Stearns and Leaming 1975, Rao et al 1978) and megavoltage radiotherapy (Allum et al 1987, Taylor et al 1987) in patients with advanced rectosigmoid tumours, metastases and poor general condition, have reported similar results with doses of 20-35Gy in ten fractions over 2 weeks. The advantages of using a smaller "palliative" dose are that complications are reduced and treatment can be repeated if necessary, but both the rate and duration of response are less as they are dose dependent (Soleimani et al 1972, Rao et al 1978). In these studies symptomatic responses were observed in up to 92% of patients with pain, 86% with bleeding, 85% with mucoid discharge, 81% with diarrhoea and 77% with tenesmus; response was complete in only one to two thirds of patients. For pain relief it has been demonstrated that single fractions of 10Gy are equally efficacious to fractionated courses of 45Gy, producing satisfactory palliation in two thirds of patients (Allum et al 1987). The time scale and duration of the response to radiotherapy are poorly documented. In the study of Allum and colleagues (1987) the median duration of pain relief was 3 months. Wang and Schultz (1962) reported that
only 12% of patients treated with 20-30Gy had symptomatic benefit lasting more than 6 months compared with 58% of those treated with 40 to 50Gy. These figures should be examined in the context of the limited patient survival (median 6-7 months) after palliative radiotherapy (Taylor et al 1987, Allum et al 1987). Palliative radiotherapy is generally well tolerated without serious morbidity; up to one third of patients develop nausea, vomiting, diarrhoea and dysuria which respond to simple medication (Taylor et al 1987).

For patients with small tumours (diameter less than 5cm) and good general condition who are considered inoperable because of high anaesthetic risk, radical radiotherapy (45-60Gy in twenty fractions over 4 weeks) is usually recommended. The rationale for such treatment is that both symptomatic response and survival (median 14 months) are greater after radical than palliative treatment but at the expense of a higher complication rate (Taylor et al 1987).

### 3.2.2.2 Intracavitary Radiotherapy

Intracavitary radiotherapy for the treatment of low rectal cancers was employed as early as 1950 by Cade. Recent series report rapid shrinkage of small tumours without significant serious morbidity despite total doses up to 150Gy and a 5 year disease-free survival up to 78% (Papillon 1975, Sichy et al 1980). The technique, which has not been widely adopted outside a few specialist centres, is suitable only for the palliation of distal rectal tumours and may seriously impair continence in elderly patients as significant anal dilatation is required. Papillon (1984) found that intracavitary radiotherapy was far less satisfactory for the treatment of advanced rectal cancers than of small lesions. Although pain and rectal bleeding were reasonably palliated, a diverting colostomy was required for obstructive symptoms in the majority of patients during the course of treatment. The combination of external and interstitial radiotherapy has produced encouraging results. In a series of 40 patients (Puthawala et al 1982) with locally advanced rectal cancers treated by 40Gy of external irradiation followed by interstitial irradiation to a total dose of 70-90Gy, complete local tumour control was achieved in 28 (70%). Of these, 82% were still alive after a mean follow-up of 3 years and the remaining patients had died without evidence of local tumour. Serious complications (rectal wall necrosis and bleeding, fistulation and pelvic sepsis) occurred in 20% which is probably unacceptable for a palliative treatment; the procedure
related mortality was 5%. The complications could be reduced by modifications of the dose and fractionation of the radiotherapy.

3.2.3 Electrocoagulation

Electrocoagulation for the treatment of inoperable rectal cancer was introduced by Strauss and coworkers (1935). The technique was later modified and perfected and over the last decades has been strongly advocated by several groups (Wittoesh and Jackman 1958, Madden and Kandalaft 1971, Crile and Turnbull 1972, Hughes et al 1982). It is suitable for tumours located below the peritoneal reflection and is performed under general or spinal anaesthesia through an operating sigmoidoscope or anal speculum. The necessary prolonged anal dilatation may result in compromised continence especially in elderly patients. Procedures are repeated at intervals of up to 2 weeks.

Very good results have been achieved when electrocoagulation is employed with a curative intent in patients with small operable rectal tumours who either refuse or are unfit for surgery. The rate of failure of local tumour control in most series is 20-30% (Crile and Turnbull 1972, Hughes et al 1982, Madden and Kandalaft 1983) although in one study it was only 6% as a result of careful patient selection (Hoekstra et al 1985); on average one half of the treatment failures can be salvaged by subsequent surgery. Treatment complications occur in 8-28% of patients. The most frequent are haemorrhage which is self limiting in most cases but may necessitate transfusion, perforation, recto-vaginal fistulation and the late development of a rectal stricture. The majority of studies report no operative deaths. The 5 year survival rate of patients with small rectal tumours treated by electrocoagulation is 42-71%, the majority dying of unrelated diseases without evidence of local tumour recurrence.

The ability of electrocoagulation to palliate symptoms in patients with advanced tumours is not well documented as most studies focus on curative treatment for early lesions. Hoekstra and coworkers (1985) reported "satisfactory" symptom control in 14 of 18 (78%) such patients but the long-term palliation rate was not stated; all patients who failed to improve were managed surgically and died within 1 year. Of the initial responders, 79% survived less than 1 year and 93% less than 2 years, the vast majority dying because of disseminated malignancy.
3.2.4 Cryosurgery

Despite initial enthusiasm for the technique, it is currently used in a few centres only. Treatment involves the destruction of rectal tumours with a cryoprobe which uses liquid nitrogen and is inserted through a rigid proctoscope. In most cases it is performed as an ambulatory procedure. Anaesthesia, general or spinal, is required only for tumours close to the anal canal. The procedure is not suitable for tumours above the peritoneal reflection because of the risk of perforation. The luminal tumour is frozen in an overlapping manner and procedures are repeated at intervals of up to 2 weeks according to tumour size and response.

Heberer and colleagues (1987) presented a detailed analysis of the results of cryosurgery in 268 patients. In 31 patients with early stage, small (less than 3cm diameter) carcinomas who were considered inoperable because of high anaesthetic risk, complete tumour eradication was possible in 77% with a complication rate of 9%. In 217 patients with advanced tumours, one third of whom had distal metastases, significant reduction in tumour mass was possible in 56%. The need for colostomy until death (median survival 10 months) was avoided in 81% of patients presenting with obstructive symptoms. Cryosurgery was much less effective in palliating other symptoms. Discharge was controlled in 79%, bleeding in 47% although treatment proved ineffective for brisk haemorrhage (haematochezia) and pain in 50%. Significant complications were reported in 32% of patients: perforation 4%, bleeding 7%, late rectal stenosis 13% and incontinence 8%. The mortality of the procedure was only 1% and accounted for entirely by rectal perforation. Mlasowsky and coworkers (1985) have reported similar results with a lower but still significant complication rate of 18%.

3.2.5 Endoscopic Transanal Resection

Although local resection by the transanal (Parks and Stuart 1973) or transphincteric route (Mason 1972) can be used to successfully manage small potentially curable tumours, it is not suitable for the treatment of large, locally advanced rectosigmoid cancers. An alternative palliative approach for such lesions is transanal resection using the urological resectoscope which was first described by Zinken and colleagues in 1979. The operative technique is very similar to transurethral resection of the prostate or of a bladder tumour and the procedure is performed under general or spinal anesthesia.
Although the potential upper limit of resection is dictated by the length of the resectoscope (usually 20cm), in practice treatment is limited to below the peritoneal reflection because of the risk of free perforation. Repeated sessions may be required to achieve adequate tumour debulking and maintain luminal patency.

Following Zinken's original description, several small studies suggested that transanal resection was simple, effective and could be repeated according to symptomatic response (Weese and Bruskewitz 1984, Ottery et al 1986, Kurtz et al 1988). The largest and most detailed study is that of Berry and colleagues (1990) who treated 81 patients with both large benign rectal polyps and rectal carcinomas, 90% of which were located below the peritoneal reflection. Tumour debulking required an average of 1.7 procedures. 31 patients (mean age 78 years) with carcinoma underwent treatment for palliation because of advanced disease or frailty. After treatment, rectal bleeding was abolished or improved in 66%, diarrhoea in 77%, faecal incontinence in 50% and rectal pain including tenesmus in 50%. Long-term results were not assessed. In patients with benign polyps symptoms were universally abolished. Although the overall complication rate in the series was 15%, in patients with rectal cancers post-operative complications occurred in 27%. Severe haemorrhage requiring transfusion or rectal packing occurred in 10%, free perforation in 5%, retroperitoneal perforation resulting in pelvic sepsis in 3.5%, recto-vaginal fistulation in 3.5%, septicaemia in 3.5% and rectal stricture in 1.5%. Average post-operative stay in survivors was 6 days. The high complication rate in this study is probably related to radical extent of tumour resection, often down to the level of the perirectal fat. The 30-day mortality rate was 13.5% but only half the deaths could be attributed to treatment complications.

3.3 Comments

Doctors' attitudes regarding the management of patients with advanced or incurable rectosigmoid cancer are changing. The emphasis is shifting away from survival towards low morbidity symptomatic palliation which aims to improve both the quality of remaining life and the dying process itself. The literature review presented in this chapter has attempted to establish as far as possible the treatment indications, efficacy, morbidity and mortality and identify the limitations of each of the palliative treatments in current use. Formal trials of alternative treatments have not been performed and
comparison of results reported in different studies is usually difficult and in
some cases misleading mainly because of patient selection and variability in
definition and assessment of treatment success. Unlike the case of palliative
treatment for oesophageal cancer where changes in dysphagia can be assessed
objectively and quantified using a formal grading system, evaluation of the
effect of treatment in patients with advanced rectosigmoid cancer is more
difficult and to a great extent subjective, especially in those with non-
obstructive symptoms.

There is considerable published evidence that Nd:YAG laser therapy achieves
good control of local symptoms with low morbidity and mortality but a
couple of recent studies have questioned the efficacy of the technique in
providing long-term palliation. It has advantages over other available
techniques in that it can be applied to lesions both above and below the
peritoneal reflection of the rectum and does not require general or spinal
anaesthesia or prolonged anal dilatation. Despite the difficulties and
limitations of comparing the results of studies evaluating different
treatments, it appears that laser therapy is superior to alternative palliative
techniques in terms of morbidity and mortality and probably efficacy as well.
Additional detailed studies of laser therapy are required to clearly document
its long-term efficacy. More importantly, well designed comparative trials
with other treatments especially the promising technique of endoscopic
transanal resection are also required in order to establish their proper clinical
role. Such studies should examine not only efficacy, morbidity, mortality and
survival but also the important issues of quality of life and cost-effectiveness.
As in the case of palliation of malignant dysphagia, it is likely that best results
will be achieved by a combination of intraluminal tumour debulking with
the Nd:YAG laser and external beam radiotherapy which may allow
prolonged palliation and perhaps survival. Such combination therapies in
selected patients with advanced rectosigmoid cancer are also worth exploring
in the context of formal clinical trials.

Although there is no doubt that tumour resection provides the best control of
local symptoms, careful audit of surgical results in patients with incurable
rectosigmoid cancer suggests that overall it may not provide the best
palliation as it is a formidable procedure with significant disadvantages. A
formal comparison, preferably a randomised study, of laser therapy and
surgery is clearly necessary in order to provide data on which rational
therapeutic decisions can be based. However, failure to gain sufficient support from surgeons will render such a study non feasible, as has been clearly demonstrated by the disappointing experience of the aborted MRC trial of radiotherapy versus surgery for operable oesophageal cancer (Earlam 1991). If this proves to be case, metachronous audit and retrospective comparisons despite their methodological limitations may still provide useful, clinically relevant data.
Chapter 4

Aims of present studies

4.1 Introduction

When any new treatment or therapeutic procedure is introduced into clinical practice, four hurdles have to be overcome. Firstly, the demonstration of feasibility and efficacy; secondly, the definition of indications and limitations; thirdly, comparison with alternative treatments and lastly, peer and popular acceptance. Since the early 1980s when the first procedures were performed, a considerable experience with endoscopic Nd:YAG laser therapy for the palliation of gastrointestinal cancers has accrued. Review of the literature shows that the first two hurdles have more or less been surmounted but in a number of important areas the information is still incomplete and often contradictory. At the time when the present studies were initiated in early 1987, only a few attempts at overcoming the third of the above hurdles, had been performed in the form of retrospective comparisons of laser therapy and alternative treatment modalities. Additionally, the important issues of quality of life and cost-effectiveness had not been addressed. The aim of this thesis was to attempt to partially fill these gaps in medical knowledge. Nd:YAG laser therapy for the palliation of advanced gastrointestinal cancers was evaluated by means of clinical studies in the context of alternative treatment modalities and specific problem areas addressed in an attempt to establish its role in an overall rational treatment policy.

4.2 Palliation of Malignant Dysphagia

4.2.1 A Prospective Comparison of Nd:YAG Laser Therapy and Endoscopic Intubation for the Palliation of Malignant Dysphagia (Chapter 5)

The aim of the study was to perform a prospective, concurrent comparison of Nd: YAG laser therapy and endoscopic intubation for the palliation of dysphagia due to thoracic oesophageal and gastric cardia cancer. Laser therapy was carried out at the National Medical Laser Centre, University College
Hospital, London and intubation at Queen's Medical Centre, Nottingham.

The study objectives were to assess:

1. short and long-term efficacy
2. quality of palliation
3. treatment related morbidity and mortality
4. hospitalisation requirements and survival
5. impact of treatment on quality of life
6. economic costs

4.2.2 Nd:YAG Laser Therapy plus Adjuvant External Beam Radiotherapy for the Palliation of Malignant Dysphagia (Chapter 6)

The aim of this prospective pilot study was to investigate combination treatment with Nd:YAG laser therapy plus external beam radiotherapy for the palliation of dysphagia in patients with thoracic oesophageal and gastric cardia cancer. The objectives were:

1. to establish the appropriate radiation dose
2. to study efficacy and quality of palliation, duration of palliation and laser treatment requirements, complications and survival and assess the potential value of adjuvant radiotherapy by retrospectively comparing the results of this study with those obtained in a similar group of patients treated with laser monotherapy as part of the trial outlined above in 4.2.1.

4.2.3 Nd:YAG Laser Therapy for Recurrent Dysphagia after Surgery or Intubation (Chapter 7)

The management of late dysphagia due to anastomotic tumour recurrence after surgery or occlusion of an endoprosthesis by tumour growth poses major challenges. The aim of this study was to prospectively assess the efficacy and safety of Nd:YAG laser therapy in these problem clinical situations.
4.2.4 Treatment of High Cervical Oesophageal Cancer by Endoscopic Intubation using Modified Endoprostheses (Chapter 8)

Endoscopic intubation for high cervical oesophageal cancer has traditionally been contraindicated because of serious potential complications. The aim of the study was to develop and evaluate clinically a specially modified Celestin prosthesis (Medoc Ltd) suitable for endoscopic placement as a means of palliating extrinsic and fistulating carcinomas involving or within 2cm of the cricopharyngeus sphincter muscle.

4.3 Palliation of Rectosigmoid Cancer

4.3.1 A Prospective Study of Nd:YAG Laser Therapy for the Palliation of Rectosigmoid Cancer (Chapter 9)

The aim of the study was to prospectively audit endoscopic Nd:YAG laser therapy for rectosigmoid cancer in patients considered unsuitable for surgery because of advanced disease or high anaesthetic risk; special emphasis was placed on the collection of detailed long-term data. The objectives were to assess:

1. initial and long-term efficacy
2. morbidity and mortality
3. treatment and hospitalisation requirements
4. survival
5. various parameters as prognostic indicators of treatment outcome
6. the feasibility of complete eradication of small tumours

4.3.2 Surgery or Nd:YAG Laser Therapy for the Palliation of Incurable Rectosigmoid Cancer? (Chapter 10)

The aim of the study was to document the effectiveness of Nd:YAG laser therapy in relation to palliative surgery for patients with incurable rectosigmoid cancer. The outcome of a group of such patients treated surgically at University College Hospital prior to the availability of laser therapy was determined by case note review and compared with that of a similar group treated with the laser as part of the prospective audit outlined in section 4.3.1. The following parameters were assessed:
1. long-term efficacy
2. treatment related morbidity and mortality
3. hospitalisation requirements
4. survival
Part II: Palliation of Malignant Dysphagia
5.1 Introduction

Nd:YAG laser therapy and intubation are the two most widely used endoscopic treatments for the palliation of malignant dysphagia. Despite extensive clinical experience and the definition of specific indications for the two techniques, no formal comparison of endoscopic intubation and laser therapy in the context of a prospective trial had been reported by the time this investigation was initiated in mid 1987. Such a study was therefore performed in patients with carcinomas of the thoracic oesophagus and gastric cardia in an attempt to establish a rational management policy. Trials such as this may be subject to bias as a result of the particular interests and expertise of the investigators. To avoid this, it was decided to carry out laser treatments at the National Medical Laser Centre, University College Hospital, London, a tertiary referral centre with long-standing laser expertise and intubations at Queen's Medical Centre, Nottingham, a unit which pioneered the technique of endoscopic oesophageal prosthesis insertion.

5.2 Patients and Methods

5.2.1 Study Design and Objectives

The study was prospective and concurrent (June 1987 - January 1989), non-randomised and based at University College Hospital, London and Queen's Medical Centre, Nottingham. Consecutive patients referred to the two centres for palliation of dysphagia were considered for inclusion in the trial; patients recruited in London were treated initially by laser therapy and those in Nottingham by endoscopic intubation. The aims of the study were to evaluate the two treatment modalities by assessing early and long-term functional efficacy, quality of palliation, procedure related morbidity and
mortality, hospitalisation requirements, impact of treatment on quality of life (reported in Section B) and also to perform an economic analysis of the relative cost of the two techniques (reported in Section C).

5.2.2 Patients

Only patients with predominantly exophytic carcinomas of the thoracic oesophagus and gastric cardia which are suitable for treatment by both techniques were eligible for inclusion in the study. Anastomotic recurrent tumours, carcinomas of the cervical oesophagus (proximal margin less than 20cm from the incisors at endoscopy) for which intubation has traditionally been contraindicated and tumours of extrinsic origin or with established tracheo/broncho-oesophageal fistulae which are unsuitable for laser therapy, were all excluded from the study. All recruited patients were inoperable either because of advanced disease (metastases, local invasion) or high anaesthetic risk (marked cachexia, age and severe concomitant disease). Patient and tumour details are shown in Tables 5.1 and 5.2. Only two patients, both in the intubation group, were treated with radiotherapy after endoscopic therapy; none had chemotherapy. 14% (n=6) of patients in the laser group and 18% (n=5) in the intubation group had recurrent dysphagia after previous radiotherapy. Distant metastases were documented by imaging techniques in 42% (n=25) and 40% (n=18) of patients respectively in the two groups.

5.2.3 Instrumentation and Endoscopic Techniques

A "Flexilase" Nd:YAG laser (Living Technology, Glasgow), which can generate up to 100W of continuous wave emission at a wavelength of 1064 nm, was used. A red aiming beam is provided by coupling the output of a low power (5mW) He-Ne laser into the beam path of the Nd:YAG laser. The laser output is focused onto the end of a 400-600 micrometre quartz fibre contained in a 2mm diameter Teflon catheter as described in Chapter 1, 1.3.6. This catheter gives the fibre mechanical strength so that it can be passed down the working channel of an endoscope. It also enables the passage of a coaxial stream of carbon dioxide or air, which keeps the fibre tip clean and cool and helps to clear blood and debris from the target surface. As treatment is often prolonged, insufflated gas and smoke generated by tumour vaporisation must be vented; this is achieved by connecting the working channel of the endoscope to a water-seal drain under a head of about 20cm using a specially designed two-way valve which can be closed when suction is performed. An
Table 5.1: Details of patients with malignant dysphagia treated by laser therapy or endoscopic intubation.

<table>
<thead>
<tr>
<th></th>
<th>LASER (n = 43)</th>
<th>INTUBATION (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : Female</td>
<td>26 : 17</td>
<td>21 : 9</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>75 (49-93)</td>
<td>74 (58-85)</td>
</tr>
<tr>
<td>SCC : ANC</td>
<td>9 : 34</td>
<td>10 : 20</td>
</tr>
<tr>
<td>Mean tumour length (range), cm</td>
<td>5.9 (3-13)</td>
<td>5.8 (2-12)</td>
</tr>
<tr>
<td>Mean dysphagia duration (range), months</td>
<td>3.6 (1-6)</td>
<td>3.8 (1-6)</td>
</tr>
</tbody>
</table>

SCC: Squamous Cell Carcinoma; ANC: Adenocarcinoma
Table 5.2: Tumour details in patients treated by laser therapy or endoscopic intubation.

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>LASER SCC</th>
<th>LASER ANC</th>
<th>LASER Total</th>
<th>INTUBATION SCC</th>
<th>INTUBATION ANC</th>
<th>INTUBATION Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper half TO</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Lower half TO</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Cardia ± Lower half TO</td>
<td>-</td>
<td>22</td>
<td>22</td>
<td>-</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LENGTH (cm)</th>
<th>LASER SCC</th>
<th>LASER ANC</th>
<th>LASER Total</th>
<th>INTUBATION SCC</th>
<th>INTUBATION ANC</th>
<th>INTUBATION Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5cm</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>6-10cm</td>
<td>9</td>
<td>28</td>
<td>37</td>
<td>7</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>&gt;10cm</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

SCC: Squamous Cell Carcinoma; ANC: Adenocarcinoma; TO: Thoracic oesophagus, upper half: 20-30cm from incisors, lower half: 30cm from incisors-cardia
Olympus GIF 1T (Keymed Ltd, Southend) therapeutic upper gastrointestinal endoscope, modified by the insertion of an appropriate filter in the eyepiece to protect the endoscopist’s eye from back scattered radiation, was used.

Laser procedures were performed under conscious sedation with intravenous Diazemuls (diazepam in a lipid suspension) and Pethidine. The aim of treatment was to destroy as much tumour as possible in one session, concentrating on those parts causing the worst obstruction. Using a high power non-contact technique (60-90W, 1-2 sec shots) exophytic tumour was gradually shaved back towards the wall by vaporisation; flat areas of tumour tissue were treated by coagulation. Where possible recanalisation was performed in a retrograde manner starting at the distal tumour margin, if necessary after dilatation with Celestin bougies (Medoc Ltd, Tetbury), as immediate oedema in unvaporised areas can hinder forward progress and make orientation difficult. The advantage of the retrograde technique is that the lumen is visualised at all times. Impassable tumours which could not be adequately dilated, were treated in a prograde (forward) manner. The major problem with this technique is that the direction of the luminal axis along which laser recanalisation should proceed, cannot be accurately assessed thus increasing the risk of perforation. It is therefore recommended that only 1-2cm of tumour should be recanalised in this fashion in a single session. All laser treatments were performed by the author and Professor S G Bown and repeated at intervals of 3 to 4 days, allowing necrosed tumour to slough, in order to complete initial tumour recanalisation. Unless indicated earlier, treatments were repeated electively at intervals of 4 to 5 weeks, if possible on a day-case basis. After treatment, patients were advised to consume an unrestricted diet of their choice. Where clinically appropriate, laser treatment failures underwent endoscopic or surgical intubation with Celestin prostheses.

All endoscopic intubations in Nottingham were performed by two experienced operators, Mr C Robertson and Professor M Atkinson, usually under general anaesthesia. Tumours were dilated with Tridil olives and Atkinson (Keymed, Ltd) endoprostheses of appropriate length placed using the Nottingham introducer under fluoroscopic control (Ogilvie et al 1982). These prostheses have a luminal diameter of 11mm and an external diameter of 14mm. Post-intubation, a chest X-ray and contrast swallow were performed within 24 hours to detect and localise instrumental perforations and assess
tubefunction. On discharge patients were given general dietary advice to prevent tube blockage; solid food items were not specifically excluded.

5.2.4 Patient Assessment

Quality of swallowing and quality of life were serially documented in detail from the time of inclusion in the trial until death by Sister D Grigg-Rampton, who alternated between the two institutions. Patients were interviewed during clinic visits and at other times were followed-up by telephone. All patients, or their relatives or carers, were contacted at least once a month and at more frequent intervals if their condition was changing rapidly. The severity of dysphagia was assessed by reviewing the consistency of a patient’s diet since the previous evaluation and graded from 0-4 on a 5 point scale:

Grade 0: able to eat normal diet
Grade 1: able to eat most solid food
Grade 2: able to eat semi-solids only
Grade 4: able to swallow liquids only
Grade 4: complete dysphagia

Individual dysphagia profiles over time were constructed by plotting dysphagia grade against time. The mean quality of swallowing over a given time interval was calculated by estimating the area under the curve. Assessment of quality of life is described in Section B.

5.2.5 Statistics

Statistical analyses were performed using a $\chi^2$ test with Yate’s correction and the Wilcoxon signed rank and two sample test for non-parametric data. Survival and dysphagia palliation (DP) curves were constructed using the life table (Kaplan-Meier) method and tested for disparity by log rank analysis. The DP curves depict the probability of successful palliation of dysphagia as defined below at varying times from the start of treatment; for the calculation of DP distributions, patients dying palliated were censored, that is lost to follow-up. Significance was set at the 5% level ($p<0.05$).
5.3 Results

5.3.1 Functional Efficacy, Recurrent Dysphagia and Survival

For the purposes of this study, laser therapy and intubation were considered functionally successful if a patient's dysphagia improved by at least 1 grade on the dysphagia scale. Such an improvement within 2 weeks of intubation or initial laser therapy was defined as an early success; maintenance of improved swallowing, with or without repeat endoscopic therapy, until death was defined as a long-term success. The results are shown in Table 5.3. In contrast to tumour location, tumour length less than 5cm (for the whole group and according to tumour site) and a pre-treatment dysphagia grade equal to or greater than 2, had no prognostic significance by statistical analysis as indicators of good initial functional outcome after laser therapy.

All patients in both groups have been followed-up until death. Mean survival (sd) from inclusion in the trial was 6.1 (5.1) and 5.1 (4.8) months in the laser and intubation groups respectively. Survival and dysphagia palliation interval (DP) distributions, calculated using the life table method, for both groups are shown in Figure 5.1. Median survival was only 4.4 months in the laser and 3.5 months in the intubation group, with 1 year survival rates of 8% and 10% respectively. The significant separation of the laser and intubation DP distributions, reflects the greater probability of achieving long-term palliation with intubation. In both groups survival was significantly longer in patients without documented metastases; Laser: mean (sd, range): 8.4, (6.4, 2-28) vs 3.6, (2.3, 1-9) months; p<0.004); Intubation: mean (sd, range): 6.7, (5.8, 1-22) vs 3.1, (2.1, 0.5-8) months; p<0.03).

Details of patients who failed to improve with endoscopic therapy and their further management are shown in Table 5.4. Laser failures were classified as functional, if dysphagia failed to improve despite adequate recanalisation and the ability to pass a 13mm diameter fibroscope through the tumour without resistance. Late laser failures occurred on average 4.8 months after the initiation of therapy predominantly due to compression by extrinsic tumour and possibly some degree of mural stricturing secondary to laser induced fibrosis. Unlike early laser failures, late failures did not occur predominantly in patients with carcinomas of the cardia. In the intubation group, 7 patients developed recurrent dysphagia due to prosthesis malfunction: food blockage in 2 (7%), tumour overgrowth in 2 (7%) and distal migration in 3 (10%).
Table 5.3: Palliation of malignant dysphagia with laser therapy or endoscopic intubation: success rates, survival and treatment requirements.

<table>
<thead>
<tr>
<th></th>
<th>LASER</th>
<th>INTUBATION</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL SUCCESS</strong></td>
<td>33/43 (77%)</td>
<td>30/30 (100%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>TO</td>
<td>20/21 (95%)</td>
<td>14/14 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardia ± lower TO</td>
<td>13/22 (59%)(^a)</td>
<td>16/16 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LONG-TERM SUCCESS</strong></td>
<td>27/43 (63%)</td>
<td>27/30 (90%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TO</td>
<td>16/21 (77%)</td>
<td>12/14 (86%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardia ± lower TO</td>
<td>11/22 (50%)</td>
<td>15/16 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MEAN SURVIVAL TIME</strong></td>
<td>6.1 (5.1)</td>
<td>5.1 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>(sd), months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEAN TOTAL No. OF</strong></td>
<td>5 (3-11)</td>
<td>2 (1-5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PROCEDURES (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TO: Thoracic oesophagus; \(^a\): p<0.01; NS: not significant
Figure 5.1: Survival and dysphagia palliation (DP) distributions (life table method) for patients treated by laser therapy (L) or endoscopic intubation (EI). Intubation vs Laser DP: p<0.02 by log rank analysis.
Table 5.4: Palliation of malignant dysphagia with laser therapy or endoscopic intubation: treatment failures and further management.

<table>
<thead>
<tr>
<th>REASON</th>
<th>SITE</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LASER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid regrowth (3)</td>
<td>Cardia (3)</td>
<td>EI (3)</td>
</tr>
<tr>
<td>Functional (5)</td>
<td>Cardia (5)</td>
<td>EI (2), TLC (3)</td>
</tr>
<tr>
<td>Extrinsic compression (1)</td>
<td>Cardia</td>
<td>EI</td>
</tr>
<tr>
<td>Perforation (1)</td>
<td>Upper TO</td>
<td>SI</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrinsic compression/</td>
<td>Upper TO (1), lower TO (1)</td>
<td>EI (3), SI (2)</td>
</tr>
<tr>
<td>fibrous stricturing (5)</td>
<td>TO (1), Cardia (3)</td>
<td></td>
</tr>
<tr>
<td>Functional (1)</td>
<td>Lower TO</td>
<td>TLC</td>
</tr>
<tr>
<td><strong>INTUBATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube migration/</td>
<td>Cardia</td>
<td>TLC</td>
</tr>
<tr>
<td>failed re-intubation(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional (2)</td>
<td>Lower TO</td>
<td>TLC</td>
</tr>
</tbody>
</table>

TO: Thoracic oesophagus; EI: Endoscopic intubation; SI: Surgical intubation
TLC: "Tender Loving Care" ± enteral tube feeding
Further endoscopic therapy (food disimpaction or prosthesis replacement), was successful in all except one patient with prosthesis migration which occurred 10 weeks after intubation and in whom prosthesis replacement proved impossible. The other two late failures in the intubation group, which were functional and predominantly due to anorexia, occurred in patients treated with additional external beam radiotherapy. Intubation of patients who were classified as laser treatment failures was accomplished without significant complications; all achieved adequate palliation during their remaining survival (mean 4.5 months) with transient dysphagia in four. The long-term success of the policy of laser therapy followed by intubation, where appropriate, for the management of treatment failures in providing palliation of dysphagia, was very similar to that of endoscopic intubation alone (91% vs 90%).

5.3.2 Quality of Swallowing

In patients who achieved long-term palliation of dysphagia, the mean dysphagia grade decreased from 2.9 (sd 0.64) to 1.6 (sd 0.55) in the laser group and from 3.2 (sd 0.7) to 2.0 (sd 0.55) in the intubation group (p<0.0001 for both techniques); the mean post-treatment dysphagia grade was significantly lower in the laser group (1.6 vs 2.0, p<0.01). In addition, the proportion of patients who were able to eat a virtually normal diet (most or all solids), was significantly greater in the laser group (33% vs 11%, p<0.05); approximately two thirds of the remaining patients in both groups could swallow semi-solids without difficulty - Figure 5.2. With a management policy of laser therapy plus intubation for treatment failures, the proportion of all patients who were able a normal diet for more than 50% of their survival was significantly greater than in the group treated by intubation alone (33% vs 10%, p<0.05) - Figure 5.3.

5.3.4 Treatment Complications and Hospitalisation

Pharyngeal or oesophageal perforation occurred in one patient (2%) in the laser group after preliminary dilatation and in four patients (13%) in the intubation group (p<0.02). Three of the latter patients had unsuspected pharyngeal tears which were detected by routine contrast swallow studies. The patient in the laser group underwent surgical intubation while the remaining patients made an uneventful recovery with conservative treatment. One patient in the laser group required transfusion of two units of
Figure 5.2: Mean lifetime consistency of diet in patients palliated until death with laser therapy (n = 27) or endoscopic intubation (n = 27).

* p<0.05
Figure 5.3: Long-term functional outcome of all patients managed by laser therapy with intubation for laser failures when indicated (n = 43) or by endoscopic intubation alone (n = 30).

* p<0.05
blood following a delayed haemorrhage. Bleeding, late pressure necrosis or symptomatic gastroesophageal reflux did not occur after intubation. A few patients had minor, transient (less than 24 hours) chest discomfort after dilatation either for tube insertion or prior to laser therapy. Other patients had more persistent chest and back pain associated with the underlying disease, but unaffected by the endoscopic procedures. No procedure related deaths occurred in either group.

Hospitalisation time, excluding terminal care, was significantly longer in the laser therapy group (mean 13.8 vs 8.5 days, p<0.05) reflecting the more frequent need for endoscopic treatment with this technique in order to maintain long-term symptomatic palliation. 40% of laser treatments were performed on an out-patient basis.

5.4 Discussion

Although specific indications for the use of laser therapy and endoscopic intubation in patients with malignant dysphagia have been defined, the majority are suitable for palliation with either technique. The purpose of the present study was to compare the efficacy of each as single modality treatments in providing palliation until death. As the success of any endoscopic therapy is greatly operator dependent, it was decided to prospectively compare the results from two specialist centres with unique expertise in laser therapy or intubation.

The 77% initial functional success rate with laser therapy in this series is comparable to that from other centres (Fleischer and Sivak 1985, Ell et al 1986, Krasner et al 1987, Brunetaud et al 1989, Manoury et al 1992). The long-term outcome after such treatment is not very well documented in the literature. Success rates of 45-75% over a follow-up of 2-5 months have been reported (Mathus-Vliegen 1986a, Rutgeerts et al 1988, Brunetaud et al 1989, Barr et al 1990a); the 63% palliation rate until death in the present study is in agreement with this experience. 75% of patients who failed to derive long-term control of symptoms with laser therapy in the present study, were managed by intubation which provided adequate palliation until death in all cases; the remaining patients were considered unfit for any further treatment. Thus, a management policy of laser therapy with salvage of treatment
failures by intubation when appropriate, provided long-term palliation in a similar proportion of patients as endoscopic intubation alone (91% vs 90%).

In two subsequent randomised prospective studies comparing laser therapy and endoscopic intubation as single modality treatments for the palliation of malignant dysphagia, the success of laser therapy was higher than in the present investigation. Alderson and Wright (1990) randomised twenty patients to each group, including patients with anastomotic recurrence. Successful palliation until death was possible in 85% of patients in the laser and 90% in the intubation group. Two of the three laser failures were treated by intubation and one of the two intubation failures by laser, so that overall 95% of patients in this series were successfully palliated with endoscopic therapy. In a different study, Carter and coworkers (1992) randomised twenty patients to each group but those with anastomotic recurrent tumours were excluded. Their findings were similar; successful palliation was achieved in 85% in the laser and 90% in the intubation group. Two of the three laser failures were salvaged by intubation and one of the of the two intubation failures by laser therapy, resulting in an overall 95% success rate with endoscopic therapy. The higher success rate of laser therapy in these two studies can probably be accounted for by the lower proportion of gastroesophageal junction cancers (55% and 53% respectively vs 79% in this series), given that the results of the present trial demonstrate a significantly lower treatment efficacy for such tumours than for cancers of the thoracic oesophagus. In the two randomised studies treatment outcome was not analysed according to tumour histology or location and although Alderson and Wright (1990) state that these two parameters did not influence outcome, a type II statistical error cannot be excluded given the relatively small size of the groups. In contrast to our findings, tumour site had no influence on initial functional outcome after laser therapy in Fleischer and Sivak's study (1985) and in a multivariate analysis by Naveau and colleagues (1990) patients with cardioesophageal junction adenocarcinomas were shown to have the best long-term outcome. Additional studies involving large numbers of patients are needed in order to clearly document the possible influence of tumour location and histology on outcome after laser therapy.

The majority of initial failures of laser therapy with cancers of the cardia were functional and may be at least partly explained by the growth characteristics and effects of these tumours on oesophageal motility. Adenocarcinomas at
this site have a tendency to extend proximally along the oesophageal submucosa and to form a large extrinsic mass around the cardioesophageal junction which cannot be fully appreciated endoscopically (Mahoney and Condon 1986). As a consequence, the distensibility of the cardia, which is inversely proportional to its wall thickness, is greatly reduced. In addition, secondary or pseudoachalasia which has been most frequently reported in association with adenocarcinomas of the gastric cardia and fundus, may have contributed to the poor functional outcome (Robertson et al 1988); the impaired oesophageal motility may be unable compensate for the reduced distensibility of the cardia resulting in functional obstruction. In these cases, as in primary achalasia, the endoscope can be passed into the stomach with little resistance. It is interesting that in a subsequent study from our unit (Sargeant et al 1992a), 55% of patients with circumferential cancers of the cardia measuring greater than 2cm in thickness on endosonography did not derive a significant improvement in swallowing despite complete tumour recanalisation. Late laser failures in the present study occurred after a mean of 4.8 months and were due to extrinsic tumour compression and probably some degree of mural stricturing resulting from laser induced fibrosis. In two of these seven cases, the strictured segment did not even admit a guide wire, necessitating surgical intubation.

Successful prosthesis placement was possible in all patients of the intubation group in the present study; most series report an 85% - 95% success rate (Ogilvie et al 1982, Tytgat et al 1986, Buset et al 1987, Alderson and Wright 1990, Carter et al 1992, Hahl et al 1991). Most failures occur with multiangulated and poorly distensible tumours and those causing complete luminal occlusion (Buset et al 1987). In these situations, preliminary laser recanalisation should facilitate tube placement and reduce the risk of instrumental perforation. In a study by Barr and colleagues (1990), laser therapy prior to endoscopic intubation facilitated tube placement in four of twenty patients in whom either a guide wire could not be passed through the tumour or adequate dilatation could not be performed without a high risk of oesophageal perforation; preliminary laser treatment however, resulted in an increased rate of distal prosthesis migration. As stated by the authors, the aim of laser therapy in this situation is to provide an adequate lumen that will allow easy intubation and no attempt should be made to clear the oesophagus of all exophytic tumour. It is believed that the risk of perforation is increased if intubation is attempted after multiple laser treatments, as a result of the
splitting of laser induced fibrous oesophageal strictures. In the present study however, none of the three late laser treatment failures who underwent intubation sustained a perforation; obviously a larger number of patients needs to be studied before firm conclusions can be made.

After intubation seven patients (24%) in the present study experienced recurrent dysphagia due to food bolus obstruction, tumour overgrowth or prosthesis migration, a figure comparable to that from other series (Tytgat et al 1986, Gaspari et al 1987); further endoscopic procedures restored swallowing function in all except one patient with distal tube migration. If recurrent dysphagia due to prosthesis tumour overgrowth cannot be successfully managed by tube manipulation or replacement, laser therapy offers an effective and safe means of restoring tube function although repeated procedures are usually necessary to maintain patency long-term (Krasner et al 1987). An evaluation of the use of laser therapy in this clinical setting is presented in chapter 7.

An important issue to consider in the assessment of any palliative treatment for malignant dysphagia is the quality of swallowing achieved. There is more or less general agreement in the literature regarding swallowing function after intubation. With Atkinson or Celestin endoprostheses (luminal diameter 11mm), 10-15% of patients can eat a virtually normal diet, 50-60% a semi-solid diet while the rest can manage liquids only (Ogilvie et al 1982, Gaspari et al 1987, Watson 1988). Buset and coworkers (1987), reported that after intubation using purpose made prostheses with internal diameter of 14mm, 100% of patients palliated until death were able to eat a normal diet. Although it is logical to expect a better quality of swallowing with a larger diameter prosthesis, the authors' claim probably has to be questioned especially as the method of assessing severity of dysphagia was not stated. On the same theme, use of the newly developed larger diameter expanding metal stents should provide a superior quality of swallowing. However, in a recent comparative trial of plastic and metal prostheses by Knyrim and colleagues (1993) which has been described in Chapter 2, 2.4.2, dysphagia scores improved to a similar degree with both stent types. After laser therapy, Krasner and colleagues (1987) found that 32% of patients managed a virtually normal diet, 56% semi-solids and some solids and 12% liquids only. The experience of most other authors is similar (Bown et al 1987, Naveau et al 1990, Alderson and Wright 1990) although in a few studies normal
swallowing after laser therapy has been reported in 80%-93% of patients (Carter and Smith 1986, Buset et al 1987). The majority of prospective studies comparing laser therapy and intubation which have documented dysphagia in detail using a standard scale, demonstrate that the laser provides a superior quality of palliation. In Alderson and Wright's study (1990), the proportion of patients enjoying a relatively normal diet was significantly greater in the laser group (41% vs 11%); it was noted that patients with normal swallowing after laser therapy had significantly shorter tumours than those with a less successful result. In the study by Carter and coworkers (1992), the best dysphagia grade achieved was significantly better with laser treatment than intubation (median 4 [normal diet] vs 3 [semi-solids]). Barr and colleagues (1990a) found no significant difference in the mean or best dysphagia grade after treatment in either group, but 40% of laser treated patients had normal swallowing for at least part of their survival compared with none in the intubation group. In the present study, laser therapy proved superior both in terms of the mean dysphagia grade after treatment and the proportion of patients palliated until death who were able to eat a virtually normal diet. The policy of initial laser therapy with salvage of treatment failures by intubation proved equally effective as intubation alone in palliating dysphagia until death, but enabled significantly more patients to enjoy a virtually normal diet for at least half of their survival.

Good palliation implies not only high efficacy but also low morbidity and mortality and short hospitalisation. There is general consensus in the literature that the overall complication rate, including problems due to prosthesis occlusion or migration, is significantly greater after intubation (20%-48%) than laser therapy (4%-25%) (Alderson and Wright 1990, Barr et al 1990a, Fuchs et al 1991, Carter et al 1992, Buset et al 1987, Hahl et al 1991). It should be noted however, that the rate of oesophageal perforation in prospective comparative studies (Alderson and Wright 1990, Barr et al 1990a, Fuchs et al 1991, Carter et al 1992), was not significantly different after laser therapy (4%-15%) or intubation (5%-15%). Although perforations occurred more frequently after intubation in the present study, the majority of these were unsuspected pharyngeal tears detected by routine contrast swallow studies; the experience of Barr and colleagues (1990) is similar. The procedure related mortality reported in several descriptive series appears to be higher for intubation (3-12%) than laser therapy (1-5%) (Ogilvie et al 1982, Tytgat et al 1986 Buset et al 1987, Ell et al 1986), but in the present and other prospective
studies quoted above, no significant difference in mortality was apparent and only occasional deaths occurred in either treatment group. The low mortality could be accounted for by the early radiological detection of leaks and the institution of appropriate conservative therapy (Anderson 1990).

In patients with a terminal disease and limited life expectancy, it is clearly important to avoid prolonged hospitalisation. This was certainly achieved in the present study as the average in-patient stay of laser treated patients, excluding terminal care, as a proportion of their total survival was only 8%; Barr and colleagues (1990a) and Carter and coworkers (1992) report corresponding figures of 11% and 14% respectively. Laser treated patients in the present and other studies (Alderson and Wright 1990, Carter et al 1992), required significantly more procedures during their lifetime than those managed by intubation as a result of the necessity for elective re-treatments in order to maintain the symptomatic improvement. Although this is a significant burden for elderly terminally ill patients, the regular hospital attendance provides an opportunity for counseling and support through the close relationship that they are allowed to develop with members of the medical and nursing staff. Prolongation of the dysphagia free interval and consequently reduction of the number of repeat laser treatments would certainly be worthwhile. The use of adjuvant radiotherapy in an attempt to achieve these aims is described in the next chapter.

What are the clinical implications of the present findings? For patients with poor general condition, severe anorexia and documented metastases, endoscopic intubation should be considered the treatment of choice as it provides quick and lasting palliation and obviates the need for repeat treatments. For reasonably fit patients with a better life expectancy, in whom quality of swallowing is an important determinant of quality of life, laser therapy should be attempted first. If the functional result is good (ability to eat a normal diet or most solid food), further treatment sessions should be arranged and adjuvant radiotherapy considered in an attempt to prolong the palliation interval as discussed in chapter 6. For patients with a mediocre result after laser therapy (ability to swallow semi-solids or liquids only), endoscopic intubation should be considered early during their follow-up. Lasting and good quality palliation of malignant dysphagia can best be achieved if laser therapy and endoscopic intubation are used in a complementary fashion.
A prospective comparison of Nd:YAG laser therapy and endoscopic intubation for the palliation of malignant dysphagia

Section B: Quality of Life Assessment

5.5 Introduction

It has been underscored in the foregoing discussion that the primary aim of any therapy for advanced oesophageal and gastric cardia cancers is to palliate symptoms, predominantly progressive dysphagia, with minimum morbidity and thus ultimately improve both the quality of remaining life and the dying process itself. From a purely ethical point of view, improvement in quality of life is more important than prolongation of survival, especially if the latter is achieved at the cost of disabling side-effects and prolonged hospitalisation. Unfortunately however, this issue has received little attention in published studies until now. The present study prospectively evaluated the effect of treatment on quality of life as part of the comparative evaluation of Nd:YAG laser therapy and endoscopic intubation for the palliation of malignant dysphagia.

5.6 Patients and Methods

5.6.1 Patients

Patient inclusion criteria and details have been described above in Section A, 5.2.2. Quality of life assessment was offered to all recruited patients. However, only 23 of 43 patients (male to female ratio, 12:11; mean age 74 years; age range 49-93 years) in the laser group and 15 of 30 patients (male to female ratio, 10:5; mean age 75 years; age range 58-86 years) in the intubation group agreed to partake in such an evaluation. Serial assessments until death could only be obtained from 13 patients (male to female ratio, 7:6; mean age 72 years; age range 49-86 years) in the former and 9 (male to female ratio, 5:4; mean age 73 years; age range 60-83 years) in the latter group.
5.6.2 Patient Assessment

Patients' quality of swallowing and quality of life were documented before endoscopic therapy and serially at various times during their follow-up until death by the author or Sister D Grigg-Rampton who alternated between the National Medical Laser Centre in London and Queen's Medical Centre in Nottingham. Grading of dysphagia and definition of treatment success have been described in Section A, 5.2.4.

Prospective evaluation of quality of life was performed using the Quality of Life Index (QLI) as described by Spitzer and colleagues (1981) and a Linear Analogue Self Assessment (LASA) as described by Priestman and Baum (1976). The QLI assessment consisted of a structured interview of the patient performed by the attending doctor or nurse lasting approximately five minutes which examined five specific items: activity, daily living, health, support and outlook. Each item is scored between 0 and 2 and the individual scores added together to obtain a single sum with minimum and maximum scores 0 and 10.

The LASA questionnaire consisted of twenty visual analogue scales (VAS) and was completed by the patient after necessary explanation and instruction. The VAS examined physical well-being and symptom control including dysphagia (nine items: pain, shortness of breath, tiredness, appetite, nausea, vomiting, constipation, diarrhoea, swallowing ability), psychological well-being (five items: anxiety/irritability, depression, difficulty sleeping, anger, concentration) and personal relationships and social interaction (five items: self care, relationship with partner/other people, ability to perform indoor activities, ability to perform outdoor activities, social life and recreation); the remaining VAS assessed the patient's subjective impression of his/her quality of life ("How would you rate your quality of life?). Each scale uses a 10 centimetre line with a word at each end denoting the poorest (zero point) and best extremes of a subjective response. The patient marked each scale at a point that best reflected his/her response to a specific question; the distance in centimetres of this mark from the zero point was the score of the item. The overall score was obtained by summing the individual scores. Each assessment using both instruments, focused on a patient's quality of life during the week preceding to the interview.
5.6.3 Statistics

The degree and significance of correlation between various measurements was calculated using Spearman's rank correlation method. Numerical differences between measurements were tested for statistical significance using the Wilcoxon signed rank and two-sample tests for non-parametric data and the unpaired t-test for parametric data. Statistical significance was set at the 5% level (p<0.05).

5.7 Results

5.7.1 Correlation Between Dysphagia and Quality of Life

Correlation coefficients between 86 paired scores of various measurements obtained from 38 patients at different times during their survival and their statistical significance are shown in Table 5.5. There was a strong correlation between the severity of dysphagia as measured by the dysphagia grade and quality of life as measured by the two instruments LASA and QLI - Figure 5.4. In addition, the LASA and QLI scores correlated strongly, indicating good agreement between a patient's subjective assessment of his/her quality of life and that of the attending doctor or nurse. The overall LASA score correlated strongly with the score of the individual VAS entitled "How would you rate your quality of life?".

5.7.2 Effect of Treatment on Dysphagia and Quality of Life

Dysphagia was palliated until death in all patients in the laser (n=13) and intubation (n=9) groups in whom serial assessments of dysphagia grade and quality of life were available; mean dysphagia grade fell from 2.9 (sd 0.6) before treatment to 1.2 (sd 0.8) after treatment (p<0.001) in the former group and from 3.2 (sd 0.7) to 1.8 (sd 0.7) (p<0.004) in the latter. QLI and LASA scores in the two groups are shown in Figure 5.5 and 5.6. There was no statistically significant difference in the pre-treatment, best post-treatment and last post-treatment scores between the laser and intubation groups. In both groups, the mean pre-treatment LASA and QLI scores were significantly worse than the corresponding mean best post-treatment scores and significantly better than the corresponding mean last post-treatment scores. Last scores were recorded after a mean follow-up of 19 weeks (sd 11 weeks) in the laser and 24 weeks
Table 5.5: Spearman correlation coefficients between 92 paired scores of various measurements obtained at different times during the survival of 40 patients with malignant dysphagia treated by laser therapy (n=25) or endoscopic intubation (n=15).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation Coefficient</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DG vs LASA</td>
<td>-0.51</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>DG vs QLI</td>
<td>-0.43</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>LASA vs QLI</td>
<td>0.678</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>LASA vs &quot;How do you rate your quality of life?&quot;</td>
<td>0.765</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

DG: dysphagia grade
Figure 5.4: Scatter diagrams of relation between (top) dysphagia grade and LASA and (bottom) dysphagia grade and QLI in 38 patients with malignant dysphagia palliated with laser therapy (n=23) or endoscopic intubation (n=15). 86 paired scores obtained at different times throughout patient survival have been plotted in each diagram. Negative correlation shown in both top and bottom figures is highly significant (p<0.0001) with Spearman coefficients of -0.49 and -0.43 respectively.
Figure 5.5: Mean (sd) QLI and LASA scores of 13 patients with malignant dysphagia palliated until death by laser therapy. Statistical testing performed using the Wilcoxon signed rank test.

QLI SCORE

5.8 (0.8) 7.1 (0.8) 4.4 (0.5)

p < 0.001

LASA SCORE

135 (17) 155 (15) 113 (24)

p < 0.001

Pre-Rx score  Best post-Rx score  Last post-Rx score
Figure 5.6: Mean (sd) QLI and LASA scores of 9 patients with malignant dysphagia palliated until death by endoscopic intubation. Statistical testing performed using the Wilcoxon signed rank test.

QLI SCORE

5.6 (0.5) 6.8 (0.4) 4.2 (0.4)

p<0.004

LASA SCORE

138 (12) 156 (12) 116 (10)

p<0.004

Pre-Rx score Best post-Rx score Last post-Rx score
(sd 10 weeks) in the intubation group; these follow-up times were not significantly different from the respective mean total survival times: laser 24 weeks (sd 12 weeks), intubation 28 weeks (sd 13 weeks).

5.8 Discussion

Traditionally, the success of any cancer treatment has been measured by assessing tumour response (changes in tumour volume) and/or patient survival rates. The problem with such an approach is that in the pursuit of improvements in these parameters, the quality of remaining life is often ignored. Interest in quality of life of cancer patients has developed only since the mid 1970s and reflects a changing attitude on the part of doctors and other health care personnel (Priestman and Baum 1976, Burge et al 1975, Hutchinson et al 1979). The majority of studies measuring quality of survival after cancer therapy have employed the Karnofsky and Zubrod scales (Karnofsky and Berchenal 1948, Zubrod et al 1960). These measure performance status, which correlates with tumour response and survival, but do not provide quantitative information about other important aspects of quality of life. In the present study two extensively evaluated instruments of quality of life measurement have been employed. The QLI developed by Spitzer is an interview category rating method that has proved reliable and valid in detailed assessments; however, it provides limited information (for example dysphagia is not specifically assessed in patients with oesophageal cancer) and only a single summation score is given to describe quality of life. Its main advantage is that it is quick and easy to complete and can be used repeatedly during patient follow-up. The responses yielded by LASA methods have proved both reliable and valid. They provide more detailed information than the QLI and their content can be varied slightly to assess specific items of interest, for example dysphagia in oesophageal cancer patients. The LASA method is time consuming and some patients in the present study found it difficult to use and required explanation and assistance during their initial attempts at completing the questionnaire. Concurrent validity of the two instruments was demonstrated in this study by the significant correlation between patient self-ratings (as measured by LASA) and physician estimates (as measured by QLI) of quality of life.

Only one half of the patients in the present study initially agreed to partake in quality of life assessment; of these, one third subsequently refused serial
measurements until death. This unwillingness of cancer patients to undergo quality of life assessment probably represents a psychological defence mechanism; patients with terminal illness often attempt to deny the inevitable progressive deterioration in their quality of life and are unprepared to submit to an "objective" test which may validate their worst fears. Simple explanation by the attending medical and nursing staff regarding the aims of quality of life assessment and a measurement index that is easy and quick to use may improve patient participation. To this end, an alternative would be to use a "single scale" LASA. In the present study, the score of the VAS entitled "How do you rate your quality of life?" correlated significantly with the overall LASA score ($r^2 = 0.59$) and could be used clinically if its validity as a measure of quality of life is proven by future assessments.

The current results show a highly significant correlation between quality of swallowing and quality of life as measured by the QLI and LASA validating the subjective impression of physicians and surgeons caring for patients with malignant dysphagia. Because the patient's subjective judgement of the endoscopic treatment was not specifically assessed in the present study, the question whether the benefits of treatment outweigh its physical and emotional discomfort cannot be answered directly. However, it can be inferred that benefits outweigh morbidity because treatment resulted in a significant initial improvement in quality of life as measured by QLI and LASA. Thus, therapeutic interventions aimed at achieving the maximum possible improvement in swallowing function, are justified for patients in good general condition for whom quality of swallowing is a more important determinant of overall quality of life than for those with more advanced disease.

The best post-treatment score recorded by patients in both the laser and intubation groups who were assessed serially until death, were significantly higher than the pre-treatment scores indicating an improvement in quality of life as a result of palliation of dysphagia by endoscopic therapy. The last post-treatment scores, recorded within 5 weeks of death, however, were significantly lower than the pre-treatment scores despite continued palliation of dysphagia. This probably can be accounted for by the decreasing importance of swallowing ability as a determinant of overall quality of life with
progression of the disease; patients with advanced malignant disease frequently suffer from anorexia and have no desire for solid food.

Only two other published studies have attempted to quantify the effect of treatment for carcinoma of the oesophagus and gastric cardia on quality of life. In a randomised comparison of Nd:YAG laser therapy alone and laser therapy followed by endoscopic intubation, Barr and colleagues (1990a) used the QLI and a LASA questionnaire very similar to the one employed in the present study. Their findings, which are in close agreement with those of the present study, demonstrate a significant correlation between dysphagia grade and QLI and LASA scores and also between the LASA and QLI scores. In addition, the mean best post-treatment score in both groups was significantly higher than the mean pre-treatment score; pre and post-treatment scores did not differ significantly between the two groups. In another study from Japan, patients who had undergone oesophageal resection at least one year previously and were free of recurrent disease participated in an assessment of quality of life using a category rated questionnaire (Sugimachi et al 1986). These authors concluded that quality of life in their patients was maintained and recommended surgical treatment for oesophageal carcinoma. Because this was a highly selected group, no such conclusion is valid and direct comparisons with the patients included in the present study are impossible.

In conclusion, it is apparent that the quality of swallowing is an important determinant of overall quality of life in patients with malignant dysphagia; however, its relative importance decreases with progression of the disease. Palliation of dysphagia with laser therapy or endoscopic intubation results in a similar significant initial improvement in quality of life. This improvement is only transient, with appreciable worsening of quality of life as the illness enters its final stages.
A prospective comparison of Nd:YAG laser therapy and endoscopic intubation for the palliation of malignant dysphagia

Section C: Cost Analysis

5.9 Introduction

The evaluation of new or existing treatments from the clinical and policy perspectives involves several steps, primarily the demonstration of efficacy and the assessment of efficiency or cost-effectiveness (Sinclair et al 1981). The latter considers both the effectiveness of a particular treatment or health care intervention as well as the resources required. Cost-effectiveness analysis assumes that the objective is to maximise the net health benefit for all patients in a target population under conditions of fixed resources; it is relevant for policy makers and administrators seeking to allocate scarce resources across competing uses. This type of economic analysis however, has a very limited role in the everyday practice of doctors caring for individual patients. From the perspective of the clinician making allocation decisions for his/her patients, the objective is solely to maximise the patients' health status and he/she may not be concerned about the constraint of a fixed amount of resources and the effect that use of scarce resources may have on other groups of patients. Although clinicians may not participate in the allocation of scarce resources in their hospital or health organisation, they must practise under the consequences of economic policies and decisions. Although most economic analyses are far too complex and incomprehensible to clinicians, it is important that they should have a basic understanding of costing studies and cost-effectiveness so that they can advise and help those who do have direct responsibility for financial planning. In the case of endoscopic therapy for the palliation of malignant dysphagia, none of the several studies comparing laser therapy and intubation published to date has attempted to perform an economic analysis of the two treatments. This study aims to fill this important gap in the literature, by estimating the relative lifetime cost of Nd:YAG laser therapy and endoscopic intubation using data from the prospective comparison of the two techniques presented in section A of this chapter and other published sources. The economic analysis has been
performed by Mr Mark J Sculpher of the Health Economics Group, Brunel University, Uxbridge and is presented here in a simplified from the perspective of the clinician.

5.10 Methods

The objective of the analysis was to estimate the additional cost or saving resulting from the use of Nd:YAG laser therapy as the primary treatment for the palliation malignant dysphagia compared to endoscopic intubation using plastic prostheses. The life-time cost of the major health service resources used by patients undergoing these two treatments were assessed. For the purposes of the analysis, the average survival of patients undergoing laser therapy and intubation was assumed to be equal based on the results presented in Section A. A cost model describing key clinical pathways for patients undergoing endoscopic palliation was defined and the probability of progression along each pathway gleaned from published studies. The use of resources associated with each pathway was estimated using data reported in Section A; the costing of these resources was based on data obtained from the financial records of University College Hospital or relevant suppliers.

5.10.1 Basic Cost Model

Depending upon which technique is chosen as the primary treatment, a patient will undergo a different profile of endoscopic procedures. For the purposes of the cost analysis, a decision tree showing each possible treatment option or combination of treatments and each possible outcome was constructed - Figure 5.7. At the first and only decision node in the tree, a choice is made between laser therapy and endoscopic intubation as the primary treatment. There is a risk that some patients will die as a result of treatment related complications; for the remaining patients, there is a possibility of early or late treatment failure. The definitions of early (initial) and late (long-term) success of treatment used in the cost model are the same as in Section A, 5.3.1. For patients treated initially with laser, early or late failure would lead to selection of either intubation or no further intervention ("tender loving care"); for those managed initially by intubation, if treatment fails and laser therapy is unavailable the only management option is "tender loving care". As shown in Figure 5.7, when laser therapy is chosen as the
Figure 5.7: Decision tree showing structure of model for costing laser therapy and intubation as palliative treatments for malignant dysphagia and the probability, patient traffic and cost for each pathway. Branch probabilities shown in parentheses.
primary treatment there are six possible outcome pathways (A to F); when endoscopic intubation is chosen, there are four possible pathways (G to J).

5.10.2 Resource Use

Health service resources are used whenever patients pass down any of the pathways shown in Figure 5.7. Resource use data were available on 42 of 43 patients in the laser and 27 of 30 patients in the intubation group of the comparative study presented in Section A of this chapter. Additionally, data on 26 patients with malignant dysphagia who received laser therapy (using an identical treatment protocol) as part of a different study performed in our unit (Sargeant et al 1992a), were also included in order to increase the power of the analysis. Patient traffic along each pathway is shown in Figure 5.7. In order to estimate life-time cost of treatment, four categories of resource use have been defined:

(i) Diagnostic resource use
Use of diagnostic resources as part of initial patient evaluation was assumed to be equal in both groups and was not therefore included in the cost analysis. Resource use after initial assessment includes the performance of a full blood count prior to every endoscopic procedure.

(ii) Endoscopic procedures
For patients whose primary treatment was laser therapy, possible procedures included diagnostic endoscopy (assessment), dilatation, laser therapy alone, dilatation plus laser therapy, dilatation plus laser therapy plus intubation and dilatation plus intubation. For patients treated initially by intubation, possible procedures included diagnostic endoscopy (assessment) and dilatation plus intubation.

(iii) In-patient hospital stay

(iv) Follow-up
It is likely that patients treated by laser or intubation receive a similar form and intensity of hospital follow-up, for example visits to an out-patient clinic. Given the assumption of equal patient survival, the expected hospital follow-up costs for the two treatments should also be equal and were therefore excluded from the analysis. In the base-case analysis, the resource use implications of any treatment complications were assumed to be fully
reflected in the trial data; the impact of this assumption was assessed by sensitivity analysis. In addition to hospital care, patients usually require further support in the community, especially in the terminal phase of their illness. In practice, this involves a mix of inputs from general practitioners, district and Macmillan nurses as well as friends and relatives and hospice care. Although the actual cost of community care is impossible to estimate as only few data are available, the important issue is whether there is any difference in this type of support received by patients palliated with laser therapy or intubation. In the base-case analysis it was assumed that no such difference exists and these costs were excluded; the implications of this assumption were explored using sensitivity analysis.

5.10.3 Valuing Resource Use

The mean health service cost of each of the pathways in Figure 5.7 was estimated employing mean resource use data derived from the patient data base. Resource use was valued using a set of unit costs based on supplier prices or derived from the accounts of University College Hospital relating to the financial year 1991-92. The unit costs of endoscopic procedures include the costs of staff, consumables such as gloves and tubes, drugs to induce and reverse conscious sedation and an allocation of hospital overheads. The cost of equipment such as the laser and endoscopes, calculated as an annual cost using a 6% discount rate and estimates of expected useful life and annual utilisation, was also included. In the case of the Nd:YAG laser, an annual utilisation of 620 patient-treatment sessions has been used, based on University College Hospital data; variation in this rate was explored using sensitivity analysis. The estimated duration of endoscopic procedures was based on clinical experience.

The cost of patients passing down each of the pathways of the cost model was estimated by multiplying the average resource use by the relevant unit costs. As indicated in Figure 5.7, none of the patients in the database passed down four of the pathways; the cost of each of these was estimated by adjusting the cost of similar pathways. For pathway C, the procedure cost is assumed to be equivalent to that of a late success with laser therapy and the in-patient care cost to be equivalent to that of a late failure with endoscopic intubation. For pathway I, the procedure cost is assumed to be equivalent to that of a late success with intubation and the in-patient care cost equivalent to that of an early failure with laser therapy managed by "tender loving care". As the
probability of procedure related death after laser therapy is taken as zero, the expected cost (pathway F) is not estimated; for deaths after intubation (pathway J), the expected cost is based on one intubation procedure plus one night stay in hospital.

To calculate the total expected cost of the two endoscopic treatments, the mean cost associated with each pathway was multiplied by its assigned probability and the products obtained added up. The probabilities $p_1 - p_8$ in Figure 5.7, were calculated by pooling the results of the present study (Section A) and six other studies comparing laser therapy and intubation for the palliation of malignant dysphagia published prior to April 1992 when this analysis was performed (Carter and Smith 1986, Buset et al 1987, Alderson and Wright 1990, Hahl et al 1991, Fuchs et al 1991, Carter et al 1992). It should be pointed out, that the present study (Section A) is the only one that provides data regarding the clinical management decisions taken as a consequence of early or late treatment failure and an estimate of the probability of late failure.

The expected cost of the two endoscopic treatments is to some extent influenced by patient survival; for laser treated patients in particular, the longer they survive the more procedures they are likely to require. As patient survival after laser therapy or intubation was assumed to equal in this analysis, the expected cost of laser palliation was adjusted accordingly on a proportional basis.

5.10.4 Sensitivity Analysis

Sensitivity analysis is used to assess whether changes in the assumptions and parameters used in a cost model alter the conclusions of an economic analysis. In the present study, sensitivity analysis was used to assess whether the derived cost estimates are applicable to hospitals with different patterns of clinical practice from those at University College Hospital. As alternatives to the base-case analysis, resource sparing and resource intensive analyses were also performed.

A resource sparing analysis re-estimates the cost differential between the two treatments assuming rather lower levels of resource use. Instead of using the mean levels of resource use related to each pathway as calculated from our
database, the lower 95% confidence intervals were incorporated into the model.

A resource intensive analysis assumes that resource use is somewhat higher than in the base-case analysis. Three parameters were consequently altered. Firstly, instead of mean estimates of resource use, the upper 95% confidence intervals were used. Secondly, instead of assuming that the cost of caring for patients in the community during the terminal phase of their illness is zero, it was assumed that patients spent the whole of their remaining survival after their last endoscopic treatment in a hospice. Thirdly, instead of assuming that the costs of any complications of therapy are already reflected in the resource use estimates in the study data (for example in terms of additional endoscopic procedures or in-patient stay) a specific analysis of the costs of complications was performed. This analysis involved pooling the probabilities of complications related to laser therapy or endoscopic intubation from the present and six other comparative studies (Carter and Smith 1986, Buset et al 1987, Alderson and Wright 1990, Hahl et al 1991, Fuchs et al 1991, Carter et al 1992) and providing a cost for each complication with an incidence equal to or greater than 1%, based on clinical experience of the typical resource use implications. Thus an expected total cost of treatment complications was estimated.

5.11 Results

The unit cost estimates for each type of endoscopic procedure are detailed in Table 5.6. Other key unit costs include overnight stay in hospital at £83 (based on University College Hospital data) and a daily accommodation rate of £210 in a hospice (Eden Hall Hospice, London); the latter cost was used in the sensitivity analysis only. Table 5.7 provides details of the number of endoscopic procedures performed according to primary treatment and pathway.

Table 5.8 shows the probability of patient passage along each of the pathways and the associated mean procedure, in-patient and total costs for the base-case analysis. The total cost estimates of each pathway are also shown in Figure 5.7.
Table 5.6: Unit cost estimates of procedures used for endoscopic palliation of dysphagia.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Staff</th>
<th>Consumables</th>
<th>Equipment</th>
<th>Drugs</th>
<th>Tests</th>
<th>Overheads</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>£19</td>
<td>£1</td>
<td>£3</td>
<td>£13</td>
<td>-</td>
<td>£18</td>
<td>£54</td>
</tr>
<tr>
<td>Laser</td>
<td>£56</td>
<td>£1</td>
<td>£28</td>
<td>£13</td>
<td>-</td>
<td>£18</td>
<td>£116(^a)</td>
</tr>
<tr>
<td>Dilatation</td>
<td>£25</td>
<td>£1</td>
<td>£6</td>
<td>£13</td>
<td>-</td>
<td>£18</td>
<td>£63</td>
</tr>
<tr>
<td>Dilatation plus laser</td>
<td>£75</td>
<td>£1</td>
<td>£34</td>
<td>£13</td>
<td>-</td>
<td>£18</td>
<td>£141(^a)</td>
</tr>
<tr>
<td>Dilatation plus intubation</td>
<td>£75</td>
<td>£33(^b)</td>
<td>£6</td>
<td>£13</td>
<td>£69(^c)</td>
<td>£18</td>
<td>£214</td>
</tr>
<tr>
<td>Dilatation plus laser plus intubation</td>
<td>£93</td>
<td>£33(^b)</td>
<td>£34</td>
<td>£13</td>
<td>£69(^c)</td>
<td>£18</td>
<td>£260(^a)</td>
</tr>
</tbody>
</table>

\(^a\): Cost of £57 for laser fibre added per patient (one fibre irrespective of number of procedures)

\(^b\): Includes cost of Celestin tube

\(^c\): Barium swallow
Table 5.7: Patient traffic and number of procedures performed according to pathway.

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>NUMBER OF PATIENTS</th>
<th>NUMBER OF PROCEDURES Mean</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser: late success (A)</td>
<td>42</td>
<td>5.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Laser: late failure, tube (B)</td>
<td>18</td>
<td>8.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Laser: late failure, TLC (C)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laser: early failure, tube (D)</td>
<td>4</td>
<td>5.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Laser: early failure, TLC (E)</td>
<td>4</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Laser: procedure related death (F)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intubation: late success (G)</td>
<td>24</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Intubation: late failure, TLC (H)</td>
<td>3</td>
<td>2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Intubation: early failure, TLC (I)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intubation: procedure related death (J)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 5.8: Probability of patient traffic and estimated cost per patient for each pathway for the base-case analysis.

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>PROBABILITY</th>
<th>PROCEDURE COST</th>
<th>IN-PATIENT CARE COST</th>
<th>TOTAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>LASER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.46</td>
<td>£701</td>
<td>£1072</td>
<td>£1773</td>
</tr>
<tr>
<td>B</td>
<td>0.23</td>
<td>£1067</td>
<td>£1494</td>
<td>£2561</td>
</tr>
<tr>
<td>C</td>
<td>0.05</td>
<td>£701</td>
<td>£1328</td>
<td>£2029</td>
</tr>
<tr>
<td>D</td>
<td>0.18</td>
<td>£634</td>
<td>£2407</td>
<td>£3041</td>
</tr>
<tr>
<td>E</td>
<td>0.08</td>
<td>£398</td>
<td>£249</td>
<td>£647</td>
</tr>
<tr>
<td>F</td>
<td>0.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INTUBATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>0.81</td>
<td>£247</td>
<td>£869</td>
<td>£1116</td>
</tr>
<tr>
<td>H</td>
<td>0.09</td>
<td>£228</td>
<td>£1328</td>
<td>£1616</td>
</tr>
<tr>
<td>I</td>
<td>0.06</td>
<td>£247</td>
<td>£249</td>
<td>£496</td>
</tr>
<tr>
<td>J</td>
<td>0.04</td>
<td>£215</td>
<td>£83</td>
<td>£298</td>
</tr>
</tbody>
</table>
Table 5.9 details the mean total expected cost of the two endoscopic treatments for the base-case analysis and average patient survival. In the case of laser therapy, an adjusted cost has been calculated assuming that survival is equal to that of patients undergoing intubation. For the base-case analysis the adjusted mean life-time cost of laser therapy is £710 more per patient than that of intubation. Table 5.9 also shows the cost estimates from the resource sparing and intensive analyses. The assumptions underlying the cost estimates of procedure related complications are detailed in Table 5.10. Although these alternative analyses reduce the excess relative life-time cost of laser therapy, it still remains dearer than endoscopic intubation by £153 - £562.

5.12 Discussion

The present analysis indicates that palliation of malignant dysphagia with Nd:YAG laser therapy will cost between £153-£710 more per patient than endoscopic intubation. An important issue to be considered is whether these results can be generalised, as a number of important parameters in the model may vary from centre to centre.

The first of these parameters is the length of in-patient stay required for endoscopic therapy. It is possible that in other centres more procedures may be performed on a day-case basis than at University College Hospital. If neither form of endoscopic therapy required any in-patient care, intubation would lose its cost advantage for the resource intensive analysis. Additionally if more laser than intubation procedures could be performed on a day-case basis, intubation would lose its cost advantage both for the base-case and alternative analyses. Although these scenarios are possible, the fact that laser therapy is more likely to be carried out in specialist centres rather than in local hospitals creates a need for overnight hospital stay for some patients who have to travel long distances. The cost of hospital stay may also vary and the £83 per night used in this analysis may be lower than in other centres. Given the longer in-hospital stay of laser treated patients, any increase in this unit cost would augment the cost advantage of intubation.

The second parameter that may vary between centres is the annual utilisation of the laser equipment. If utilisation is high, there is a greater number of
Table 5.9: Survival and total expected cost per patient for the base-case and sensitivity analysis (resource sparing and intensive).

<table>
<thead>
<tr>
<th></th>
<th>BASE-CASE</th>
<th>RESOURCE SPARING</th>
<th>RESOURCE INTENSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LASER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure cost</td>
<td>£751</td>
<td>£599</td>
<td>£991</td>
</tr>
<tr>
<td>In-patient care cost</td>
<td>£1353</td>
<td>£834</td>
<td>£1879</td>
</tr>
<tr>
<td>Community support cost</td>
<td>£0</td>
<td>£0</td>
<td>£866</td>
</tr>
<tr>
<td>Total cost</td>
<td>£2104</td>
<td>£1433</td>
<td>£3736</td>
</tr>
<tr>
<td>Patient survival (days)</td>
<td>161</td>
<td>161</td>
<td>161</td>
</tr>
<tr>
<td>Adjusted total cost*</td>
<td>£1802</td>
<td>£1227</td>
<td>£3202</td>
</tr>
<tr>
<td><strong>INTUBATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure cost</td>
<td>£249</td>
<td>£211</td>
<td>£398</td>
</tr>
<tr>
<td>In-patient care cost</td>
<td>£843</td>
<td>£454</td>
<td>£1237</td>
</tr>
<tr>
<td>Community support cost</td>
<td>£0</td>
<td>£0</td>
<td>£1414</td>
</tr>
<tr>
<td>Total cost</td>
<td>£1092</td>
<td>£665</td>
<td>£3049</td>
</tr>
<tr>
<td>Patient survival (days)</td>
<td>138</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td>Adjusted laser minus intubation total cost</td>
<td>£710</td>
<td>£562</td>
<td>£153</td>
</tr>
</tbody>
</table>

* Adjusted to a level consistent with survival following intubation
Table 5.10: Estimated costs of procedure related complications used in resource intensive analysis.

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>PROBABILITY PER PROCEDURE</th>
<th>RESOURCE IMPLICATIONS</th>
<th>EXPECTED COST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LASER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>1.6%</td>
<td>Placement of cuffed tube</td>
<td>£8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOTAL: £8</td>
<td></td>
</tr>
<tr>
<td>INTUBATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>7.7%</td>
<td>Barium swallow, antibiotics, extra hospitalisation</td>
<td>£46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>3%</td>
<td>Two units of blood</td>
<td>£3</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1.8%</td>
<td>Antibiotics, 3 extra nights in hospital</td>
<td>£6</td>
</tr>
<tr>
<td>Tube migration</td>
<td>13%</td>
<td>New tube</td>
<td>£28</td>
</tr>
<tr>
<td>Food impaction</td>
<td>6%</td>
<td>Endoscopy to clear tube</td>
<td>£3</td>
</tr>
<tr>
<td>Peptic oesophagitis</td>
<td>1%</td>
<td>Omeprazole</td>
<td>£1</td>
</tr>
<tr>
<td>Tumour overgrowth</td>
<td>2%</td>
<td>New tube</td>
<td>£4</td>
</tr>
<tr>
<td>Tube dislocation</td>
<td>2%</td>
<td>New tube</td>
<td>£4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOTAL: £95</td>
<td></td>
</tr>
</tbody>
</table>

* Cost weighted by probability of complication
treatment sessions over which to divide the capital and maintenance laser costs. It is unlikely however, that annual utilisation would reach sufficiently high levels to remove the cost advantage of intubation. For example, if annual utilisation were to increase from 620 in this analysis to 2000 treatment sessions as a result of greater multi-speciality use of the laser, the expected cost differences would fall by only £58 - £91.

The third parameter that may vary is the cost of a procedure related death after intubation, which in the present analysis is assumed to be equivalent to one intubation procedure plus one night in hospital. In practice it may be much higher especially if a patient requires intensive care, reducing the cost advantage of intubation over laser therapy. However, based on a 4% probability of mortality after intubation, the cost would need to be very high amounting to £17,750 in the base-case analysis and £14,050 and £3,825 in the resource sparing and resource intensive analysis respectively, in order to fully cancel out this advantage. It is unlikely therefore, that this parameter could have significantly influenced the conclusions of the analysis.

The fourth parameter that may vary between centres is the level of operator expertise. In general, lasers are only available in specialist centres treating large numbers of patients. Endoscopic intubation on the other hand, may be the only available option in small units treating far fewer patients and as a consequence, the complication rate and hence the cost of treatment is likely to be higher.

The final parameter in the model that may vary is the type and hence cost of the prosthesis used. For example, self expanding metal stents cost £500-£700 compared to £32 for a standard plastic prosthesis of the type used in the present study (Section A). Use of metal stents would remove most of the cost advantage of intubation in the base-case analysis and produce a cost advantage for the laser in the sensitivity analysis provided that the complication rate and need for hospitalisation are the same as with plastic prostheses.

Prolongation of the dysphagia free interval after laser treatment by adjuvant radiotherapy (see Chapter 2, 2.4.1 and Chapter 6) and hence fewer treatments during follow-up, may, depending on the cost of radiotherapy, result in a reduction in the overall treatment cost. In a recent pilot study from our unit
for example, day-case brachytherapy reduced the number of laser procedures by about half (Spencer et al 1994). Given a unit cost of day-case brachytherapy at University College Hospital of £380, it can be calculated that this would diminish the cost advantage of intubation to about £188 in the base-case analysis and £432 in the resource sparing analysis and would lead to a cost advantage for the laser of £697 in the resource intensive analysis. The cost of external beam radiotherapy as an adjuvant to laser treatment (see Chapter 6) has not been assessed but may well be higher than that of brachytherapy given its longer duration and frequent need for hospitalisation during treatment.

Although the results of the present analysis indicate that, under most assumptions, palliation of dysphagia with laser therapy is likely to cost more than with endoscopic intubation, it cannot be assumed that intubation is the more cost-effective form of treatment. As pointed out in the introduction, cost-effectiveness depends both on the cost and clinical outcome associated with the two treatments. Given that survival of patients with malignant dysphagia is limited and that statistically it is no different with laser therapy or intubation, the key outcome is their impact on quality of life. None of the published studies, including the investigation reported in Section B, comparing quality of life after laser therapy or intubation has detected a statistically significant difference but it should be noted that the number of patients evaluated was small.

To estimate the relative cost-effectiveness of laser therapy and intubation, further research is necessary to assess the value that patients attach both to the process and the outcome of the two treatments. If these values are measured on a 0 to 1 scale where 0 represents death and 1 good health (Torrance 1986), they can be used to estimate the quality-adjusted life years (QALYs) generated by the two treatments (Loomes and McKenzie 1989). If laser palliation is to prove cost-effective, it needs to generate sufficiently more QALYs than intubation to justify its additional cost. It has been suggested in the context of the Canadian health care system, that if a new intervention can generate more QALYs than conventional therapy at an incremental cost of less than Canadian $20,000 (approximately £10,500) per QALY, its cost-effectiveness would justify clinical use (Laupacis et al 1992). If this threshold were to used in the UK, the results of the present analysis suggest that the process and outcome of laser therapy would need to be valued by patients at
least 18% more highly than those of intubation in the base-case analysis and at least 14% and 3% more highly in the resource sparing and intensive analysis respectively. Further studies are required to test whether patients do indeed value the outcome of laser therapy more highly than that of intubation and if they do, whether the above cost-effectiveness thresholds are exceeded.
Nd:YAG laser therapy plus adjuvant external beam radiotherapy for the palliation of malignant dysphagia

6.1 Introduction

It has been underscored in previous chapters, that the necessity for repeat treatments at intervals of 4 to 6 weeks in order to provide continued palliation of malignant dysphagia constitutes a significant drawback of Nd:YAG laser therapy. Although such treatment is reasonably well tolerated and can usually be performed on an out-patient basis, it can prove a burden for elderly, terminally ill patients with a limited life expectancy. Radiotherapy which has the potential to treat the whole of the tumour and the regional lymph nodes, may prolong the interval between laser procedures by retarding intraluminal tumour regrowth and prevent or delay extrinsic compression by shrinking extraluminal tumour. Preliminary information published prior to the initiation of the present study indicated that adjuvant brachytherapy with or without external beam radiotherapy may prolong the "dysphagia free interval" after laser therapy (Bader et al 1986). In addition, it is possible that radiotherapy may also confer a survival advantage when given in combination with laser therapy but there is a paucity of information regarding this matter in the literature. The present pilot study of external beam radiotherapy used as an adjuvant to laser palliation for malignant dysphagia, was initiated to address some of these issues particularly the possibility of reducing the need for follow-up laser treatments.

6.2 Patients and Methods

6.2.1 Study Design and Objectives

Consecutive patients referred to University College Hospital during the period September 1988 to February 1989 for laser palliation of malignant dysphagia were prospectively assessed for recruitment into the study. All patients were informed about the nature of the study. Formal ethical committee approval was not considered necessary as all patients received
active treatment with well established modalities. The aims of this investigation were to establish an appropriate dose of external beam radiotherapy to be used an adjuvant to Nd:YAG laser therapy and to evaluate this combination treatment for malignant dysphagia in terms of long-term efficacy, need for repeat laser treatments and survival. The outcome of these patients was compared retrospectively with that of a similar group treated by laser therapy alone as part of the prospective study reported in chapter 5, fully recognising that comparisons between non-randomised groups are subject to bias.

6.2.2 Study Protocol and Patients

Only patients with predominantly exophytic (intraluminal) tumours of the thoracic oesophagus and gastric cardia which are suitable for laser therapy were eligible for inclusion. Patients with extrinsic oesophageal compression and fistulating tumours were excluded as were patients who had been previously treated with radiotherapy. After completion of the initial laser course, all patients with a good technical and functional result who were at least able to swallow fluids, were assessed by a Consultant Radiotherapist (Dr J.S Tobias) and if considered suitable for external beam radiotherapy were included in the trial. The dose and fractionation of irradiation was decided according to each patient's clinical and functional status.

All 22 patients recruited to the study were considered unsuitable for surgery. Five patients had documented metastases, five locally advanced tumours on computed tomography and three unresectable tumours at laparotomy. The remaining nine patients were not considered for surgery because of high anaesthetic risk (marked cachexia, age and comorbid conditions). Patient and tumour details are shown in Table 6.1.

6.2.3 Treatment Techniques

The technique of endoscopic laser therapy has been described in detail in chapter 5, 5.2.3. All treatments were performed by the author, Professor S G Bown or Dr I R Sargeant.

All patients were irradiated using supervoltage teletherapy (cobalt 60) after completion of initial laser therapy. The target volume was determined by the length of the tumour with a 5cm margin at its upper and lower borders and a
Table 6.1: Patient and tumour details.

<table>
<thead>
<tr>
<th>Patient Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males : Females</td>
<td>15 : 7</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>67 (46-85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for Laser Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>5</td>
</tr>
<tr>
<td>Advanced local disease</td>
<td>8</td>
</tr>
<tr>
<td>High surgical risk</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC : ANC</td>
<td>6 : 16</td>
</tr>
<tr>
<td>TO : Cardia : Anastomotic</td>
<td>6 : 16</td>
</tr>
<tr>
<td>Mean tumour length (range), cm</td>
<td>7 (3-13)</td>
</tr>
</tbody>
</table>

SCC: Squamous Cell Carcinoma; ANC: Adenocarcinoma
TO: Thoracic oesophagus
3cm margin circumferentially. Radiation was delivered by opposed anterior and posterior fields. In the early part of the study, all patients were treated in the Radiotherapy Department at University College Hospital; subsequently, all outside referrals received radiotherapy at their local hospitals. The dose and fractionation of radiotherapy (30Gy in 10 fractions or 40Gy in 20 fractions) was decided after the initial clinical assessment of the patient. An interim analysis of the outcome of the first ten recruited patients, revealed that all those treated with 40Gy experienced significant morbidity and a marked deterioration in their general condition whereas patients receiving 30Gy tolerated treatment well. For the remainder of the study therefore, only the lower dose was used.

6.2.4 Patient Follow-up and Assessment

Patients were endoscoped electively 3 to 4 weeks after completion of radiotherapy to assess the technical result of combination therapy. During the "check" endoscopy, laser treatment of residual viable tumour or stricture dilatation was performed as necessary. Subsequently, endoscopic assessment and further treatment was performed only if indicated because of recurrent symptoms. When clinically appropriate, patients with persistent dysphagia after combination therapy underwent intubation using Celestin prostheses.

Following initial treatment, patients were advised to consume an unrestricted diet of their choice. Quality of swallowing was documented in detail serially from the time of inclusion into the trial until death by the attending physicians or an experienced research nurse attached to the unit. Follow-up was performed by hospital attendance or by telephone. All patients or their relatives or carers, were contacted monthly, or at more frequent intervals if their condition was changing, to assess the necessity for further treatment. The severity of dysphagia was assessed by reviewing the consistency of a patient's diet since the previous evaluation and graded from 0 to 4 on a five point scale as described in chapter 5, 5.2.4. Thus, individual dysphagia profiles over time were constructed and the mean quality of swallowing calculated from the area under the curve.

The definitions of treatment success are the same as those employed in the comparative study of laser therapy and intubation - see chapter 5, 5.3.1 Laser treatment plus adjuvant radiotherapy was considered functionally successful if a patient's dysphagia improved by at least one grade on the dysphagia scale.
within 2-3 weeks of treatment completion. Maintenance of improved swallowing until death, with or without repeat laser therapy or dilatation, was defined as a long-term success.

6.2.5 Statistics

As emphasised above, comparisons between non-randomised groups are subject to bias. In the present study, statistical analyses were performed only for the purpose of demonstrating apparent differences and indicating possible treatment effects and should be interpreted with caution as they can be misleading. The $\chi^2$ test with Yate's correction and the Wilcoxon signed rank and two sample test were used. Survival distributions were calculated using the life table (Kaplan-Meier) method and tested for disparity by log rank analysis. Significance was set at the 5% level ($p<0.05$).

6.3 Results

6.3.1. Efficacy, Treatment Requirements and Indicators of Outcome

Table 6.2 compares the long-term functional success of laser treatment plus adjuvant radiotherapy with that of a similar group of historical controls receiving laser therapy alone as part of the prospective study reported in chapter 5. All patients except one who was still alive at the time of writing, have been followed-up until death. The overall long-term success rate was similar in both groups and higher in patients with thoracic oesophageal than gastric cardia tumours; in the combination therapy group the latter difference was not statistically significant probably as a result of the small number of patients involved. The success rate of treatment was significantly greater in patients irradiated with 30Gy rather than 40Gy; however, all tumours in the latter subgroup were adenocarcinomas compared to ten out of sixteen in the former. Five of seven treatment failures in the combination therapy group were initial failures and three of these patients were only able to swallow liquids prior to radiotherapy. Two of the initial failures were technical, that is significant residual tumour was present at "check" endoscopy and three were functional, that is no improvement in swallowing function despite adequate tumour recanalisation. One of the initial failures underwent endoscopic intubation and was able to swallow semi-solids until his death a few weeks later; and remaining patients received terminal care as they were considered unfit for any further therapy. The two late failures (one squamous cell
Table 6.2: Long-term palliation of dysphagia with laser therapy plus radiotherapy or laser therapy alone.

<table>
<thead>
<tr>
<th></th>
<th>LASER + RT</th>
<th>LASER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>15/22 (68%)</td>
<td>27/43 (63%)</td>
</tr>
<tr>
<td>SCC</td>
<td>5/6 (83%)</td>
<td>16/21 (77%)</td>
</tr>
<tr>
<td>ANC</td>
<td>10/16 (63%)</td>
<td>11/22 (50%)</td>
</tr>
<tr>
<td>RT 30Gy</td>
<td>13/16 (81%)</td>
<td></td>
</tr>
<tr>
<td>RT 40Gy</td>
<td>2/6 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

RT: External Beam Radiotherapy
SCC: Squamous Cell Carcinoma; ANC: Adenocarcinoma; *: p<0.01
carcinoma and one adenocarcinoma) occurred as a result of extrinsic tumour compression at 5 and 14 months respectively after the start of treatment. Both patients underwent endoscopic intubation and were successfully palliated until their death several months later.

In addition to radiotherapy dose, the following variables were tested statistically as possible indicators of successful outcome after combination therapy: tumour site (thoracic oesophagus vs gastroesophageal junction), patient age less than 65 years, tumour length less than 5cm, absence of lymph node or distant metastases, dysphagia grade ≤2 (able to swallow at least semi-solid food) after laser therapy and prior to radiotherapy. Only the latter two proved to have significant prognostic value; multivariate analysis of treatment outcome using these variables was not performed.

Treatment requirements and time intervals between procedures in patients palliated until death are shown in Table 6.3. After completion of combination therapy, 8 patients required further endoscopic treatment (including treatment at the time of "check" endoscopy): three patients had dilatation alone for fibrous oesophageal strictures, three laser therapy alone and two dilatation plus laser therapy. Importantly, the time interval between treatments was significantly longer in the combination therapy group than in historical laser controls (median 12.6 vs 4.3 weeks, p<0.01). Although the treatment interval after combination treatment was longer in patients with squamous tumours than adenocarcinomas (median 23 vs 12 weeks), the difference was not statistically significant possibly due to a type II error as the number of squamous cell carcinomas was very small.

6.3.2 Quality of Palliation

Figure 6.1 shows bar chart plots of mean dysphagia grade before and after treatment with laser plus radiotherapy. In those palliated successfully, laser therapy resulted in a significant initial reduction in dysphagia grade with a further numerical reduction noted after completion of radiotherapy; patients were on average able to swallow most solids and the improvement was maintained until death. In the treatment failures, laser therapy did not result in a significant initial improvement in swallowing, which subsequently worsened further after radiotherapy.
Table 6.3: Treatment requirements in patients palliated until death (One patient in Laser + RT group still alive at 170 weeks). Endoscopic treatments refers to laser therapy and/or dilatation performed during a patient's lifetime, including treatments at "check" endoscopy in the combination therapy group.

<table>
<thead>
<tr>
<th></th>
<th>LASER + RT (n=15)</th>
<th>LASER (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopies to complete initial treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (sd)</td>
<td>2.5 (1.4)</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td>median (range)</td>
<td>2 (1-6)</td>
<td>2 (2-5)</td>
</tr>
<tr>
<td><strong>Endoscopic treatments during follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (sd)</td>
<td>2.5 (2.4)</td>
<td>2.4 (1.9)</td>
</tr>
<tr>
<td>median</td>
<td>2 (0-8)</td>
<td>4 (2-9)</td>
</tr>
<tr>
<td><strong>Time between follow-up treatments, weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (sd)</td>
<td>35 (46) *</td>
<td>7.2 (9.3) *</td>
</tr>
<tr>
<td>median (range)</td>
<td>12.6 (3-170)</td>
<td>4.3 (2-49)</td>
</tr>
</tbody>
</table>

RT: External Beam Radiotherapy; * p<0.01
Figure 6.1: Bar chart plots of mean dysphagia grade (error bars represent one sd) of patients treated by laser therapy plus external beam radiotherapy (L: Laser therapy; RT: External beam radiotherapy; Rx: Treatment).

Failures (n=7)

Successes (n=15)

*d = p<0.001 compared to pre-Rx

<table>
<thead>
<tr>
<th></th>
<th>Pre-Rx</th>
<th>Post-L+RT(long-term)</th>
<th>Post-L+RT(initial)</th>
<th>Post-L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.3.3 Survival

When the survival of patients treated by combination therapy was analysed, it proved better than expected from our previous experience with similar patients managed by laser therapy or intubation alone. It was therefore decided to analyse the data in detail and perform a statistical comparison with the group of historical laser controls, despite the obvious methodological limitations of such an approach. Survival data are shown in Table 6.4. As can be seen, the significantly greater overall survival of patients receiving combination therapy was accounted for by prolongation of survival in the group treated with 30Gy of radiation. Survival distributions (life table method) for patients receiving combination therapy and laser treatment alone are shown in Figure 6.2. The overall survival of the group treated with 30Gy was significantly greater than that of patients managed by laser alone; the survival curves of patients treated with 30Gy and 40Gy were not significantly disparate but a type II error cannot be excluded given the small number of patients involved. One year survival rate in the 30Gy, 40Gy and laser only groups was 38%, 16% and 12% respectively. One patient in the 30Gy group is still alive at the time of writing. She is a 78 year old with a 3cm squamous cell carcinoma of the upper thoracic oesophagus who has remained well with entirely normal swallowing for 170 weeks after combination therapy.

6.3.4 Treatment Morbidity and Hospitalisation

Toleration of radiotherapy was assessed subjectively by questioning the patient regarding possible symptoms during treatment, for example nausea, vomiting, fatigue, malaise, chest pain, odynophagia or shortness of breath. Treatment was deemed to be well tolerated if a patient experienced no or mild symptoms which were easily controlled with simple medication and poorly tolerated if the side-effects resulted in a deterioration in the general condition and performance status of the patient or necessitated hospitalisation. Only two of sixteen patients treated with a dose of 30Gy reported significant symptoms. In contrast, radiotherapy was poorly tolerated in half of the patients treated with 40Gy. Five of the six patients with significant radiotherapy side effects died fairly quickly after treatment without any improvement in swallowing. None of the patients developed an oesophago-respiratory fistula or tumour haemorrhage as a result of radiotherapy but fibrous oesophageal strictures were identified in three patients. Two of these
Table 6.4: Survival data for patients treated by laser therapy plus external beam radiotherapy (30 or 40Gy) or laser therapy alone (One patient in Laser+30Gy group still alive at 170 weeks).

<table>
<thead>
<tr>
<th></th>
<th>LASER + 30Gy (n=16)</th>
<th>LASER + 40Gy (n=6)</th>
<th>LASER (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (sd), weeks</td>
<td>52 (43) *</td>
<td>29 (27)</td>
<td>27 (24) *</td>
</tr>
<tr>
<td>Median (range), weeks</td>
<td>44 (8-170)</td>
<td>19 (7-73)</td>
<td>22 (4-116)</td>
</tr>
</tbody>
</table>

* p<0.02)
Figure 6.2: Survival curves (life table method) for patients treated by laser therapy plus external beam radiotherapy (RT, 30Gy or 40Gy) and historical laser only controls. Laser+30Gy vs Laser only: p<0.05 and Laser+30Gy vs Laser+40Gy: not significant by log rank analysis.
required only a single dilatation whereas the other patient needed repeated dilatations at intervals of about 9 weeks for one year. There were no procedure related deaths.

Whenever feasible radiotherapy was given on an out-patient basis. Median (range) hospitalisation time (excluding admissions for terminal care) was 21 (8-35) days for the laser plus radiotherapy group and 14 (4-30) days for the historical group treated by laser alone.

6.4 Discussion

Logically, the results of palliative management for malignant dysphagia could be optimised by the use of different therapies in combination, exploiting their individual advantages and minimising their side-effects. Laser therapy plus radiotherapy is an attractive, conceptually complementary combination. The former provides rapid, good quality palliation of dysphagia with very low morbidity but repeated procedures are required to maintain the symptomatic improvement long-term. The latter, has the potential to provide sustained relief of dysphagia after laser recanalisation and to prolong the interval between follow-up procedures by retarding the regrowth of intraluminal tumour. In this respect intracavitary radiotherapy (brachytherapy) may be preferable to external irradiation, as very high local doses can be delivered with relative sparing of adjacent normal tissues thus minimising morbidity. In addition, brachytherapy can be delivered as a single treatment, usually on a day-case basis, in contrast to external beam radiotherapy which is fractionated over several weeks. External beam radiotherapy was used in the present study as at the time there were no facilities for performing brachytherapy at University College Hospital, but also because this form of radiotherapy is widely available and would have enabled patients to receive treatment at their local hospitals after completion of initial laser therapy. The major objectives of the study were to determine the appropriate dose of adjuvant radiotherapy and to assess whether the theoretical attributes of this treatment combination translated into meaningful clinical benefits.

As radiotherapy was given with palliative intent, patient tolerance of such treatment is crucially important. Irradiation with 40Gy was associated with significant morbidity and rapid deterioration in functional status whereas a dose of 30Gy was well tolerated. Our experience is in agreement with
published information which indicates that 30Gy of radiation in ten fractions is better tolerated by patients with marked dysphagia and poor general condition than a higher dose (Wara et al 1976, Caspers et al 1988, Oliver et al 1990). The long-term success of combination therapy was greater for tumours of the thoracic oesophagus than of the gastric cardia as in the group of historical laser controls. The ability to swallow at least a semi-solid diet prior to commencing radiotherapy proved a significant prognostic indicator of successful palliation in the present study in agreement with the findings of Caspers and colleagues (1988).

The current results suggest that adjuvant radiotherapy is of value in reducing the need for repeated laser treatments. Nearly half of the patients palliated long-term did not require additional endoscopic treatment after initial combination therapy. Compared to historical laser controls, the median interval between procedures was three times longer in the combination therapy group and the median total number of procedures reduced by half, despite the longer duration follow-up. These benefits were greater for patients with squamous cell carcinomas. In addition, adjuvant radiotherapy at a dose of 30Gy provided an apparent doubling of survival compared to historical laser controls. Although the two groups were very similar, patients undergoing radiotherapy were to some extent selected; as a consequence, the results of such comparisons should be interpreted with caution as they are subject to bias and require confirmation by randomised studies.

A major concern with the use of external beam radiotherapy in combination with laser treatment, both of which are capable of inducing tumour necrosis and fibrosis, is that it may result in an unacceptable rate of complications such as fistulation or the development of fibrous strictures. No fistulae developed in the present series and oesophageal strictures were seen in 20% of patients but were easily managed by dilatation. As the treatment was purely palliative, duration of hospital stay is important given the limited patient survival. The majority of patients in the present study received radiotherapy as in-patients mainly because of logistic reasons, for example long travelling distances or poor general condition and as a result their cumulative hospital stay was greater than that of historical laser controls (median 21 vs 14 days). However, given the longer survival of patients who received combination therapy, the proportion of total survival spent in hospital was less than 10% in both groups.
The published experience with Nd:YAG laser therapy plus radiotherapy for the palliation of malignant dysphagia is rather limited and the majority of studies have employed brachytherapy. Bader and colleagues (1986) treated 48 patients with inoperable oesophageal and gastric cardia carcinomas with laser recanalisation plus two to six sessions (7Gy each) of $^{192}$Ir brachytherapy; patients with squamous cell carcinomas also received 50-60Gy of external beam irradiation. 37 patients (77%) derived long-term palliation of dysphagia while the rest required further laser treatment, dilatation or intubation for recurrent symptoms. The overall follow-up period was not stated and the mean survival of 16 patients who died by the time of publication was 6 months. Fatal treatment complications occurred in 2 patients (4%). In a prospective pilot study, Renwick and coworkers (1992) treated 21 patients with advanced oesophageal and gastric cardia cancers with a single session of laser therapy plus 15Gy of brachytherapy. All but two patients (10%), who died in hospital, tolerated the procedure well and were able to eat a virtually normal diet until death (average 20 weeks after treatment). However, five patients (26%) required oesophageal dilatation for recurrent dysphagia. Treatment outcome was not influenced by tumour histology. In a prospective non-randomised study, Maunoury and colleagues (1992) reported that in a small number patients with malignant dysphagia treated by laser therapy, adjuvant external beam radiotherapy (no details provided) produced a virtual doubling of survival (mean 4.5 vs 7.7 months) as in the present investigation.

Sander and coworkers (1991) randomised 39 patients with advanced oesophageal and gastric cardia cancers to receive Nd:YAG laser therapy alone or laser therapy followed by three to six sessions of $^{192}$Ir brachytherapy (7Gy). Successful recanalisation was possible in all cases but in contrast to the findings of Bader and colleagues (1986) and Renwick and colleagues (1992), all patients except those with very short survival developed further symptoms. Although the time to recurrence of dysphagia was greater in patients receiving combination therapy (68 vs 32 days), the difference proved statistically significant only in those with squamous cell carcinomas (65 vs 30 days, p<0.001) as in the present study. The interval between repeat laser procedures during long-term follow-up was not stated. Patients who received adjuvant radiotherapy required more procedures (including brachytherapy sessions) during their lifetime than those treated by laser alone (3 vs 1.8 per month). Survival was similar in the laser and combination therapy group.
(mean 24 vs 18 weeks) and independent of tumour histology. Three patients (15%) in each group developed oesophageal fistulae which were successfully managed by endoscopic intubation and four patients (21%) developed troublesome oesophagitis after radiotherapy; no treatment related deaths occurred in either group.

Following the encouraging preliminary results of this pilot study, a randomised comparison using the same protocol has been performed in our unit to confirm or refute these findings (Sargeant et al 1992a). All patients in the combination therapy arm of the study received 30Gy external beam radiotherapy in ten fractions. Long-term palliation of dysphagia was possible in 19 of 30 patients (63%) in the laser and 23 of 37 patients (62%) in the combination therapy group; quality of swallowing was similar in the two groups. The time interval between follow-up procedures, was significantly longer in the radiotherapy group (mean 9 vs 5 weeks, p<0.01) but the difference was less marked than in the present study and significant only in patients with adenocarcinomas. Survival was similar in both groups (mean 26 weeks) and independent of tumour histology. Radiotherapy was generally well tolerated but two patients (5%) developed oesophageal fistulae and died a few weeks later and one suffered from persistent radiation oesophagitis. Lifetime hospitalisation was longer in the combination therapy group (median 19 vs 14 days).

The question whether radiotherapy confers a survival advantage in patients receiving endoscopic therapy for the palliation of malignant dysphagia was also addressed by a retrospective study from Nottingham (Oliver et al 1990). 32 patients with squamous cell oesophageal carcinomas managed by intubation were compared retrospectively with 27 similar patients treated by intubation plus external beam radiotherapy (30-60Gy). Survival was virtually double after combination therapy (median 188 v 98 days, 1 year survival 19% and 10% respectively) but the difference was not statistically significant. 15% of patients in the radiotherapy group tolerated treatment poorly and required longer hospitalisation (median 46 vs 23 days).

On the basis of current evidence, what is the clinical role of radiotherapy as an adjuvant to laser treatment for the palliation of malignant dysphagia? In the present study, 30Gy of external beam radiotherapy significantly reduced the need for repeat endoscopic treatments and provided a marginal survival
advantage without major morbidity and only slight prolongation of hospital stay. Thus it would seem that adjuvant radiotherapy is clinically worthwhile, its benefits outweighing the disadvantages. It should be noted however, that the opposite will hold true if higher radiotherapy doses are used as they result in significant morbidity and rapid deterioration in the condition of treated patients. As emphasized above, given the design of the present study the results are subject to bias and the conclusions should be considered tentative. Subsequent randomised studies employing brachytherapy or external beam radiotherapy have provided less encouraging messages. The prolongation of the interval between treatments was less marked than in the present investigation and in practical terms would result in a saving of only one endoscopic procedure on average during a patient's lifetime; in addition, a significant prolongation of survival has not been demonstrated in these studies. Such results, indicate that radiotherapy as an adjuvant to laser treatment is justified only for patients in good general condition and with a reasonable life expectancy in an attempt to prolong the dysphagia free interval after treatment, but it is unclear whether it should be offered only to patients with squamous cell carcinomas. What is clear is that additional well designed studies are required in order to clarify the situation, especially the issue whether adjuvant radiotherapy prolongs survival. Such studies should also investigate the use external beam radiotherapy in combination with brachytherapy, which may well provide superior results. The value of radiotherapy as an adjuvant to other endoscopic palliative treatments for malignant dysphagia such as intubation or alcohol injection must also be explored by future studies.
Chapter 7

Nd:YAG laser therapy for recurrent dysphagia after surgery or intubation

Section A: Anastomotic tumour recurrence

7.1 Introduction

Because of the propensity of oesophageal and gastric cardia cancers to extend for considerable lengths within the submucosal lymphatic plexus both superiorly in the oesophagus and inferiorly in several directions in the stomach, tumour recurrence along the resection margins is likely unless a near total removal of both organs is performed. This is clearly supported by clinical experience which indicates that the incidence of anastomotic recurrence is high when the proximal oesophageal resection margin is less than 10cm (Tam et al 1987, Wong 1987) and the distal gastric resection margin less than 12cm (Miller 1962). In practice, resection margins are narrower because of the problem of restoring gastrointestinal continuity and tumour recurrence is noted in 9-19% of patients after curative resections (Giuli and Sancho-Garnier 1986, Mahoney and Condon 1987, Wong 1987). Approximately 50%-75% of these recurrences are at the oesophago-gastric anastomosis manifesting with dysphagia and the rest in the intrathoracic stomach (Wong 1987, Giuli and Sancho-Garnier 1986). As the oesophagus is anastomosed to the fundus of the gastric remnant after a transthoracic oesophagogastrectomy, recurrence along the distal resection margin does not contribute to anastomotic recurrence but becomes manifest as tumour along the lesser curvature of the intrathoracic stomach (Wong 1987). The management of patients presenting with dysphagia due to anastomotic recurrence is difficult. Re-operation is not an option and as the majority have evidence of metastatic disease in addition to local recurrence, palliation must be achieved speedily with minimum morbidity. The present study was undertaken to evaluate the role of Nd:YAG laser therapy in this clinical setting.
7.2 Patients and Methods

7.2.1 Patients

During the period June 1987 to January 1989, all patients with dysphagia due to anastomotic tumour recurrence, who were excluded from the comparative study of laser therapy and intubation presented in Chapter 5, were studied prospectively as a separate group.

Seven men and three women were treated; median patient age was 65 years (range 49-71 years). Four patients had evidence of distant metastases on chest X-rays, CT scanning or abdominal ultrasonography. Eight patients had originally undergone standard transthoracic oesophagogastrectomy (Ivor Lewis operation) and two a total gastrectomy and oesophagojejunostomy for carcinomas of the cardia. The median time from surgery to the development of recurrent dysphagia was 21 months (range 14-36 months); there was an additional median delay of 3 months before patients were referred and treatment initiated.

Seven of the recurrent tumours were adenocarcinomas and three squamous cell carcinomas. All patients had exophytic (endoluminal) tumour; all but one of the recurrences involved at least two thirds of the anastomosis circumference and four were 100% circumferential. The proximal tumour margin was located between 25-35cm from the incisors and the median tumour was length 5cm (range 3-12cm).

7.2.2 Treatment Techniques and Patient Assessment

Treatment technique has been described in detail in Chapter 5, 5.2.3 and grading of dysphagia and patient assessment in Chapter 5, 5.2.4. All patients were followed-up until death.

7.2.3 Statistics

Dysphagia scores before and after treatment were compared using the Wilcoxon signed rank test. Significance was set at the 5% level (p<0.05).
7.3 Results

The mean dysphagia grade prior to treatment using the standard five point scale was 3.1; two patients had complete dysphagia at presentation and the rest were only able to swallow liquids. Laser treatment was initially successful in improving the quality of swallowing in eight patients. The dysphagia grade in the treatment successes improved from a mean of 3.4 (median 3) to 1.4 (median 2), \(p<0.05\). This improvement in quality of swallowing was maintained until death in all patients with repeated laser treatments; the total median number of procedures was 3 (range 1-4). Mean patient survival from inclusion into the study was 12 weeks (median 11, range 5-19 weeks). All patients died because of relentless progression of their malignancy. Total median hospitalisation was 9 days (range 6-17 days); three patients were hospitalised longer than required for completion of endoscopic therapy because of personal and family circumstances. No procedure related complications occurred in this series.

One of the treatment failures was a patient with a recurrent adenocarcinoma, a malignant pleural effusion and documented distal metastases who was only able to swallow liquids at presentation. As his dysphagia failed to improve despite complete tumour recanalisation, this was classified as a functional failure. In view of his poor general condition no further active treatment was offered and he died three weeks later. The second treatment failure was a patient with a recurrent adenocarcinoma and no documented metastases. Following ablation of all intraluminal tumour it became apparent that there was significant extrinsic compression; the anastomotic tumour measured 2.5cm in thickness on CT scanning. As he was only able to swallow liquids following laser treatment, he underwent endoscopic intubation with a Celestin endoprosthesis and managed semi-solid and some solid food for the remaining 20 weeks of his survival.

7.4 Discussion

Local recurrence after surgery for carcinoma of the oesophagus and gastric cardia can present as tumour involving the anastomosis, the intrathoracic stomach or the mediastinum. Anastomotic recurrence presents with dysphagia and weight loss whereas gastric and mediastinal recurrence leads to overt or occult gastrointestinal haemorrhage, pain and pulmonary symptoms.
due to a tracheo-oesophageal fistula or pleural effusion. Surgery, radiotherapy and chemotherapy are usually disappointing and rarely applicable in this setting due to the poor general condition of the patients. The main aim of management is to palliate the dysphagia due involvement of the anastomosis.

This series is probably the largest in the literature dealing with laser therapy for anastomotic recurrences after oesophagogastrectomy. As the recurrent tumour was predominantly exophytic and of short length (3-5cm) in the majority of cases, it proved eminently suitable for laser therapy with completion of initial treatment in one or two sessions; extrinsic tumour compression did not prove a significant problem. This experience is in agreement with that of several authors who have reported on smaller groups of patients (Fleischer and Sivak 1985, Rutgeerts et al 1988, Alderson and Wright 1990). Only Maunoury and colleagues (1992) reported a less successful outcome for anastomotic recurrences compared to mid and distal oesophageal carcinomas, with only three of six patients deriving long-term palliation. Treatment was technically easy in patients with oesophagogastrostomies after an Ivor Lewis operation but proved more difficult in those with a total gastrectomy and gastrojejunostomy because of sharp angulation of the distal part of the tumour. Laser treatment provided good quality long-term palliation of dysphagia equivalent to that achieved with primary tumours as described in Chapter 5. The prognosis of patients with anastomotic recurrence is very poor, with a mean survival of only 12 weeks compared to 26 weeks for patients with primary tumours treated by laser therapy (see Chapter 5). It is important therefore to minimise hospital stay, an objective which was achieved in the present study as patients required on average only one endoscopic procedure during their survival after completion of initial treatment. Given this and the limited patient survival, there appears to be no rationale for the use of adjuvant external beam radiotherapy. In addition if the functional result after initial treatment is at best only mediocre, endoscopic intubation should be resorted to early rather than persevering with laser therapy.

It can be concluded that Nd:YAG laser therapy is suitable for the majority of cases of anastomotic tumour recurrence and provides good quality palliation of dysphagia without significant morbidity. Given that endoscopic intubation for anastomotic recurrences is frequently fraught with technical difficulties
because of tumour angulation, laser therapy probably represents the most appropriate first line treatment.
Nd:YAG laser therapy for recurrent dysphagia after surgery or intubation

Section B: Prosthesis tumour obstruction

7.5 Introduction

Several problems, which have been discussed in chapter 2, 2.4.2, may be encountered following endoscopic intubation for the palliation of malignant dysphagia. Of these, recurrent dysphagia due to obstruction of the proximal or distal end of a prosthesis by tumour growth is probably the most challenging and has been reported to occur with a frequency of 2-6% (Ogilvie et al 1982, Buset et al 1987, Gaspari et al 1987, Spinelli et al 1994); in the prospective study of intubation presented in chapter 5, it was encountered in 7% of patients. Endoprosthesis obstruction by tumour usually occurs late, on average 5 to 6 months, after intubation and its low incidence is explained by the very limited survival of these patients. The traditional management of this problem, involves dilatation the tumour followed by removal of the obstructed prosthesis and its replacement by a longer one; however, this is technically possible in only about half of the patients (Ogilvie et al 1982, Buset et al 1987, Gaspari et al 1987, Spinelli et al 1994). The remaining ones are faced with a miserable demise unless the obstructing tumour can be dealt with by other means. The present study was undertaken to evaluate the role of Nd:YAG laser therapy in this difficult group of patients.

7.6 Patients and Methods

7.6.1 Patients

Fourteen patients with prosthesis tumour occlusion were seen in our unit between December 1986 and April 1991; twelve were referred from outside centres. Correct positioning of the prosthesis after initial placement had been documented endoscopically in all patients. When patients developed recurrent dysphagia they were re-endoscoped and tube position checked; if tube displacement had occurred, they were excluded from the study.
Eleven men and three women were treated; median patient age was 75 years (range 46-90 years). Twelve of the intubated tumours were located in the distal oesophagus or cardia and two were anastomotic recurrences after surgery; histologically, eleven were adenocarcinomas and three squamous cell carcinomas. Ten of the patients had undergone endoscopic intubation after being considered unsuitable for surgery because of age or advanced disease and two because of tumour recurrence after surgery; the remaining two patients had been intubated at laparotomy (with the distal end of the prosthesis sutured to the gastric wall) as their tumours proved unresectable. Nine prostheses were of the Celestin and five of the Atkinson type. Until the development of recurrent dysphagia, all patients had been able to eat a semi-solid diet.

The median time from intubation to referral for laser treatment was 7 months (range 4-14 months). Eleven prostheses were obstructed by tumour at their proximal end, two at their distal end and one at both ends; the median length of obstructing tumour was 3cm (range 2-5cm).

7.6.2 Treatment Techniques and Patient Assessment

Nd:YAG laser treatment was performed using a high power non-contact technique as described in Chapter 5, 5.2.3. Nodules of exophytic tumour causing prosthesis obstruction were vaporised and gradually shaved back to within 2-3mm of the oesophageal wall; flat parts of the tumour were coagulated and allowed to slough. Tumour overgrowing and obstructing the proximal end of a prosthesis almost invariably could not be negotiated with the endoscope and was recanalised in a prograde fashion. As the obstructing tumour was short in most cases, complete recanalisation was usually possible in one session. For prostheses obstructed by tumour at their distal end, an endoscope slim enough to pass through an Atkinson or Celestin tube was used instead of a large calibre therapeutic endoscope. Treatment of tumour undergrowth is technically more difficult than that of overgrowth because of orientation and laser targeting problems while the endoscope is confined within the prosthesis. In order to secure a good lumen, tube manipulation was considered necessary in some patients after laser recanalisation; in one patient a second prosthesis was inserted and impacted into the first from above. Manipulation of tube position was performed with an Atkinson introducer. In some cases, particularly if the tumour was very hard and the prosthesis had been in situ for several months, this could not be achieved as
it proved impossible to obtain a strong enough grip (especially with Celestin tubes). Three examples of prosthesis tumour overgrowth are shown in Figures 7.1 to 7.3.

Dysphagia was graded on a five point scale as described in Chapter 5, 5.2.4. All patients were assessed prior to and following treatment while still in hospital and subsequently by telephone by an experienced research nurse (D. Grigg-Rampton, M. Tulloch, S. Thorpe).

7.6.3 Statistics

Dysphagia scores before and after treatment were compared using the Wilcoxon signed rank test. Significance was set at the 5% level (p<0.05).

7.7 Results

In all eleven patients with overgrowth, the obstructing tumour was successfully recanalised with the laser. In three patients, the prostheses were shifted up using the Nottingham introducer to cover the area of overgrowing tumour after laser therapy; additional laser treatment was only required in one patient. Treatment enabled all eleven patients to swallow a semi-solid for most of their survival.

One of the two patients with tumour obstruction of the distal end of the prosthesis underwent laser therapy using an Olympus XQ 20 endoscope passed through the tube. In the other, the prosthesis was shifted downwards with the Nottingham introducer to cover the obstructing tumour; this uncovered tumour above the upper end of the prosthesis which was subsequently successfully treated with the laser.

One of the patients presented with worsening dysphagia due to tumour obstruction of both the upper and lower ends of an Atkinson tube which had been inserted 17 weeks previously and had allowed her to eat a semi-solid diet. The dominant obstruction was at the upper end of the tube and this was successfully treated by laser therapy on four occasions over a period of 17 weeks enabling her to eat a semi-solid diet once again. She subsequently developed an extrinsic stricture proximal to the prosthesis which was not amenable to laser therapy. This was dilated and a short (9 cm) Celestin tube
Figure 7.1: A, A typical prosthesis tumour overgrowth. Polypoid tumour is seen to overgrow a Celestin prosthesis in a patient with adenocarcinoma of the cardia intubated 14 months previously. B, Appearance following laser treatment; the prosthesis was subsequently shifted upwards by 5cm to cover the area of overgrowing tumour.
Figure 7.2: A less typical example of prosthesis tumour overgrowth. The obstructing tumour in this patient with adenocarcinoma of the cardia intubated 7 months previously, may have been misdiagnosed as an oedematous mucosal fold resulting from pressure of the prosthesis on the oesophageal wall. Initial superficial treatment with the laser revealed obviously neoplastic tissue which was subsequently vaporised.
Figure 7.3: A, A further example of tumour overgrowting and obstructing an Atkinson prosthesis which had functioned well for 9 months in a patient with adenocarcinoma of the cardia. The mucosa is diffusely abnormal and there is only a pinpoint lumen. B, Barium swallow study shows a tight irregular stricture and only a trickle of contrast passing through into the prosthesis; the proximal oesophagus is dilated and contains food residue. C, Appearance following laser treatment. Treatment proceeded centrifugally starting at the luminal tumour surface, until the buried prosthesis was revealed.
placed through the stricture with its distal end impacted into the funnel of the Atkinson tube below. This enabled the patient to swallow semi-solids until her death 6 weeks later.

The median pre-treatment dysphagia grade was 4; 10 of the 14 patients had complete dysphagia at presentation. All patients except one derived an improvement in swallowing of at least one grade on the dysphagia scale after treatment and ten patients improved by two grades. After treatment, the median dysphagia grade during the patients' remaining survival was 2, an improvement which was significant at the 1% level on statistical analysis. Eight patients required only one or two endoscopic treatments and the others up to five. Median survival was 9 weeks (range 3-36 weeks). Eleven patients died of relentless progression of their malignancy; two suffered recurrent pulmonary aspiration which contributed at least partly to their death. One patient died of a myocardial infarction. Median lifetime hospital stay for endoscopic therapy was 5 days (range 3-17 days). No serious procedure related complications occurred.

7.8 Discussion

A potential danger of recanalising an oesophageal tube obstructed by tumour with the Nd:YAG laser is ignition of the prosthesis. Mousseau-Barbin tubes have been reported to ignite (Carter and Smith 1988) and if laser treatment is to be attempted in patients with such tubes in situ, carbon dioxide rather than air should be used for cooling the fibre. Several patients with this type of prosthesis have undergone laser treatment in our unit after distal displacement without any accidents. Atkinson and Celestin tubes do not ignite (but the burning rubber smells foul), so it is safe to use air for cooling the laser fibre when treating patients with such prostheses in situ.

Ethanol injection treatment and to a lesser extent BICAP therapy which have been discussed in Chapter 2, 2.4 may also prove useful for managing prosthesis tumour obstruction. The main advantage of laser therapy in this context, is the ability to vaporise tissue and immediately establish an adequate lumen through the obstructing tumour. With the other techniques mentioned above, establishment of an adequate lumen and improvement in swallowing is usually delayed for few days until necrosed tumour sloughs off; in addition, more treatment sessions may be required than with laser therapy.
Tube manipulation after laser therapy should be attempted with great caution if deemed necessary. Shifting prostheses which have been in situ for several months carries a definite risk of perforation. In addition as it is not possible to estimate the axial extent of the tumour, upward displacement of a prosthesis may expose tumour below its distal end which may prove more difficult to treat with the laser than proximal overgrowth. Although shifting of a prosthesis to cover short obstructing tumours after laser therapy was performed without complications in four patients in the present study, it is inappropriate for most cases. Given the very limited patient survival, good long-term palliation can be achieved with only a few laser procedures and the potential risks of tube manipulation avoided. It should be noted that tube manipulation without prior laser treatment may not be technically possible (because overgrowing tumours usually cause tight stenoses preventing insertion of the Nottingham introducer) and carries a greater risk of perforation as excess force is often required to shift the prosthesis.

Two patients in the series had undergone intubation at the time of laparotomy. Surgically implanted prostheses are sutured to the gastric wall in order to prevent proximal displacement. It is important that the therapeutic endoscopist is cognizant of this information as attempts to shift the prosthesis proximally can result in tearing of the gastric wall with disastrous consequences. With current endoscopic techniques and equipment it is rarely necessary to resort to surgical intubation.

In conclusion, the results of the present study demonstrate that laser treatment for prosthesis tumour obstruction is both feasible and safe and validate an active management approach for most of these patients. Treatment enables patients to resume the consumption of a "tube diet" and as the obstructing tumour is usually short, long-term palliation can be achieved with only one or two procedures during a patient's lifetime.
Endoscopic intubation using modified endoprostheses for the palliation of high cervical oesophageal cancer

8.1 Introduction

Statistics show that 7-10% of primary oesophageal carcinomas are located in the cervical portion (Parker and Moertel 1978, Goodner 1979). Unfortunately, at presentation the majority of these tumours are incurable because of local invasion of vital structures or disseminated disease (Collin and Spiro 1984). The primary aim of treatment therefore, is to palliate the distressing symptoms of dysphagia, tracheal aspiration and those resulting from the development of a tracheo-oesophageal fistula. Palliative resection if feasible, is a formidable procedure necessitating total oesophagectomy and often laryngectomy with permanent tracheostomy. Such surgery has a mortality around 10% and a high rate of local treatment failure; median duration of palliation is approximately 9 months (Collin and Spiro 1984, Kagewawa et al 1985, Kron et al 1986). High surgical risk patients and those with unresectable tumours have conventionally been treated with palliative radiotherapy. The results of such treatment however, are very disappointing; local failure occurs in 64-80% of patients and only 10% have satisfactory swallowing (Burdette and Jesse 1972, Pearson 1974, Collin and Spiro 1984). In patients with predominantly exophytic strictures, tumour photoablation using the Nd:YAG laser can provide reasonable palliation (Fleischer and Sivak 1985, Naveau et al 1990). When the tumour is predominantly extrinsic or fistulation into the tracheo-bronchial tree has occurred, effective palliation can only be achieved by the endoscopic placement of an endoprosthesis. This technique although highly efficacious for tumours of the thoracic oesophagus and gastric cardia, has traditionally been contraindicated for lesions of the cervical oesophagus involving or within 2cm of the cricopharyngeous sphincter muscle (CPSM) because of the potential problems of persistent and troublesome foreign body sensation, tracheal compression and proximal migration of the prosthesis into the hypopharynx with consequent laryngeal compression (Hegarty et al 1977, Kairaluoma et al 1977, Ogilvie et al 1982, Boyce 1982, Earlam and Cuhna Melo 1982, Tytgat et al 1986). The limited published experience with intubation for high cervical lesions using standard or custom-made
endoprostheses, indicates that the concern regarding these potential complications may be unjustified (Maercke et al 1985, Goldschmid et al 1988). These encouraging reports, prompted the author to develop a modified Celestin prosthesis for endoscopic placement in patients with carcinomas of the upper cervical oesophagus (involving or within 2cm of the CPSM). The initial clinical experience with such a prosthesis is presented in this chapter and the role of the technique in the management of cervical oesophageal cancer discussed.

8.2. Patients and Methods

8.2.1 Patients

Placement of a modified Celestin endoprosthesis was attempted in eight consecutive patients with malignant strictures located in the high cervical oesophagus, involving or within 2cm of the CPSM. Six patients had histologically proven primary squamous cell carcinomas and two anastomotic recurrence after transhiatal oesophagectomy for squamous cell carcinoma of the thoracic oesophagus. All patients were considered inoperable because of advanced disease (metastases, local invasion), high anaesthetic risk (cachexia, age, severe concomitant disease) or recurrence after surgery. Six patients had received prior external beam radiotherapy and four Nd:YAG laser therapy; laser therapy was initially successful in two, both patients (patients 1 and 6, Table 8.1) managing a virtually normal diet for 15 and 23 weeks respectively. The anatomy of the tumour was documented in all patients by a contrast swallow examination and in some by CT scanning. At presentation, half of the patients could swallow liquids only and the others had difficulty swallowing their saliva. Patient and tumour details are shown in Table 8.1. Illustrative case histories are presented below.

8.2.2 Endoprostheses

Celestin endoprostheses (Medoc Ltd, Tetbury) are made of latex rubber with a nylon spiral incorporated in the wall to prevent kinking when bent; they have a proximal inkwell funnel to collect food and liquid boluses and prevent distal migration and a distal atraumatic, collapsible umbrella-shaped flange which is designed to prevent proximal migration - Figure 8.1. The endoprostheses which are available in four lengths (9.5, 12.5, 15 and 21cm)
Table 8.1: Patient and tumour details.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Tumour position</th>
<th>CPSM</th>
<th>TOF</th>
<th>Previous RT</th>
<th>Previous Laser Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>M</td>
<td>19-24 cm</td>
<td>17cm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>M</td>
<td>12-19 cm</td>
<td>12cm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>16-21 cm</td>
<td>15cm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>F</td>
<td>Anastom.</td>
<td>16-19 cm</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>F</td>
<td>Anastom.</td>
<td>15-18 cm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>16-22 cm</td>
<td>15cm</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>14-17 cm</td>
<td>14cm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>14-20 cm</td>
<td>14cm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

All tumours were squamous cell carcinomas.
Pt: Patient; 1°: Primary; Anastom: Anastomotic; CPSM: Cricopharyngeous sphincter muscle; TOF: Tracheo-oesophageal fistula; RT: radiotherapy.
Figure 8.1: Left, Standard Celestin (Medoc) prosthesis. Right, Celestin prosthesis modified by amputation of its funnel 3mm proximal to the junction with the shaft and replacement with a distal flange removed from another tube; the flange functions as a soft, collapsible funnel for placement in the hypopharynx.
have a luminal diameter of 11mm and an external diameter of 15mm. Commercially available Celestin prostheses were modified for placement in the cervical oesophagus as follows. The funnel was amputated 3mm proximal to its junction with the shaft using a scalpel blade and replaced with a distal flange removed from another tube in order to provide a funnel which is soft and collapsible; as the amputated end of the tube fits tightly inside the new funnel, it was not necessary to fix the two parts together with glue - Figure 8.1. The 3mm rim of reinforced funnel which is left behind by the amputation, fits snugly inside the new soft funnel and serves as a retainer ring to prevent distal migration of the modified prosthesis. The height of the new funnel measured from the proximal end of the prosthesis shaft is 2cm.

8.2.3 Endoscopic Technique

Endoscopic examinations were performed with a paediatric upper gastrointestinal endoscope (Olympus GIF P20). Careful measurements of the position of the CPSM, the upper and lower limits of the tumour and the site of any tracheo-oesophageal fistula were made in order to enable accurate positioning of the prosthesis. Patients were not routinely bronchosced to detect possible tracheo-bronchial compression or invasion prior to intubation. Strictures impassable even with the paediatric endoscope were dilated to 10-12mm using Celestin dilators under fluoroscopic control to enable complete inspection of the tumour. At a second procedure after an interval of two to three days, the stricture was dilated further with Celestin bougies to 16-18mm and the modified prosthesis placed using the Nottingham introducer (Ogilvie et al 1982) under fluoroscopic control. The junction of the shaft and funnel of the prosthesis was placed just proximal to the CPSM with the funnel positioned in the hypopharynx posterior to the larynx, its upper lip lying at the level of the arytenoid cartilages. As the funnel of the modified prosthesis is soft and collapsible, it is partially compressed in an antero-posterior direction as it lies in the hypopharynx - Figure 8.2. During the act of swallowing, the anterior and upward movement of the larynx enables the funnel to expand to virtually its natural resting size in anticipation of the oncoming food bolus. Careful positioning of the prosthesis is crucial; as accurate prosthesis placement proved impossible under general anaesthesia with an endotracheal tube in situ, all intubations were performed using conscious sedation with a combination of Pethidine and Diazemuls or Midazolam. Following intubation, chest and neck X-rays and a contrast swallow were performed within 24 hours in order to detect and localise
Figure 8.2: A, Endoscopic view of the soft funnel of the modified prosthesis in the hypopharynx posterior to the larynx. B, Note that the funnel is partially compressed in the antero-posterior direction and that its upper lip lies at the level of the arytenoid cartilages.
instrumental perforations, assess tube function and document occlusion of any tracheo-oesophageal fistula.

8.3 Illustrative Case Histories

8.3.1 Case History 1 (patient 1, table 8.1)

The patient was a 73 year-old man who had received radical external beam radiotherapy for squamous cell carcinoma of the cervical oesophagus 18 months previously. After radiotherapy he was able to eat a virtually normal diet until he developed progressive dysphagia 6 weeks prior to referral to University College Hospital; when first assessed he was able to eat semi-solids only. At endoscopy an exophytic oesophageal carcinoma extending from 19-24cm from the incisors was found; the CPSM was located at 17cm. It was decided to manage the patient with Nd:YAG laser therapy. After the initial laser course (three treatments) he was able to eat a virtually normal diet. Symptomatic improvement was maintained over the next 12 weeks by repeat laser treatments at monthly intervals. By 15 weeks he was only managing to take liquids and had developed hoarseness and a cough on swallowing. Indirect laryngoscopy confirmed a right recurrent laryngeal nerve palsy. At endoscopy, there was mural/extrinsic stricturing of the tumour segment with very little luminal tumour and a 1cm diameter tracheo-oesophageal fistula located at 22cm, findings confirmed by a gastrografin swallow - Figure 8.3, A and B. The stricture was dilated and a modified Celestin prosthesis placed as described above with the funnel located above the CPSM. A post-intubation contrast swallow demonstrated free flow through the prosthesis with no tracheal aspiration and complete occlusion of the fistulous tract - Figure 8.3, C and D. The patient complained of minimal foreign body sensation in the throat which wore off completely over the next few weeks. He managed a semi-solid (pureed) diet until his death 19 weeks after intubation.

8.3.2 Case History 2 (patient 4, table 8.1)

The patient was a 75 year-old woman, an insulin dependent diabetic, who had undergone a transhiatal oesophagectomy for squamous cell carcinoma of the thoracic oesophagus 6 months previously. Three months after surgery she represented with dysphagia and anastomotic tumour recurrence was documented at endoscopy. She was managed by repeated dilatations with
Figure 8.3: Gastrografin swallow (patient 1). A, Lateral view showing an almost complete, irregular malignant stricture of the cervical oesophagus starting at the CPSM (located at the level of C₆ vertebra). A naso-gastric feeding tube has been passed through the stricture. B, Lateral film (taken following virtually complete clearance of contrast from the oesophagus) showing an oval shaped tracheo-oesophageal fistula at the level of T₁ and T₂ vertebrae (arrow). At endoscopy, the fistula measured 1cm in diameter. C and D, Lateral views of repeat gastrografin swallow taken after placement of a modified Celestin prosthesis, showing complete occlusion of the fistula and free flow of contrast into the distal oesophagus. The top lip of the funnel is situated above the CPSM in the hypopharynx at the level of C₅ vertebra.
only short lasting symptomatic benefit after each procedure. She subsequently developed complete dysphagia and was referred to University College Hospital for further management. At endoscopy, a 3cm long circumferential anastomotic recurrence was seen 2cm below the CPSM (located at 14cm from the incisors). The stricture was dilated and all exophytic tumour ablated using the Nd:YAG laser therapy at three separate sessions. As the symptomatic result was poor, a modified Celestin prosthesis was placed with its funnel above the CPSM in the hypopharynx. After intubation she developed stridor which resolved spontaneously within 48 hours. A contrast swallow study showed excellent tube function with no tracheal aspiration. She reported no foreign body sensation and managed a soft tube diet until her death 7 weeks later.

8.3.3 Case History 3 (patient 8, table 8.1)

The patient was a 65 year-old man with a squamous cell carcinoma of the mid-oesophagus which was locally invasive on CT scanning. He underwent palliative radiotherapy 3 months previously with only slight transient symptomatic benefit. His dysphagia deteriorated rapidly and by the time of referral to University College Hospital he was unable to swallow his saliva. Endoscopy showed a circumferential exophytic carcinoma extending from 26-29cm from the incisors causing marked luminal narrowing and a skip tumour nodule at 20cm. The stricture was dilated and both tumour areas treated with the Nd:YAG laser in two sessions. Following this he was able to swallow liquids without difficulty. He represented 3 weeks later with hoarseness and complete dysphagia. Bilateral vocal cord paralysis was documented at indirect laryngoscopy. Repeat endoscopy showed extrinsic compression of the cervical oesophagus starting at the CPSM (located at 14cm) and extending down to 20cm (presumably by involved lymph nodes). At this level, there was an obvious 1cm diameter tracheo-oesophageal fistula at the site of the tumour nodule treated previously with laser. There was moderate luminal narrowing through the distal tumour segment. The proximal stricture was dilated to 18mm with difficulty and a 20cm long modified prosthesis placed with its funnel above the CPSM in the hypopharynx. A contrast swallow showed free flow through the tube into the stomach and adequate occlusion of the fistula; however, there was considerable aspiration into the trachea, presumably as a result of bilateral vocal cord paralysis. He complained of no foreign body sensation and could swallow his saliva; his oral nutritional intake was minimal because of repeated tracheal aspiration.
He was fed through a percutaneous endoscopic gastrostomy until his death 6 weeks later.

8.4 Results

Successful placement of a modified Celestin prosthesis with the funnel proximal to the CPSM in the hypopharynx, was possible in all eight patients with high cervical oesophageal carcinomas. Treatment results and survival are shown in Table 8.2.

Swallowing ability improved in 6 patients; the mean dysphagia grade, using the standard five point scale described in Chapter 5, 5.2.4, improved from 3.5 pre-intubation to 2.2 post-intubation. This symptomatic improvement persisted until death in five patients (mean survival 13 weeks, range 4-30 weeks) and for 16 weeks in another patient (patient 5) not referred back to University College Hospital after distal migration of the prosthesis, who was adequately palliated for the remaining 10 weeks of her life by repeated dilatations. Both treatment failures (patients 3 and 8) were functional as swallowing ability did not improve despite accurate prosthesis placement; both had bilateral vocal cord paralysis and marked pharyngo-tracheal aspiration on a contrast swallow study. These patients died as a result of progressive malnutrition and aspiration pneumonia and the remaining patients because of malignant cachexia. None of the deaths were attributable to a procedure related complication (perforation or haemorrhage).

The modified prostheses were well tolerated. Four patients complained of no foreign body sensation, three patients of minor discomfort which subsequently disappeared completely in two and only one (patient 3) of continuous moderate throat discomfort. Stridor following intubation developed in two patients but resolved spontaneously in both cases within 72 hours. A tracheostomy did not prove necessary in any of the patients.

Distal migration of the modified prosthesis into the stomach occurred in two patients, one spontaneously (patient 3) and the other after an attempt at an outside hospital to clear an obstructing food bolus (patient 5). The prosthesis was successfully replaced in the first patient; the second patient was not referred back to University College Hospital. Prosthesis food bolus obstruction
Table 8.2: Treatment results and survival after intubation with modified endoprostheses.

<table>
<thead>
<tr>
<th>Pt</th>
<th>DG pre-intubation</th>
<th>DG post-intubation</th>
<th>Time laser → intubation (weeks)</th>
<th>Occlusion of TOF</th>
<th>Survival post-intubation (weeks)</th>
</tr>
</thead>
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<tr>
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<td>3</td>
<td>2</td>
<td>15</td>
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<td>19</td>
</tr>
<tr>
<td>2^a</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>3^a</td>
<td>3-4</td>
<td>3-4</td>
<td>-</td>
<td>-</td>
<td>2</td>
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<td>2</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>

Pt: Patient; DG: Dysphagia grade (measured on a standard five point scale); TOF: Tracheo-oesophageal fistula.

^a Dilatation induced perforation.

^b Palliation with endoprosthesis for 16 weeks; tube displaced distally in an attempt to clear a food bolus at an outside hospital. Patient managed until death by repeated dilatations.
occurred in only one patient (patient 5). Subcutaneous neck emphysema after dilatation to 18mm with Celestin bougies developed in two patients (patients 2 and 3) with very tight, fibrous strictures who had previously received radiotherapy. After prosthesis placement, no leak could be demonstrated on a contrast swallow study and both patients made an uncomplicated recovery on conservative management.

8.5 Discussion

The palliation of patients with high cervical oesophageal carcinomas is a formidable management problem. Nd:YAG laser treatment of predominantly exophytic tumours in this location can provide reasonable palliation of dysphagia, but the functional result is often worse than for tumours of the thoracic oesophagus and cardia (Fleischer and Sivak 1985, Buset et al 1987). It appears that laser therapy may predispose to or accelerate the formation of a tracheo-oesophageal fistula, especially if previous radiotherapy has been given and complete ablation of the tumour is attempted (Ell and Demling 1987). For fistulating and predominantly extrinsic tumours, the only possible means of providing effective palliation is endoscopic placement of an endoprosthesis. Conventionally, intubation has been contraindicated for cervical oesophageal tumours because of the potential problems of foreign body sensation, tracheal compression or proximal migration of the prosthesis (Kairaluoma et al 1977, Hegarty et al 1977, Ogilvie et al 1982, Boyce 1982, Tytgat et al 1986).

Using the specially modified Celestin prosthesis with its soft collapsible funnel positioned above the CPSM, did not result in troublesome foreign body sensation. Of the eight patients intubated, only two reported persistent throat discomfort (one moderate, one mild) which was tolerable and did not necessitate prosthesis removal. The absence of significant foreign body sensation in patients with advanced cervical tumours is probably due to local infiltration of the nerves innervating the hypopharynx, CPSM and upper oesophagus resulting in impaired or absent sensation; this propensity to infiltrate local neural structures is reflected by the frequent occurrence of unilateral or bilateral vocal cord paralysis. In addition, previous radiotherapy or surgery may also impair normal sensation. Compared with standard prostheses, the soft collapsible funnel of the modified Celestin tube helps to reduce hypopharyngeal irritation and the intensity of the foreign body
sensation. Goldschmid and colleagues (1988) reported that of eight patients with cervical carcinomas intubated with custom-made or modified Atkinson (Key Med) endoprostheses, only two complained of mild but tolerable foreign body sensation; in both patients the funnel had been placed in the hypopharynx. Spinelli and colleagues (1991) found that none of the eight patients with cervical oesophageal carcinomas intubated with unmodified prostheses complained of foreign body sensation irrespective of the type of tube used (Celestin, Atkinson or Wilson-Cook); it was not stated however, whether the funnel of the prosthesis was placed in the hypopharynx in any of these patients. In contrast, Maercke et al (1985) reported that of six patients with high cervical tumours intubated with unmodified Atkinson (Key Med) prostheses two experienced foreign body sensation severe enough to necessitate tube removal; the only patient in whom the prosthesis funnel was positioned in the hypopharynx did not complain of throat discomfort. The earlier limited published experience with intubation for cervical carcinomas using surgically placed unmodified Celestin prostheses (Kairaluoma et al 1977) and endoscopically placed Procter-Livingstone prostheses (Hegarty et al 1977) was unfavourable. In the present series, prosthesis placement provided good palliation of dysphagia, most patients managing a soft pureed diet; the experience of others has been very similar (Maercke et al 1985, Goldschmid et al 1988, Spinelli et al 1991). In the presence of recurrent laryngeal nerve palsy the functional result is poor despite accurate positioning of the prosthesis because of significant tracheal aspiration and associated dysmotility of the hypopharynx.

Proximal prosthesis migration did not occur in the present study. The design of the upper end of the modified prosthesis with a 3mm rim of reinforced funnel acting as a retainer ring, proved effective in preventing distal migration. Both dilatation induced perforations in this series occurred in patients with very fibrotic strictures who had previously received radiotherapy, in one patient despite gradual dilatation. The perforation was adequately occluded in both cases by the prosthesis as evidenced by the absence of a leak on a contrast swallow study and the patients made an uncomplicated recovery. In order to minimise the risk of full thickness splitting of tight fibrotic strictures, dilatation to the diameter necessary for intubation should be performed gradually at multiple sessions.
Stridor development, another of the traditional concerns regarding intubation of cervical oesophageal tumours, occurred in two patients in the present study but was transient and resolved completely within 72 hours. Significant airway compromise resulting in dyspnoea and stridor occurs in up to 10% of cases after oesophageal prosthesis insertion and it has been suggested that all patients with upper oesophageal carcinomas should undergo bronchoscopy prior to intubation (Utts et al. 1985, Buset et al. 1990, Colt et al. 1992). Routine endoscopic inspection of the trachea for tumour invasion or external compression prior to intubation was not performed in the present study. It was decided to bronchoscope patients only if they developed stridor or significant respiratory distress during preliminary oesophageal dilatation (performed under conscious sedation so that such signs could be detected) or after intubation. However, as tracheal obstruction may cause sudden death, such a policy will not eliminate fatalities from this complication and assessment of all patients for possible tracheal narrowing prior to intubation would be a safer approach. As CT scanning is a sensitive means of detecting tracheal tumour involvement (Picus et al. 1983, Thompson et al. 1984), it could be used as the initial investigation followed by bronchoscopy in patients with tracheal displacement or compression. If significant extrinsic tracheal compression is demonstrated bronchoscopically, oesophageal intubation should be performed only after the formation of a tracheostomy (for upper tracheal compression) or stenting of the trachea with plastic or expanding metal prostheses (Westaby et al. 1982, George et al. 1990, Colt et al. 1992). Combined oesophageal and tracheal stenting can be performed at a single session, usually under general anaesthesia, through the close collaboration between gastroenterologist and pulmonary physician and has proved very successful in providing relief of both dysphagia and dyspnoea (Colt et al. 1992). After insertion of a modified prosthesis, the attending nursing and medical staff should be instructed to report the development of respiratory distress early, so that endoscopic removal of the prosthesis if deemed necessary will not be delayed. In cases of imminent respiratory arrest the prosthesis can be removed rapidly by grasping it in the hypopharynx with Magill forceps under direct laryngoscopic vision.

It can be concluded that endoscopic intubation should not be absolutely contraindicated for high cervical oesophageal carcinomas. The initial clinical experience with a specially modified Celestin prosthesis presented in this chapter is very encouraging. There was no significant procedure related
morbidity or mortality, the prosthesis was well tolerated without troublesome foreign body sensation and provided worthwhile palliation of dysphagia and symptoms due to tracheo-oesophageal fistulation in a group of patients who would otherwise have suffered terribly until their death.
Part III: Palliation of Rectosigmoid Cancer
Chapter 9

A prospective study of Nd:YAG laser therapy for the palliation of rectosigmoid cancer

9.1 Introduction

At the time of diagnosis approximately one third of rectosigmoid cancers are incurable because of advanced loco-regional disease or distant metastases (Bordos et al 1974, Longo et al 1988). As discussed in Chapter 3, 3.1, the management of these patients poses several challenges. Over the past fifty years several techniques (reviewed in detail in Chapter 3, 3.2) have been developed for the treatment of local symptoms in patients unsuitable for surgery because of high anaesthetic risk and as an alternative to palliative surgery in those with incurable disease. Nd:YAG laser therapy is one of the more recent of these treatments and has been employed clinically since the early 1980s. Review of the literature (chapter 3, 3.2.1), shows that although a high initial success rate with laser therapy has been confirmed by several studies (Mathus-Vliegen and Tytgat 1986b,c, Escourou et al 1986, Naveau et al 1986, Bown et al 1986, Krasner 1989), the long-term efficacy of the technique is not well documented. What is more, some recent studies have questioned the ability of laser therapy to provide prolonged symptomatic improvement, recommending palliative surgery as a better therapeutic option (Van Custem et al 1989, Bright et al 1992). The present prospective study was performed in order to provide a detailed audit of the initial and long-term results of palliative Nd:YAG laser therapy for rectosigmoid cancer and to identify clinically relevant prognostic indicators of functional outcome.

9.2 Patients and Methods

9.2.1 Patients

Forty nine patients with rectosigmoid adenocarcinomas received endoscopic laser therapy at the National Medical Laser Centre during the period 1986-1989. They were referred because of incurable disease (documented distal metastases or advanced loco-regional disease), high surgical risk (advanced...
age, severe concomitant disease) or refusal of surgery. Patients were divided into two groups according to tumour size. Those with tumours less than 3cm in maximum diameter and involving less than one third of the bowel circumference were allocated to group 1; patients with larger lesions were allocated to group 2. Patient details, symptomatic presentation and indications for laser therapy in the two groups are shown in Table 9.1. Three patients in Group 1 had asymptomatic anastomotic recurrence after anterior resection of the rectum discovered at routine follow-up. Twelve of the sixteen cases with locally advanced disease in group 2, were patients with symptomatic tumour recurrence after anterior resection. Tumour details are shown in Table 9.2. In group 2, eight tumours (19%) were located totally below the peritoneal reflection of the rectum and twenty three (55%) had a distal margin less than 7cm from the anus. If tumour resection had been attempted in the latter patients, most would have required an abdominoperineal operation and permanent colostomy.

9.2.2 Treatment Techniques

Whenever possible treatments were performed on an out-patient basis. The rectum was evacuated by the administration of sodium phosphate enemas and occasionally a washout. Many patients required no sedation or analgesia during the procedure; if necessary Diazepam in lipid suspension (Diazemuls) and Pethidine were administered intravenously. Lesions encroaching onto the anal verge were treated under general anaesthesia as laser therapy at this site can be exquisitely painful. A flexible sigmoidoscope (Fujinon S1G ET) with a safety filter in its eyepiece was used. The laser instrumentation used was the same as for the treatment of oesophageal carcinomas. Insufflated gas and smoke produced during treatment, was vented through the working channel of the sigmoidoscope by connecting it through its auxiliary inlet to a water-seal drain under a head of about 20cm of water which maintained adequate luminal distention.

The aim of treatment was to destroy as much tumour as possible in one session using a non-contact technique was used. Exophytic tumour nodules were shaved back close to the rectosigmoid wall by vaporisation using high power pulses (60-80W, 1-2sec shots). The last 3-4mm of luminal tumour and flat sessile lesions were treated by coagulation alone (50-60W, 1sec shots) in order to minimise the risk of perforation. Whenever possible treatment of tumours causing significant luminal narrowing started at their superior
<table>
<thead>
<tr>
<th></th>
<th>GROUP 1 (n=7)</th>
<th>GROUP 2 (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Ratio (M : F)</td>
<td>4 : 3</td>
<td>20 : 22</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>71 (53-90)</td>
<td>73 (43-90)</td>
</tr>
<tr>
<td>Symptomatic presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>RD/tenesmus/incontinence</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Obstruction ± RD</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Indications for laser treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastases</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Advanced local disease</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>High surgical risk, refusal of surgery</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

RD = Rectal discharge
Table 9.2: Tumour details.

<table>
<thead>
<tr>
<th>Circumferential extent</th>
<th>GROUP 1 (n=7)</th>
<th>GROUP 2 (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1/3 (C₁)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>1/3 - 2/3 (C₂)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 2/3 (C₃)</td>
<td>0</td>
<td>34</td>
</tr>
</tbody>
</table>

Mean tumour length (range), cm

<table>
<thead>
<tr>
<th>Distal tumour margin &lt;7cm from anus</th>
<th>GROUP 1 (n=7)</th>
<th>GROUP 2 (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>23</td>
</tr>
</tbody>
</table>

Site

<table>
<thead>
<tr>
<th>Site</th>
<th>GROUP 1 (n=7)</th>
<th>GROUP 2 (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Rectosigmoid junction</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>
(proximal) margin and proceeded inferiorly, as immediate oedema in unvaporised areas can hinder forward progress and make visualisation difficult. For tumours impassable with the sigmoidoscope, dilatation with "through-the-scope" balloon dilators was attempted in order to provide access to their superior margin, although this often proved unsuccessful. Inadequately dilated and completely obstructing carcinomas were treated in a forward direction recanalising 1-2 cm of tumour at each session. Treatments were repeated at intervals of 3-7 days allowing time for sloughing of necrosed tumour, until adequate tumour destruction was achieved. After successful initial laser therapy, treatments were repeated electively every 6-8 weeks as appreciable tumour regrowth causing recurrent symptoms occurs in most patients during this time interval (Bown et al 1986, Brunetaud et al 1987). In addition, it appears that long-term outcome may be less favourable if patients are retreated at longer intervals (Van Custem et al 1989).

9.2.3 Patient Evaluation

9.2.3.1 Group 1

In asymptomatic patients treatment was considered successful if complete macroscopic and microscopic tumour eradication was achieved. In those presenting with rectal discharge or tenesmus, treatment was deemed successful if they were rendered completely asymptomatic.

9.2.3.2 Group 2

Evaluation of the effect of treatment in this group of patients is more difficult and to a great extent subjective, especially in those presenting with rectal discharge, haemorrhage, incontinence and tenesmus. Pain caused by local infiltration in the pelvis cannot be palliated by laser therapy and has not been assessed. In the past, both our group (Bown et al 1986) and others (Brunetaud et al 1987, Van Custem et al 1989), have attempted to objectively quantify these symptoms. Our subsequent experience however, has shown that this can prove extremely difficult especially in elderly, terminally ill patients. In the present study a more subjective assessment has been used. Laser therapy was considered successful if symptoms caused by intraluminal tumour were reduced to an extent that enabled the patient to lead a lifestyle appropriate for his/her age and general condition without constant concern for bowel function. Thus treatment success depended both on a patient's subjective
assessment of and attitude towards these symptoms. In patients with predominantly obstructive symptoms, clinical examination findings and plain abdominal radiographs demonstrating the degree of faecal loading proximal to the tumour were also used to assess the result of treatment.

9.2.4 Statistics

Statistical analyses were performed using a $\chi^2$ test with Yate's correction and the Wilcoxon test. Survival and symptom palliation (SP) distributions were constructed using the life table (Kaplan-Meier) method; for the calculation of the SP distribution, patients dying palliated were censored, that is considered lost to follow-up. Significance was set at the 5% level ($p<0.05$).

9.3 Results

9.3.1 Group 1

Complete control of symptoms was achieved in all four patients complaining of rectal discharge with or without tenesmus and maintained until death which occurred from unrelated causes 13-20 (mean 16) months after entry into the study. Complete macroscopic and microscopic tumour eradication was possible in only one of these patients.

In the three asymptomatic patients, complete tumour destruction with negative biopsies was achieved in two. The patient with residual microscopic tumour received external beam radiotherapy (60Gy) with complete tumour eradication. All three patients have died of unrelated causes without evidence of tumour recurrence after 26, 42 and 55 months. The average number of laser treatments required to eradicate macroscopic tumour was 3.5 (range 2-5).

9.3.2 Group 2

9.3.2.1 Symptomatic Palliation

All patients have been followed-up until death. Laser therapy was initially successful in thirty four patients (81%) and symptomatic improvement was maintained until death by repeated treatments in thirty one of these (74%).
Survival and symptom palliation distributions calculated using the life table method are shown in Figure 9.1.

Symptomatic palliation rates analysed according to circumferential tumour extent are shown in Table 9.3; tumours involving between one and two thirds of the bowel wall circumference were designated as C₂ and those which were more than two thirds circumferential as C₃. The initial success of laser therapy was significantly greater in patients with C₂ than C₃ tumours (p<0.01). Although the long-term success rate was numerically greater in patients with C₂ tumours, the difference was not statistically significant, but a type II error cannot be excluded given the small size of this patient group. In contrast to circumferential tumour extent, statistical analysis demonstrated that tumour length less than 5cm and distal margin less than 7cm from the anus, had no prognostic importance as indicators of successful initial outcome after laser therapy. In addition, the initial and long-term success rates of laser therapy in patients with anastomotic recurrences after surgery and primary tumours were very similar.

Patient outcome analysed according to main presenting symptoms and further management of treatment failures are shown in Table 9.4. Both the early and long-term success rate of laser therapy was numerically but not significantly greater in patients with rectal discharge, incontinence and tenesmus than in those with obstructive symptoms. It should be noted that after successful initial treatment, symptomatic improvement could be maintained long-term by repeated laser treatments in 91% of patients. Two thirds of the patients in whom treatment failed were managed by defunctioning colostomy; the remaining ones were considered too unwell for further intervention. In the group presenting with rectal discharge, treatment failures occurred because of anal incontinence despite adequate tumour destruction, presumably as a result of tumour involvement of the anal sphincters. In patients with obstructive symptoms, one early and one late failure were due to laser induced perforation; both patients made an uneventful recovery after defunctioning colostomy formation.

9.3.2.2 Treatment Requirements and Hospitalisation

Initial symptomatic improvement was noted early (mean 1.5 weeks) after a mean 1.6 treatments; an additional 3.5 procedures were required on average.
Figure 9.1: Survival and symptom palliation (SP) distributions (life table method) for patients with advanced rectosigmoid cancers (group 2). All patients have been followed-up until death.
Table 9.3: Functional outcome after laser therapy according to circumferential tumour extent in patients with advanced rectosigmoid cancers (group 2).

<table>
<thead>
<tr>
<th>C grade</th>
<th>Early functional success</th>
<th>Long-term functional success</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_2) (n=8)</td>
<td>8 (100%)(^a)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>C(_3) (n=34)</td>
<td>26 (76%)(^a)</td>
<td>24 (71%)</td>
</tr>
</tbody>
</table>

\(^a\) p < 0.01

\(C_2\): 1/3 - 2/3 circumferential; \(C_3\): >2/3 circumferential
Table 9.4: Functional outcome after laser therapy according to main presenting symptoms and management of treatment failures in patients with advanced rectosigmoid cancers (group 2).

<table>
<thead>
<tr>
<th>Presenting symptom</th>
<th>Early functional success</th>
<th>Long-term functional success</th>
<th>Management of failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge / Incontinence (n=27)</td>
<td>23 (85%)</td>
<td>21 (78%)</td>
<td>Early: Defunctioning colostomy (2) Terminal care (2) Late: Defunctioning colostomy (2)</td>
</tr>
<tr>
<td>Obstruction (n=15)</td>
<td>11 (69%)</td>
<td>10 (67%)</td>
<td>Early: Defunctioning colostomy (2) Terminal care (2) Late: Defunctioning colostomy (1)</td>
</tr>
</tbody>
</table>
in order to maintain this improvement until death. Approximately 30% of laser treatments were given on an outpatient basis and mean of 8000J of energy delivered per procedure. Average total lifetime hospital stay, excluding admissions for terminal care, was 9 days (each day case attendance was counted as one day in hospital).

9.3.2.3 Treatment Complications

Laser therapy was generally well tolerated. A proportion of patients, particularly those with tumours close to the anal margin, experienced mild to moderate discomfort during the procedure due to the heating effect of the laser. Following the procedure, some patients reported transient abdominal distention and discomfort as a result of the insufflated gas and others an increase in rectal discharge lasting 24-48 hours. Laser induced perforation occurred in two patients (5%) with impassable circumferential carcinomas at the rectosigmoid junction; both were managed by defunctioning colostomy. One patient developed localised peritonitis and transient pyrexia within 12 hours of laser therapy; no leak was detected on a gastrografin enema and the patient made an uneventful recovery with conservative treatment. There was no procedure related mortality in the present series.

9.3.2.4 Survival

Mean survival (sd) of group 2 patients was 5.0 (3.8) months. Survival probability decreased rapidly (0.65, 0.50, 0.30, 0.15 at 2, 4, 8, 12 months respectively) with no survivors beyond 16 months - Figure 9.1. There was no significant difference in average survival when patients were stratified according to symptomatic presentation (rectal discharge with or without tenesmus: 5.4, obstruction: 4.5 months), circumferential tumour extent (C2: 6.8, C3: 4.2 months) and the presence or absence of hepatic metastases (4.4 and 5.4 months respectively).

9.4 Discussion

The aims of any palliative treatment for rectosigmoid cancer are to improve local symptoms and patients' quality of life with minimal morbidity and mortality. Nd:YAG laser therapy was initially successful in 81% of patients with advanced tumours (group 2) in the present series, in agreement with the
experience of other groups who have reported 80%-90% success rates in similar patients (Mathus-Vliegen and Tytgat 1986b,c, Escourou et al 1986, Brunetaud et al 1987, Van Custem et al 1989, Krasner 1989). Importantly, symptomatic improvement was noted early and prolonged hospital stay was unnecessary. An average of only 1.6 treatments given over 1.5 weeks in the present study and 2.5 treatments over 2.4 weeks in Brunetaud’s study (1987) were necessary to achieve initial improvement. Long-term symptomatic palliation was possible with repeated treatments in 74% of Group 2 patients, in accordance with the experience of Brunetaud and colleagues (1987) who found that the proportion of surviving patients remaining palliated at 6, 9, 12 and 24 months was 90%, 89%, 82% and 64% respectively. In contrast, a study from Belgium (Van Custem et al 1989) reported a much lower symptomatic improvement in surviving patients - 51%, 41% and 25% at 6, 12 and 18 months respectively and the authors attributed the rather poor long-term outcome to progressive growth of extrinsic tumour which is not amenable to laser therapy. It should be noted however, that in this study patients were retreated only if they developed further symptoms resulting in an appreciably longer interval between procedures (mean 4.7 months) than in the present investigation (mean 2.6 months). With longer re-treatment intervals, endoscopic therapy becomes technically more difficult (as a result of the greater tumour bulk) and the chances of maintaining palliation are reduced. Equally disappointing results with laser therapy for advanced rectal cancers were reported by Bright and colleagues (1992). Palliation until death was possible in only 32%, both in patients with obstruction and those with rectal discharge and tenesmus; nearly two thirds of patients who failed to improve required a defunctioning colostomy.

Of the various parameters examined as prognostic indicators of initial and long-term outcome after laser therapy in group 2 patients, only circumferential tumour extent (C2 vs C3) proved significant; initial success was significantly higher in C2 tumours but the improved outcome was not maintained long-term. The findings of Brunetaud and coworkers (1989), who have a more extensive experience, are in exact agreement. In contrast, Van Custem and colleagues (1989) have found circumferential tumour extent to be of no prognostic significance. In their study, long-term outcome was significantly worse in patients with tumours greater than 4cm in length and with recurrent carcinomas after previous resection or locally advanced...
tumours (high T stage), presumably because of extensive extraluminal
disease.

At least 60% of group 2 patients in the present study would probably have
required a permanent colostomy had they been managed surgically, given the
low position of their tumours; laser therapy avoided the need for this in 70% of
cases. Two thirds of the treatment failures in patients with rectal discharge
and incontinence were functional, as symptoms persisted despite adequate
tumour destruction; the experience of Bright and colleagues (1992) is similar.
As all these patients had low rectal cancers, the lack of symptomatic
improvement could be attributed to loss of rectal compliance and tumour
involvement of the anal sphincters. The remaining failures in this group,
occurred in patients with massive tumours which could not be adequately
ablated. Failure of treatment in patients with obstructive symptoms occurred
because of inadequate recanalisation or perforation of completely
circumferential and impassable tumours. It should be noted, that half of all
patients who failed to improve after initial laser treatment were considered
too unwell for any further intervention.

A specific palliative treatment will become accepted only if high therapeutic
efficacy can be achieved with low morbidity and mortality, it is well tolerated
and requires only short hospital stay. Laser therapy for advanced rectal cancers
fulfills all these criteria. There was a 5% perforation rate, 2% minor
complication rate and nil procedure related mortality in the present study.
Other groups have reported major (perforation, fistulation, sepsis and
bleeding) and minor complications (transient pyrexia and bleeding not
requiring transfusion) in 3-10% and 5-10% of patients respectively and a
mortality of 1-2.5% as discussed in Chapter 3, 3.2.1. Laser therapy is generally
well tolerated; patients may experience minor discomfort during treatment
due to a local heating effect and have increased rectal discharge for 24-48
hours afterwards due to sloughing of necrosed tumour. Importantly, as
general anaesthesia and full bowel preparation are not required, laser
treatments can be performed on a day-case basis in ambulant patients
minimising time in hospital. Logically, all these factors should result in an
improvement of patients' quality of life which is the ultimate goal of any
palliative treatment. Such an improvement in a group of patients with
advanced rectal cancer, has been documented objectively using two validated
Other alternative treatments for the palliation of rectal cancer have been reviewed in detail in Chapter 3, 3.2. Although external beam and afterloading radiotherapy have produced excellent results in patients with small rectal tumours, palliation of more advanced lesions is much less satisfactory. Rectal discharge and tenesmus are improved in only about 50% and patients with obstructing tumours often require a defunctioning colostomy during the course of treatment. In addition, symptomatic improvement is often short-lived and radiation proctitis, delayed haemorrhage and fistulation are not uncommon (Sichy et al 1980, Puthawala et al 1982, Papillon 1984, Allum et al 1987, Taylor et al 1987). Radiotherapy in combination with laser treatment should theoretically reduce the frequency of repeat treatments by retarding intraluminal tumour regrowth, prevent or delay extrinsic compression by shrinking extraluminal tumour and reduce pain due to pelvic infiltration. The use of adjuvant radiotherapy was studied in a small pilot study by Sargeant and colleagues (1993). Of 13 patients with advanced rectosigmoid cancers who received external beam radiotherapy (30-55Gy, 10-20 fractions) after laser therapy, long-term palliation was achieved in eleven (85%); the median interval between laser procedures was 20 weeks, which is several times longer than when laser is used as monotherapy. Radiotherapy was generally well tolerated but three patients developed rectal strictures which were successfully managed endoscopically. Median survival (14 months) was appreciably longer than in the present study (4 months) but could be accounted for by patient selection. These encouraging preliminary results will require confirmation by randomised controlled trials.

Cryosurgery, like laser therapy, is easy to perform and well tolerated, does not require anaesthesia except for very low tumours but repeated applications are necessary to maintain symptomatic improvement. It is however limited to tumours below the peritoneal reflection of the rectum because of the risk of free perforation. Good tumour debulking can be achieved but tumour sloughing and rectal discharge may continue for up to two weeks (Mlasowsky et al 1985). Although in some studies the efficacy of cryosurgery is very similar to that of laser therapy, significant complications are reported in up to 40% of patients (Heberer et al 1987). Electrocoagulation has a high success rate (77-94%) but requires general or regional anaesthesia and cannot be used above the peritoneal reflection. Like cryosurgery, it carries a high complication rate, up to 30%, reflecting the lack of treatment precision and unpredictable extent of induced tissue damage with these techniques (Hughes
et al 1982, Madden and Kandalaft 1983, Hoekstra 1985). Encouraging results have been reported with endoscopic transanal resection (Berry et al 1990) but it requires general or spinal anaesthesia and prolonged anal dilatation and carries a significant complication rate, appreciably higher than that of laser therapy.

The results of the present study and the experience of others, indicate that laser therapy for small rectal carcinomas can achieve excellent symptomatic palliation and complete macroscopic and microscopic tumour eradication in up to 100% of patients with minimal associated morbidity (Escourou et al 1986, Brunetaud et al 1987). Electrocoagulation, cryosurgery and brachytherapy are equally effective as laser therapy for small lesions but their limitations and complications are the same as for the treatment of more extensive tumours. Despite such good results, curative local treatment of small rectal cancers with the laser remains controversial. At presentation, 7-12% of carcinomas involving the submucosa and muscularis propria of the rectum (UICC stage T2) have already metastasised to local lymph nodes and are therefore beyond the scope of local treatment (Goldberg and Thorson 1987). Endoscopic ultrasound is at present the most sensitive means of assessing lymph node status but its accuracy is still no greater than 80% (Hildebrandt and Feifel 1993). Therefore, in operable patients with early rectal cancers radical surgery remains the treatment of choice. However, curative laser therapy is justified in those refusing surgery and elderly and poor surgical risk patients, especially when abdominoperineal resection is the alternative.

On the basis of present evidence, endoscopic laser therapy should probably be considered the palliative treatment of choice in patients with rectal carcinoma unsuitable for surgery. It is applicable to lesions both above and below the peritoneal reflection, does not require anaesthesia or prolonged anal dilatation and provides good long-term symptomatic control in a high percentage of patients with a low morbidity and mortality unparalleled by any of the rival treatment methods. It should be noted however, that laser therapy has not been formally compared with alternative treatments; well designed clinical trials are therefore required in order to establish the proper clinical role of these palliative techniques. As complete eradication of small rectal carcinomas (less than 3cm diameter) is possible in virtually all patients with such tumours, curative local laser treatment should be considered in highly selected cases.
10.1 Introduction

The management of patients with incurable rectosigmoid cancer poses several challenges which have been discussed in detail Chapter 3, 3.1. The emphasis of any therapeutic interventions should be on improving the quality of remaining life by providing good symptomatic palliation with low risk and short necessary hospital stay, rather than on prolonging survival at all cost. The widely held belief that surgery offers good, if not the best, palliation for advanced rectosigmoid cancer is beginning to be challenged as careful audit of published results suggests that this may not be so. Although palliative tumour resection provides the best control of local symptoms, it is associated with a significant morbidity and mortality and may necessitate the formation of a permanent colostomy and prolonged patient hospitalisation. Defunctioning colostomy for unresectable tumours, which carries a mortality up to 6% and an appreciable morbidity, provides effective relief of obstructive symptoms but is of little value in palliating rectal bleeding, discharge and tenesmus (Bordos et al 1974, Wanebo et al 1978, Wobbes et al 1985, Moran et al 1987, Longo et al 1988, Lewis and Khoury 1988, Gordon et al 1993).

Several alternative treatments, including endoscopic laser therapy, have therefore been developed in an attempt to overcome some of the disadvantages of palliative surgery; these have been reviewed in Chapter 3, 3.2. Rational therapeutic choices should ideally be based on scientific data provided by well designed comparative trials of palliative surgery and alternative techniques. Despite the fact that laser therapy for advanced rectosigmoid cancer has been widely used over the last decade with considerable success and safety, its effectiveness in relation to palliative surgery is still not well documented. A randomised controlled comparison of the two techniques did not prove feasible in our experience, as the majority of patients treated at University College Hospital are referred from outside centres specifically for laser therapy after surgery has been refused because of local invasion or hepatic metastases. Instead, the results of laser treatment in
these patients were compared retrospectively with those of palliative surgery performed prior to the availability of laser therapy.

10.2 Patients and Methods

10.2.1 Study Objectives

The aims of the study were to compare surgery and Nd:YAG laser therapy for the palliation of advanced rectosigmoid cancer by assessing long-term symptomatic control, treatment related morbidity and mortality, hospitalisation time and survival.

10.2.2 Patients and Study Design

Patients with advanced rectosigmoid cancer managed surgically at University College Hospital between 1978-1987 were identified from a database comprising all patients operated on for colorectal carcinoma. Their outcome was analysed retrospectively from information obtained by review of hospital case notes and postal questionnaires completed by the patients' general practitioners. The laser group comprised patients with advanced rectosigmoid cancer treated between 1986-1988 as part of the prospective audit of endoscopic Nd:YAG laser therapy presented in Chapter 9. The majority of these patients were referred to the National Medical Laser Centre from other hospitals as they were considered unsuitable for surgery. For the purpose of this study and to allow uniform comparisons, rectosigmoid cancer was defined as advanced if it had invaded locally precluding a radical curative resection or had metastasised to the liver. The extent of local disease was assessed by digital examination and sigmoidoscopy and in some cases by pelvic CT scanning. In patients managed surgically, the extent of local disease was assessed more precisely at laparotomy. In the laser group, 12 patients were deemed to have advanced local disease based on clinical examination and pelvic CT scanning and the remaining four on clinical examination alone. None of the 9 patients in the surgery group with advanced local disease had pre-operative CT scans. Hepatic metastases were detected by ultrasound or CT scanning and in patients who underwent surgery additionally by liver palpation at laparotomy; the extent of liver involvement was not recorded.
Follow-up was available for 47 seven patients managed surgically and 35 treated with the laser. Patient details, tumour characteristics and extent of disease are shown in Table 10.1.

10.2.3. Endoscopic Laser Technique

The technique has been described in detail in Chapter 9, 9.2. After successful initial therapy, elective re-treatment was performed at intervals of 6-8 weeks, as appreciable tumour regrowth usually occurs during this time interval. Ambulant patients were treated on a day case basis.

10.2.4. Assessment of Symptomatic Palliation

Detailed symptomatic assessment after surgery was not possible as patient outcome was analysed retrospectively. Patients presenting with predominantly obstructive symptoms were considered to be successfully palliated if they had tumour resection or defunctioning colostomy alone. Those presenting with rectal discharge, bleeding or tenesmus and no significant obstructive symptoms, were considered inadequately palliated if they had a defunctioning colostomy only.

As discussed in Chapter 9, 2.3.2, objective quantitative assessment of symptoms after laser therapy is difficult especially in elderly, terminally ill patients. Therefore, a more subjective assessment of efficacy was used. In patients presenting with rectal discharge, bleeding or tenesmus without significant obstruction, laser treatment was considered successful if there was a significant objective and subjective symptomatic improvement enabling the patient to lead a lifestyle appropriate for his/her age and general condition and the need for repeated blood transfusions prevented. In patients presenting with predominantly obstructive symptoms, laser treatment was considered successful if the need for a colostomy was obviated; additional information was derived from clinical examination and plain abdominal X-rays demonstrating the degree of faecal loading proximal to the tumour.

10.2.5 Statistics

Comparisons between non-randomised groups, as in the present study, are obviously subject to bias. Statistical analyses were used only for the purpose of demonstrating apparent differences and indicating possible treatment effects
Table 10.1: Patient details, tumour characteristics and extent of disease.

<table>
<thead>
<tr>
<th></th>
<th>SURGERY (n=47)</th>
<th>LASER (n=35)</th>
<th>p-value</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M:F)</td>
<td>24 : 23</td>
<td>19 : 16</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (range), yrs</td>
<td>66 (29-84)</td>
<td>72 (43-90)</td>
<td>&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Symptomatic presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD ± Tenesmus</td>
<td>29 (61%)</td>
<td>20 (57%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>18 (39%)</td>
<td>15 (43%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>33 (70%)</td>
<td>27 (77%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>14 (30%)</td>
<td>8 (23%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Distal tumour margin ≤7 cm from anus</td>
<td>16 (34%)</td>
<td>21 (60%)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Liver metastases</td>
<td>38 (81%)</td>
<td>19 (54%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Advanced local disease</td>
<td>9 (19%)</td>
<td>16 (46%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

RD: rectal discharge; NS: not significant
and should be interpreted with caution as they can be misleading. The $\chi^2$ test with Yate's correction and the Wilcoxon two sample test were used. Survival distributions were calculated using the life table method and tested for disparity by log rank analysis. Significance was set at the 5% level ($p<0.05$).

10.3 Results

In the surgery group 34 patients (72%), underwent tumour resection - sixteen by anterior resection (three had a temporary defunctioning colostomy), thirteen by abdominoperineal excision and five by Hartmann's procedure; the remaining 13 patients had a defunctioning colostomy alone.

Long-term symptomatic palliation rates in the two groups, according to the criteria for successful treatment outcome outlined above, are shown in Table 10.2. Although the overall success of the two treatment modalities was similar, surgery proved superior in providing long-term palliation of obstructive symptoms. All five failures of laser therapy in patients with obstruction occurred with circumferential, impassable tumours because of inadequate recanalisation or perforation. Overall, of the nine long-term functional failures of laser therapy, six were managed by defunctioning colostomy (three for obstruction and three for incontinence/rectal discharge) and the remaining patients received terminal care as they were considered unsuitable for any further active treatment. Symptomatic improvement with laser therapy was noted early after a mean of 1.6 (range 1-3) treatments; on average an additional 3.5 treatments were required in order to maintain palliation long-term. 30% of procedures were performed as day cases.

Morbidity, mortality and hospitalisation time are detailed in Table 10.3. Three quarters of the complications after surgery were major in nature; 20% of these were due to haemorrhage, anastomotic leakage and sepsis and 80% related to cardiovascular, thromboembolic and respiratory events. Laser induced perforation occurred in two patients (6%) with impassable circumferential carcinomas at the rectosigmoid junction, both of whom were successfully managed by defunctioning colostomy formation. One patient developed localised peritonitis and pyrexia after laser therapy without a radiological leak, which settled on conservative management.
Table 10.2: Long-term palliation rates.

<table>
<thead>
<tr>
<th></th>
<th>SURGERY</th>
<th>LASER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>18/18 (100%)</td>
<td>10/15 (67%)</td>
</tr>
<tr>
<td>RD/Tenesmus</td>
<td>22/29 (76%)</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>40/47 (85%)</td>
<td>26/35 (74%)</td>
</tr>
</tbody>
</table>

RD: rectal discharge; NS: not significant
Table 10.3: Morbidity, mortality and hospitalisation time.

<table>
<thead>
<tr>
<th></th>
<th>SURGERY (n=47)</th>
<th>LASER (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>4 (8.5%)</td>
<td>0%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Morbidity</td>
<td>20 (44%)</td>
<td>3 (9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean hospitalisation time</td>
<td>40 (12-120)</td>
<td>10 (4-27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(range), days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Survival distributions for the two treatment groups calculated by the life table method are shown in Figure 10.1. In the laser group, all patients were followed-up until death; in the surgery group 5 patients have been lost to follow-up after a mean of 10 (range 2-38) months. Overall, there was no significant difference in survival between surgically treated patients and those managed by laser therapy, although a small proportion of patients in the former group survived beyond 15 months; mean survival (sd) of the two groups was 7.7 (9) and 4.7 (4) months respectively. Survival distributions of patients with hepatic metastases or advanced local disease in the two treatment groups were also not significantly different - Figure 10.2.

Survival after tumour resection (mean 9.3, median 5.5, range 1-38 months) was significantly better (p<0.03) than that of patients managed by defunctioning colostomy (mean 3.2, median 3, range 1-7 months) or laser therapy (mean 4.7, median 3, range 1-7 months). Survival analysis according to the type of operation performed in patients with liver metastases or advanced local disease is shown in Table 10.4. Tumour resection conferred a significant survival advantage over defunctioning colostomy or laser therapy in patients with hepatic metastases but not in those with advanced local disease. However, as this was a retrospective comparison, data on the extent of metastatic liver involvement was unavailable to allow group matching.

10.4 Discussion

The results of the prospective audit presented in Chapter 9 and the experience of other groups (Mathus-Vliegen and Tytgat 1986b,c, Naveau et al 1986, Brunetaud et al 1987, Krasner 1989) appear to justify the use of endoscopic Nd:YAG laser therapy as an alternative to surgery for advanced rectosigmoid cancer. Laser therapy provides satisfactory control of symptoms with minimal upset and risk for the patient and enables lesions on either side of the peritoneal reflection of the rectum to be treated safely under direct visual control without general anaesthesia. However, it is important to ascertain that laser therapy is not being employed indiscriminately in preference to surgery at the risk of prejudicing patient outcome. Ideally, the two treatment modalities should be compared by a randomised controlled trial but it proved impossible in our experience to organise such a study as discussed already.
Figure 10.1: Survival curves of patients with advanced rectosigmoid cancer managed by palliative surgery (n=47) or laser therapy (n=35). Distributions not significantly disparate by log rank analysis.
Figure 10.2: A, Survival curves of patients with rectosigmoid cancer and hepatic metastases managed by palliative surgery (n=38) or laser therapy (n=19). Distributions not significantly disparate by log rank analysis. B, Survival curves of patients with locally advanced rectosigmoid cancer managed by palliative surgery (n=9) or laser therapy (n=16). Distributions not significantly disparate by log rank analysis.
Table 10.4: Survival according to extent of disease and treatment.

<table>
<thead>
<tr>
<th></th>
<th>SURGERY Mean Survival [mo] (median, range)</th>
<th>LASER Mean Survival [mo] (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEPATIC METASTASES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Group</td>
<td>8.5 (5, 1-38) (n=38)</td>
<td>4.8 (2.5, 1-16)² NS (n=19)</td>
</tr>
<tr>
<td>Palliative Resection</td>
<td>10 (6, 1-38)² (n=30)</td>
<td></td>
</tr>
<tr>
<td>Colostomy</td>
<td>2.7 (2.5, 2-4) (n=8)</td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>ADVANCED LOCAL DISEASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Group</td>
<td>4.7 (3, 1-18) (n=9)</td>
<td>4.5 [4.2] NS (n=16)</td>
</tr>
<tr>
<td>Palliative Resection</td>
<td>5.4 (3,1-18) (n=4)</td>
<td>NS</td>
</tr>
<tr>
<td>Colostomy</td>
<td>4.0 (4, 1-7) (n=5)</td>
<td></td>
</tr>
</tbody>
</table>

mo: months; NS: not significant; ²: p<0.02
In view of the design of the present study, the two patient groups were dissimilar in some important respects. Mean age (72 vs 66 years, \( p<0.05 \)), the proportion of patients over age 70 years (71% vs 43%, \( p<0.01 \)) and those with low lying tumours (60% vs 34%, \( p<0.05 \)) or advanced local disease (46% vs 19%), \( p<0.001 \) were higher in the laser group. These differences reflect the hesitancy and caution exhibited by surgeons and their tendency to opt for the simpler treatment option when faced with high risk patients with a poor prognosis, especially when tumour resection can be accomplished only by an abdominoperineal approach.

Although the overall success of laser therapy and surgery in providing long-term palliation was similar (74% vs 85%), the latter proved superior in patients with predominantly obstructive symptoms. All patients with obstruction in whom laser treatment failed had advanced tumours causing virtually complete luminal occlusion and only half of these were fit for any further intervention. In the laser group, up to 60% of patients may have required a permanent colostomy had they been managed surgically in view of the low position of their tumours; this was avoided in nearly three-quarters of these patients. In the present study, the procedure related morbidity and mortality of palliative surgery was 44% and 9% respectively, figures consistent with published experience (Bordos et al 1974, Wanebo et al 1978, Moran et al 1987, Longo et al 1988, Wobbes et al 1985, Lewis and Khoury 1988, Gordon et al 1993). In contrast, there were no early deaths in the laser group and major complications occurred in only 8%. Moreover, despite the fact that repeated laser treatments were necessary in order to maintain symptomatic improvement, the average total hospital stay was still four times longer after surgery. The need for repeated treatments represents a significant disadvantage of laser therapy. As discussed in Chapter 9, 9.4, preliminary evidence (Sargeant et al 1993), suggests that adjuvant external beam radiotherapy, by retarding intraluminal tumour regrowth, may significantly prolong the re-treatment interval and reduce the total number of procedures during a patient's lifetime.

Overall survival was not significantly different in patients managed by surgery or laser therapy (mean 7.7 vs 4.7 months). As can be seen from Figures 10.1 and 10.2, the "tail" of the survival curve of the whole group of surgically treated patients can be accounted for by the survival beyond 15 months of a small proportion (approximately 6%) of patients with hepatic
metastases. In patients with advanced local disease, tumour resection did not confer an obvious survival advantage over defunctioning colostomy or laser therapy; in contrast, in patients with hepatic metastases tumour resection was associated with an apparent prolongation of survival compared to defunctioning colostomy or laser therapy. However, given the retrospective nature of the present study, patient groups were not matched in terms of extent of metastatic liver involvement which undoubtedly affects survival (Nielsen et al 1971, Wood et al 1976). The question whether resection of the primary tumour actually influences survival in patients with liver metastases was addressed by Jaffe and colleagues (1968). After controlling for the extent of liver involvement, they found no difference in survival (median 160 days) between patients managed by palliative resection or palliative colostomy although this has recently been challenged (Makela et al 1990). It is possible that in the present study the observed improvement in survival after palliative resection in patients with hepatic metastases, may be entirely due to pre-selection at the time of surgery of those with fewer hepatic metastases.

A literature search has revealed only two other studies which have attempted to compare laser therapy and surgery for advanced colorectal carcinoma (Mellow 1989, Vondeling et al 1991). In Mellow's retrospective study (1989), the outcome of 8 patients with rectal cancer and hepatic metastases who underwent surgery was compared with that of 10 similar patients who had laser therapy. The success of treatment was not stated but all surgically treated patients required a permanent colostomy. Treatment complications (38% vs 10%), mortality (20% vs 0%) and average total lifetime costs ($22,900 vs $12,154, p<0.005) were all greater in those managed surgically. Average survival in the surgery and laser groups was 28 and 36 weeks respectively (compared to 37 and 21 weeks respectively for patients with hepatic metastases in the present study). The second report by Vondeling and colleagues (1991), is a retrospective comparison of the outcome of patients with advanced colorectal cancer and predominantly obstructive symptoms treated by laser therapy (n=46) or surgery (n=17) in two university hospitals in the Netherlands. The groups were well matched for age and presence of metastases (laser 83%, surgery 71%), but tumour location and extent were not detailed. Long-term successful palliation was reported in 65% of laser treated patients (compared to 67% in the present series) and 71% of surgically treated patients; 41% of the latter required a permanent colostomy. The subsequent
management and outcome of treatment failures in both groups was not stated. Treatment related morbidity in the surgery and laser group was 24% and 8% respectively; the corresponding mortality figures were 0% and 4.5%. Survival was better after surgery (mean 11 vs 5 months) but the necessary hospital stay (mean 35 vs 19 days) and total lifetime cost (mean $15,100 vs $9,200) were greater.

An alternative palliative surgical procedure for advanced rectal cancer is that of endoscopic transanal tumour resection using a urological resectoscope; the techniques has been reviewed in detail in Chapter 3, 3.2.5. It is a simple and inexpensive technique but requires general or spinal anaesthesia and in practice treatment is limited below the peritoneal reflection of the rectum because of the risk of free perforation. In the largest and most detailed published series, the initial success rate of the technique was similar to that reported with laser therapy but the procedure related morbidity (27%) and mortality (7%) were significant, probably as a result of deep tumour resection often down to the level of the perirectal fat (Berry et al 1990). Transanal resection is a promising technique and should be formally compared with laser therapy; such studies may well derive greater support from surgeons than trials attempting to compare laser therapy with "open" palliative surgery. The combination of gross tumour debulking with the resectoscope followed by a more precise "tidy-up" with the laser may prove to be a rapid, effective and safe approach for palliating advanced rectosigmoid cancers.

In conclusion, it appears that for the patient with advanced rectosigmoid cancer, the clinical decision whether to resect, defunction or employ laser therapy should be made after careful consideration of the quality of palliation and life as well as the associated morbidity and mortality. In this respect, laser therapy is preferable for advanced loco-regional and metastatic disease. For patients with few hepatic metastases, resection of the primary tumour is probably the most logical option as additional treatment of the limited liver disease by resection (Rougier et al 1992, Allen-Mersh et al 1994) or regional perfusion chemotherapy (Nordlinger et al 1992, Scheele et al 1991) can improve ultimate survival. Careful clinical assessment, aided by imaging with CT scanning and endoscopic ultrasonography, should carefully identify patients with incurable disease who are best palliated by other methods thus preventing unnecessary laparotomies and radical non-curative resections. Tumour debulking by means of laser therapy used alone or in combination
with endoscopic transanal tumour resection plus radiotherapy may prove to be the best option for these patients; additional well designed clinical trials are required in order to define the optimum management policy.
Part IV: General Discussion
Chapter 11

General discussion and outlook for the future

11.1 Introduction

The general aim of this thesis was to place the role of endoscopic Nd:YAG laser therapy, either as monotherapy or in combination with other modalities, for the palliation of advanced gastrointestinal tract malignancies into its proper perspective by performing studies asking clinically relevant questions. A specific treatment should be employed clinically only after an objective examination of its efficacy, complications, advantages and limitations and not merely because it is available. In the early days following the introduction of lasers into clinical practice, the therapeutic laser endoscopist was often portrayed, in the words of Mark Twain, as "a man with a hammer, (to whom) a lot of things look like a nail that needs pounding". A large body of good quality research on the applications of lasers in gastroenterology has helped to permanently erase this picture; hopefully, the work presented in this Thesis has contributed in a small way to this end. In this final chapter the implications of the present findings will be discussed and an attempt will be made to provide an outlook for the future.

11.2 Palliation of Malignant Dysphagia

11.2.1 Lasers and Tubes

Several descriptive studies, reviewed in detail in chapter 2, have helped to define the indications and contraindications for laser therapy and intubation and to identify the advantages and limitations of the two endoscopic techniques. The majority of carcinomas of the oesophagus and gastric cardia have a major intraluminal component and are therefore suitable for treatment with either technique. If optimum results are to be achieved when should laser therapy or intubation be employed and if they are to be used in a complementary rather than a mutually exclusive fashion, in which order? The comparative study of the two techniques presented in chapter 5 was performed in an attempt to answer these questions. Patients with malignant dysphagia form a wide spectrum, some with very advanced disease and very
limited life expectancy and others whose general condition and prognosis are better. Management should therefore be individualised and adoption of rigid treatment protocols avoided. It is also important that the objectives of treatment for each patient should be clearly defined at the outset. Are we aiming to achieve a near normal quality of swallowing or is rendering the patient able to eat a semi-solid diet adequate? Are we attempting to prolong survival in addition to palliating dysphagia? These are important questions that need to be carefully considered in order to make the right therapeutic choices.

The first priority for the patient is the rapid and long-lasting relief of dysphagia. In the comparative study presented in chapter 5, both laser therapy and intubation achieved this aim in a high percentage of patients; although the efficacy of the two techniques was similar for cancers of the thoracic oesophagus, intubation proved superior for tumours of the gastric cardia. It should be noted however, that location of the tumour at the gastroesophageal junction has not emerged as a negative prognostic indicator of functional outcome after laser therapy in other series (Fleischer and Sivak 1985, Naveau et al 1990, Alderson and Wright (1990); clearly additional studies are indicated to clarify this issue. The long-term efficacy of the two techniques in the present investigation is comparable to that reported in the majority of published series of laser therapy and intubation (reviewed in chapters 2 and 5), although occasional studies (Alderson and Wright 1990, Carter et al 1992) have reported a significantly higher efficacy for the laser of the order of 85%. It should be noted however, that the latter studies were relatively small and not only included a significantly lower proportion of adenocarcinomas but also patients with anastomotic recurrent tumours which, in our experience (chapter 7) and that of others, have a generally favourable outcome after laser therapy. This clearly emphasises the importance of controlling for differences in the composition of patient groups resulting from variations in inclusion criteria when attempting comparisons between clinical trials.

Although the ultimate aim of any palliative treatment is to improve the quality of remaining life, this issue has received little attention in studies dealing with the management of malignant dysphagia. The results of the present investigation, which are in agreement with those Barr and colleagues (1990a) who used very similar methodology, demonstrate that both laser
therapy and intubation by improving swallowing and preventing inanition and pulmonary aspiration result in a significant initial improvement in quality of life. These findings not only validate the subjective clinical impression of doctors and nurses caring for these patients, but also indicate that the relative importance of quality of swallowing as a determinant of overall quality of life decreases with progression of the disease. The obvious practical implication is that therapeutic interventions aiming to achieve the best possible quality of swallowing are justified only for patients with good general condition and not those with advanced disease and very limited life expectancy.

The economic costing of endoscopic palliation of dysphagia indicates that the lifetime cost is likely, under most assumptions, to be greater with laser therapy than intubation using plastic prostheses. However, it should be stressed that this does not imply that intubation is more cost-effective. Given that survival after laser therapy and intubation is not significantly different, cost-effectiveness is crucially dependent on the impact of treatment on patients’ quality of life which in turn is significantly influenced by the quality of swallowing achieved and the treatment related morbidity. Neither the study in chapter 5, Section B nor that of Barr and colleagues (1990a), have detected a significant overall difference in quality of life after laser therapy or intubation, but the sample sizes in both studies were relatively small. Further work to establish the cost-effectiveness of the two endoscopic treatments is required, as increasingly decisions on allocation of limited resources are based on such data.

The quality of swallowing after endoscopic therapy for the palliation of malignant dysphagia is clearly an important issue. There is a general consensus in the literature that, as in the present investigation, the quality of swallowing provided by laser therapy is superior to that after intubation but it is more variable. On average some 30-40% of patients are able to eat a normal diet after laser therapy compared to 10-15% after intubation. Given the limited and fixed diameter of commercially available plastic prostheses, it is not surprising that only a small minority of patients are able to eat a normal diet.

In the majority of descriptive studies, the overall complication rate and mortality are significantly greater after endoscopic intubation than laser
therapy. It should be noted that most of the procedure related deaths with both interventions occur as a result of oesophageal perforation. The experience from the prospective comparative studies, all from specialist centres, is somewhat different. Both in the present investigation and the study of Barr and colleagues (1990a) the higher perforation rate after intubation was accounted for by the radiological detection of unsuspected pharyngeal tears; in the studies of Alderson and Wright (1990) and Carter and colleagues (1992) the perforation rate after laser therapy or intubation was equal. In these studies, both endoscopic treatments were associated with a similar and very low procedure related mortality. These findings can probably be accounted for by the expertise of the operators and the early detection and appropriate management of complications (Anderson 1990), emphasizing the importance of tertiary referral centres for the management of malignant dysphagia.

The experience presented in this thesis indicates that laser therapy and endoscopic intubation should be considered complementary rather than mutually exclusive both in terms of absolute indications, which have been discussed in chapter 2, and for the management of treatment related complications. Endoscopic intubation is very effective in the management of oesophageal perforation and oesophago-pulmonary fistulae (Robertson and Atkinson 1986) which may develop during the course of laser therapy, if necessary with the use of cuffed endoprostheses (Lux et al 1987, Sargeant et al 1992b). It is also very useful in salvaging failures of laser treatment occurring as a result of extrinsic tumour compression or mural stricturing, functional dysphagia and rapid tumour regrowth or inadequate tumour recanalisation. In the present investigation and other prospective studies of laser and intubation, 66-75% of patients who developed refractory dysphagia or complications during the course of laser therapy were successfully managed by intubation, resulting in an overall long-term palliation rate with combined endoscopic therapy greater than 90%. Such a policy of initial laser therapy with intubation at a later stage if necessary, is equally effective as intubation alone in providing long-term palliation of dysphagia but has the advantage of enabling significantly more patients to eat a normal diet during their remaining survival. Laser therapy on the other hand, comes to the aid of intubation in two main situations thus helping to optimize patient management. Where intubation fails because of complete luminal occlusion or excessive tumour angulation, preliminary laser recanalisation facilitates
tube placement without significant morbidity (Barr et al 1990a; Chatlani et al 1990). The second situation is the use of laser therapy to deal very effectively with the difficult problem of prosthesis tumour overgrowth for which few other therapeutic options are available (chapter 7).

The encouraging initial experience with intubation for the palliation of high cervical oesophageal carcinomas (chapter 8) shows that specific modifications in the design of endoprostheses enables them to be successfully employed in situations previously considered as absolute contraindications for the technique. Technological developments in the design and manufacture of prostheses, will help to overcome many of the problems associated with the use of plastic tubes and hence improve the safety of the technique and the quality of palliation provided. An important recent such development is the introduction into clinical practice of self expanding metal stents. Back in 1934, Sir Henry Souttar proposed that the ideal oesophageal tube should "be flexible, incompressible, non-traumatic and compact, have an adequate lumen and remain in place". The expanding metal stents of the 1990s possess many of these attributes and theoretically their use in preference to their plastic counterparts should result in several clinical benefits. The published experience, reviewed in chapter 2, indicates that metal stents provide a quality of swallowing similar to that of laser therapy with an equivalent morbidity and mortality. Although it is logical to expect that the larger the luminal diameter of a prosthesis the better the swallowing should be, in the only formal comparison of plastic and metal prostheses (Knyrim et al 1993) no difference in swallowing quality was apparent probably as a result of incomplete metal stent expansion in a proportion of patients. The study by Knyrim and colleagues (1993), confirmed the potential safety advantage of metal stents which resulted in a significant reduction in hospital stay and total patient expenditure despite their appreciably higher cost. An exciting potential of the silicone coating of metal stents, developed in order to prevent tumour ingrowth and seal oesophago-pulmonary fistulae, is that it may be impregnated with and serve as a carrier for pharmacological agents. A coronary artery stent impregnated with slow release heparin has previously been conceived and it is possible that for oesophageal carcinoma the coating could be impregnated with cytotoxic agents providing sustained local chemotherapy. Metal stents represent a valuable addition to the armamentarium of the therapeutic endoscopic. It is important to establish
their proper clinical role with carefully designed clinical trials and to avoid their indiscriminate use.

Of the alternative palliative treatments for malignant dysphagia, endoscopic alcohol injection treatment and brachytherapy appear most promising. Injection treatment is an appealing new technique and the preliminary experience has been encouraging. Like laser therapy it is performed under direct vision enabling targeting and can be repeated if required. Unlike laser therapy no special equipment is required, it is inexpensive and technically simple and potentially could be carried out in most gastroenterology units and not just in specialist centres. Future clinical trials are warranted in order to establish its clinical role as an alternative or adjunct to other treatment modalities. Despite its low cost, data on cost-effectiveness are also required as the need for repeated procedures and alternative modalities for the management of treatment failures, may prove to be equally or more costly than a single potentially "one-off" treatment such as endoscopic intubation. Although brachytherapy is generally well tolerated and provides fairly rapid tumour debulking and palliation of dysphagia, it is less appropriate for asymmetric tumours than endoscopic treatments performed under direct vision as the circumferential effect it produces exposes normal tissues to radiation leading to persistent oesophagitis. Repeat treatments are required by a significant proportion of patients but are limited by cumulative toxicity. Brachytherapy may prove very useful as an adjuvant to laser therapy as discussed below.

11.2.2 Laser Therapy in Combination Treatment Protocols

11.2.2.1 Optimizing the Results of Laser Therapy

The combination of laser treatment and radiotherapy is conceptually highly complementary. Laser therapy is very effective for debulking intraluminal tumour but has little or no effect on intramural and extraluminal tumour which can be treated effectively by radiotherapy. If the aim is to treat all the tumour bulk in the organ of origin and its local lymph node metastases, which can practically be encompassed by a moderately sized field, external beam radiotherapy is necessary. Brachytherapy is adequate for treating intraluminal and intramural tumour and limited local extension. When considering such combination treatment it is important to be clear about its objectives. As highlighted in previous discussion, a significant disadvantage
of laser therapy is the need for repeated treatments; compared to endoscopic intubation, patients undergoing laser therapy require significantly more procedures and longer hospitalisation, accounting for 8-14% of their remaining survival. The major objective of adjuvant external beam radiotherapy in these patients is to slow down regrowth of intraluminal tumour and reduce the need for repeated treatments; possible prolongation of survival should be considered of secondary importance.

The pilot study of combined laser therapy and external beam radiotherapy presented in chapter 6, has demonstrated a significant increase in the interval between laser procedures and a marginal prolongation of survival compared to historical laser controls; it should be remembered however, that the recruited patients were selected introducing bias into the comparison. An important observation was that patients were very sensitive to radiotherapy and increasing the dose above 30Gy resulted in a worse outcome. Subsequent randomised studies employing external beam radiotherapy (Sargeant et al 1992a) and brachytherapy (Sander et al 1991) have provided less encouraging messages. Although a significant increase in the treatment interval was demonstrated, it was of lesser magnitude than in the study presented in chapter 6 and on average would result in a saving of only one endoscopic treatment during a patient's lifetime given the limited prognosis. In addition, these studies did not demonstrate a significant prolongation of survival after combination therapy.

It would thus appear that external beam radiotherapy or brachytherapy as an adjuvant to laser treatment is justified only in patients with good general condition and better life expectancy in an attempt to prolong the dysphagia free interval; it remains unclear whether such treatment should be offered only to patients with squamous cell tumours. Logically these treatment recommendations should apply to the use of radiotherapy in combination with other endoscopic techniques of intraluminal tumour debulking such as alcohol injection and BICAP therapy. In the case of endoscopic intubation, the only potential benefit of adjuvant external beam radiotherapy is prolongation of survival. On the basis of the present and other evidence (Oliver et al 1990), such treatment is not indicated outside the setting of clinical trials.

Better definition of patient groups who are more likely to benefit from adjuvant radiotherapy after laser therapy or other methods of intraluminal
tumour debulking is clearly required. This would spare some patients from
unnecessary treatment and morbidity and result in substantial cost savings.
Available evidence suggests that endoscopic ultrasound may be of value in
predicting response to treatment. In studies of patients with inoperable
oesophageal or gastric cardia carcinoma treated with external beam
radiotherapy after initial debulking of intraluminal tumour with laser
therapy (Sargeant et al 1992a and personal communication) or brachytherapy
(Tio et al 1994), the presence of metastatic lymph nodes and tumour thickness
have emerged as significant indicators of prognosis. Patients with multiple
(usually more than 5) metastatic lymph nodes and a tumour thickness
(excluding the intraluminal component) greater than 16-20mm on
endosonography, generally tolerated adjuvant radiotherapy poorly and
derived no significant benefit in terms of survival.

Additional well designed studies of radiotherapy used in combination with
laser therapy for the palliation of malignant dysphagia are required before
firm conclusions can be drawn. Such studies should also investigate new
types of fractionation, including hyperfractionation (Bleehen et al 1991), and
the use of external beam radiotherapy in combination with brachytherapy
which may reduce treatment duration and provide superior results. Clinical
trials of radiotherapy as an adjuvant to other endoscopic treatments for
malignant dysphagia, such as alcohol injection, should also be encouraged.

11.2.2.2 Optimizing the Results of Radiotherapy and Chemotherapy

The work of Caspers and colleagues (1988) demonstrates clearly that patients
with severe dysphagia at presentation gain little from external beam
radiotherapy used as single modality therapy regardless of their general
condition or whether palliative or radical doses of radiotherapy are used. In
contrast, patients who are able to eat at least a semi-solid diet prior to
treatment do significantly better and derive a meaningful prolongation of
survival after radical doses of radiotherapy. Preliminary laser recanalisation
may result in a sufficient improvement in nutritional and general health
status to enable patients who were initially regarded as untreatable or, at best,
suitable for palliative doses of radiotherapy only, to undergo radical
radiotherapy and intensive chemotherapy as part of multimodality treatment
protocols. Such treatment is proposed for patients with relatively good
general condition who are not considered surgical candidates because of
advanced disease or medical contraindications, in an attempt not only to

201
palliate symptoms but also to alter the natural history of the disease. Multimodality treatment should also be considered for operable patients as an alternative to palliative resection in the context of clinical trials.

Multimodality treatment protocols are based on the synergistic effect of concurrent chemotherapy and radiotherapy. Chemoradiation ensures a complete tumour response in 25-40% of cases of oesophageal squamous cell carcinomas and has been shown to alter the natural history of the disease (Forrastiere et al 1993). Survival after chemoradiation (around 38% at 2 years) is comparable to that achieved with tumour resection but is significantly better than with radiotherapy alone (Araujo et al 1991, Herskovic et al 1992). However, side effects are common and the morbidity and mortality, which is of the order of 3% (Coia et al 1991), must be taken seriously into consideration when contemplating such treatment. Recently, Nd:YAG laser therapy has been included in such multimodality treatment protocols (Sibille et al 1994). The rationale for laser therapy is not only to provide prompt relief of dysphagia and improve the nutritional and general condition of the patient but also to reduce total tumour volume by destroying its intraluminal component and enhance the efficacy of radiotherapy. Laser therapy is performed at the first stage of such protocols but after the initial course of chemotherapy, as it is believed that chemosensitised tumour tissue is more susceptible to thermal destruction. Preliminary clinical experience indicates that long-term palliation of dysphagia is possible without the need for repeated laser sessions, although dilatation of oesophageal strictures is not infrequently required (Sibille et al 1994). Laser therapy is expected to play an increasing role in non-surgical multimodality treatments for oesophageal cancer in the future.

11.3 Treatment of Large Bowel Cancers

The results presented in chapter 9 indicate that endoscopic laser therapy is an effective non-surgical treatment for the palliation of advanced rectosigmoid cancers. However, it is still unclear whether the results from our own and other specialist units can be reproduced by less experienced endoscopists. Laser therapy is the only non-surgical local treatment which can be applied safely on either side of the peritoneal reflection of the rectum, without general or regional anaesthesia and with minimal upset to patients. It should be underscored however, that to date no controlled studies have compared
laser therapy with alternative treatment modalities. Such studies, including those investigating combinations of treatments, are clearly required. Best results will probably be achieved when different treatments are used in combination rather than in competition. As with the treatment of upper gastrointestinal tract tumours, the major disadvantage of laser therapy for advanced rectosigmoid cancer is the need for repeated treatments. Radiotherapy can be given as an adjuvant to laser therapy with the same rationale as in the treatment of oesophageal cancer but also in an attempt to palliate pelvic pain, which not infrequently accompanies advanced rectal cancer and is unlikely to respond to laser therapy. The preliminary evidence is very encouraging and shows that adjuvant external beam radiotherapy can result in a significant prolongation of the treatment interval and survival (Sargeant 1993). Additional randomised studies are required in order to verify these results; the combination of external beam radiotherapy and brachytherapy should also be investigated as it may yield superior results.

What guidelines can be set regarding the appropriate use of laser therapy for rectosigmoid cancer? It is the view of this author that laser therapy is not indicated in operable patients if cure is possible, even if an abdominoperineal resection is required. It also has no role for the treatment of tumours with unfavourable endoscopic characteristics, for example those which are submucosal or extremely ulcerated. On the other hand laser therapy is clearly indicated, and is probably the treatment of choice, for patients who are considered inoperable because of high anaesthetic risk especially if the disease is incurable and those who refuse the option of surgery. Although these indications are rational and clear cut, the role of laser therapy in certain other situations is not fully defined. For example the best treatment for a patient who is a reasonable operative candidate but is incurable because of advanced local disease or hepatic metastases remains unclear. Therapeutic choices should be made after careful consideration of quality of palliation and quality of life as well as the treatment related morbidity and mortality. The retrospective comparison of laser therapy and surgery presented in this thesis (chapter 10) has attempted to define the best management for this group of patients. The findings suggest that laser therapy is preferable for advanced loco-regional and extensive metastatic disease whereas for patients with few hepatic metastases, resection of the primary tumour is probably the most logical option as additional treatment of the limited hepatic disease can improve ultimate survival. These tentative conclusions need to be confirmed
by future randomised trials; such studies will prove feasible only if they derive the enthusiastic support of our surgical colleagues.

It should be emphasised that laser therapy should not be viewed as being in competition with surgery; certainly it is not an "either or situation". Best results for the patient will be achieved when there is close collaboration between laser endoscopist and surgeon. This was clearly demonstrated in the prospective audit of laser therapy presented in chapter 9 in which the majority of patients who sustained complications or failed to improve after laser therapy were salvaged by limited surgery which offered reasonable palliation until their death. Another situation in which laser therapy and surgery can be used in a complementary fashion to optimize outcome is the treatment of patients with obstructing carcinomas of the left colon. Such tumours carry a disappointingly high morbidity and operative mortality and poor long-term survival when compared with elective cases. The series of Phillips and colleagues (1985) and Kaufman and coworkers (1989) for example, showed an operative mortality of 23% and 22% respectively for patients presenting with obstruction compared to 11% and 7% respectively for elective cases. The traditional management of obstructing carcinomas of the left colon is a three stage approach but this has gradually given way to primary resection with immediate or delayed anastomosis. Immediate anastomosis however, is associated with a higher risk of leakage than after an elective operation. Nd:YAG laser tumour recanalisation can potentially convert an acutely obstructed case into an elective non-obstructed case, with a consequent reduction in operative mortality and morbidity and the possibility of avoiding a stoma. The use of pre-operative laser treatment for acutely obstructing colonic cancers was reported by Kiefhaber and colleagues (1986). Successful recanalisation was possible in 54 out of 57 cases (95%) and as a result the operative mortality was 8.8%, which is considerably lower than that quoted for obstructed cases (Phillips et al 1985, Kaufman et al 1989). Similar results have been reported in smaller series by Eckhauser (1987) and Dittrich and colleagues (1992).

The ability of Nd:YAG laser therapy to effect complete macroscopic and microscopic eradication in a high proportion of selected patients with small rectal tumours has been demonstrated both in this thesis and in other studies which have been reviewed in chapters 2 and 8. Such potentially curative laser treatment should be recommended only in elderly, high surgical risk patients.
especially if an abdominoperineal resection is the alternative and in younger patients who refuse surgery because of unwillingness to accept a colostomy or fear of possible micturition and impotence problems. In operable patients, even with the best means of preoperative tumour staging currently at our disposal, we have not reached a level of sophistication to accurately predict that laser treatment will be as effective as surgical treatment. However, things may change in the near future with developments in imaging techniques and the treatment of involved local lymph nodes.

11.4 Implications for the Provision of Laser Services

An important issue regarding the provision of services, is whether endoscopic laser therapy for the treatment of gastrointestinal tract tumours should be made available at most district general hospitals or only at specialist tertiary referral centres. Before attempting to answer this question, it is important to provide an estimate of the likely workload involved. Using the incidence figures of oesophageal and rectal carcinoma for the United Kingdom and the proportions of these patients who according to published experience are considered unsuitable for surgical treatment (see chapters 2 and 3), it can be calculated that roughly two thousand new patients with oesophageal cancer and an additional two thousand with rectal cancer per year would be potential candidates for laser therapy. It can be predicted that this demand will be even greater in the future if laser therapy becomes increasingly used in multimodality treatment protocols given not only with palliative but also curative intent. Based on these figures, the total workload for laser palliation at an average district general hospital would be only twenty to twenty five cases per year. On the other hand if laser therapy were to be provided only by specialist centres, fifteen to twenty such units would be required on a national level to cope with the entire demand on the assumption that four to five new cases can be treated weekly, which is the experience at the National Medical Laser Centre.

Given the current capital cost of a Nd:YAG laser which is around £50,000, it would be difficult to justify its availability in small district general hospital endoscopy units with a potential workload of only twenty to twenty five cases per annum. Although costs are expected to fall to some extent with the production of more compact lasers and inexpensive disposable fibres, significant savings and an improvement in the cost-effectiveness of laser
therapy will result only by the establishment of tertiary referral, multi-specialty laser endoscopy units treating large numbers of patients. At the National Medical Laser Centre for example, in addition to the five laser sessions for the treatment of gastrointestinal tumours there are two sessions dedicated for the treatment of tracheo-bronchial tumours and a single session for bladder tumours.

There are additional, more important, arguments for not recommending the widespread availability of lasers. The results of laser therapy, like those of other endoscopic therapeutic procedures, are highly operator dependent. Efficacy will be maximised and complications and morbidity minimised, if treatment is performed by highly skilled endoscopists working in specialist referral centres with a large patient turnover rather than by "occasional" endoscopists in small units. In addition, the availability of highly trained nursing staff in specialist endoscopy units contributes greatly to patient safety and comfort. It has been stressed in the foregoing discussion that best results for the palliation of gastrointestinal cancers will be achieved if laser therapy is used in a complementary fashion with other endoscopic techniques or in combination treatment protocols with radiotherapy and chemotherapy. It is logical therefore, that laser units should be based in referral centres with specialised departments of radiotherapy, oncology and radiology. The close collaboration between doctors of different backgrounds working as part of a multi-disciplinary team and the specialist input they provide to the management of patients with gastrointestinal malignancies, will help to optimise treatment outcome. Nurses with an oncological training should be an integral part of such multi-disciplinary or palliative care teams as they provide invaluable counseling and support for patients through the close relationship that develops between them.

11.5 Outlook for the Future

Lasers have become established as important and versatile tools in gastroenterology especially in the field of endoscopic therapy. Although there are a number of different possible applications, the future of lasers seems to lie in the treatment of gastrointestinal malignancies. At the present time, such treatment is primarily palliative. It is hoped that future technologic advances will not only improve its efficacy but will allow it to be used as a
primary treatment modality in place of conventional surgery if not for most, at least for early or small cancers.

Both the Nd:YAG laser and photodynamic therapy, or a combination of the two techniques, can be used with a prospect of cure. The potential of Nd:YAG laser therapy to effect cure has been demonstrated both with early gastric cancers (Takemoto 1986) and small colorectal cancers (see chapters 2 and 8). Photodynamic therapy, involves destruction of previously photosensitised gastrointestinal tract tumours by the cytotoxic action of singlet oxygen which is released when the neoplastic tissue is exposed at endoscopy to laser light of an appropriate wavelength either by surface illumination or interstitial application (Krasner et al 1990). Some photosensitisers are retained in neoplastic tissue for a longer time than in normal tissues offering the possibility of selective tumour destruction. A significant biological advantage of photodynamic therapy is that healing occurs by regeneration and as the submucosal collagen is spared, the mechanical strength of the gut wall is not reduced after full-thickness injury (Barr et al 1988). In contrast, healing of thermal lesions induced by the Nd:YAG laser occurs by fibrous tissue formation and scarring (Kelly et al 1983). Although photodynamic therapy is theoretically an attractive treatment option, the available clinical evidence suggests that best results are obtained with early carcinomas treated with a prospect of cure (Kato et al 1986, Barr et al 1990b). Late tumour recurrence after initial eradication was recorded in most series so careful follow-up is advisable. The results of photodynamic therapy for large inoperable tumours are much less satisfactory (McCaughan et al 1984, Thomas et al 1987) and great caution should be exercised as significant delayed haemorrhage after sloughing of necrosed tumour has been recorded (Barr et al 1990b). The use of high power Nd:YAG laser treatment should be preferred for advanced tumours. Conceivably the two techniques could be used in combination, with or without adjuvant chemoradiation, photodynamic therapy being used after initial tumour debulking with the Nd:YAG laser in order to treat residual intramural areas of tumour.

If laser therapy is to be used with curative intent, the endoscopist must have information regarding the extent of the pathologic process and the completeness of treatment. Accurate definition of tumour extent has been greatly facilitated by the advent of endoscopic ultrasound (Tio and Tytgat 1986); the accuracy of the technique is expected to improve even further with
the development of ultrasound probes of higher resolution. Two exciting prospects in the precise assessment of gastrointestinal tract lesions are three-dimensional video endoscopy (Sivak et al 1987) and holographic endoscopy (Epstein and Friedman 1989). The major advantage of holographic endoscopy is the ability to produce detail comparable to that of light microscopy and may render tissue sampling unnecessary. These techniques could be used, in combination with endoscopic ultrasonography, not only to assess a tumour but also to monitor and control the treatment itself. The ability to monitor the spread of thermal damage during interstitial treatment of neoplastic hepatic lesions by real-time ultrasonography has been demonstrated (Hashimoto 1989), so it is conceivable that endosonography could be used to monitor the extent of endoscopic Nd:YAG laser treatment. The development of "smart or intelligent" endoscopes is another significant advance which in combination with new types of fibres will also help to improve the efficacy and safety of laser treatment. These endoscopes which are self-advancing and lumen seeking, will facilitate passage through even the narrowest of lumens rendering the entire extent of a tumour accessible for laser therapy. In addition, their ability to keep the target in view during treatment, which is often difficult in real life, is an important advantage. Having acquired the target, laser treatment can proceed with computer assistance and the extent of damage induced controlled by the various monitoring and feedback systems described above.

The great strides which have been made over the last decade with endoscopic laser therapy for gastrointestinal tract tumours, have earned the technique an important place in the therapeutic armamentarium of medical and surgical gastroenterologists. The progress is set to continue as a result of recent technological developments and the future of laser therapy appears bright indeed.
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Appendix 1: Publications arising from this work


Appendix 2: Statement of individual contribution to studies

None of the studies described in this thesis, either whole or in part, have previously been submitted for a higher degree. As with most clinical research, the present studies were the result of cooperation between a number of individuals.

The prospective comparative trial of laser therapy and endoscopic intubation for the palliation of malignant dysphagia (chapter 5) was designed and conducted by the author who was responsible for data collation and analysis. All patients who received laser therapy were treated, or their treatment closely supervised, by the author or Professor S G Bown. Patients in the intubation arm of the study were treated at Queen's Medical Centre, Nottingham by Professor Michael Atkinson or Mr Charles Robertson. The cost analysis of the two endoscopic treatments, was performed by Mr Mark J Sculpher of the Health Economics Research Group, Brunel University, Uxbidge, Middlesex.

The study of laser therapy plus adjuvant radiotherapy for the palliation of malignant dysphagia (chapter 6) was designed and conducted by the author who enrolled all twenty two patients. The author, in collaboration with Professor S G Bown, treated and followed-up until death all but two patients; the treatment of these remaining patients was completed by Dr I R Sargeant under the supervision of S G Bown. The data collection and analysis was performed by the author.

All patients with malignant dysphagia due to tumour recurrence after surgery who received laser therapy (chapter 7) were treated by the author or Professor S G Bown; patient follow-up, data collection and analysis was performed by the author. The author was also responsible for the treatment, follow-up until death and the necessary data collection and analysis for seven of the fourteen patients included in the series of laser therapy for prosthesis tumour obstruction (chapter 7); the remaining patients were treated by Dr I R Sargeant.
The author personally developed the modified Celestin prosthesis and performed the intubation of all patients with cervical oesophageal cancer (chapter 8).

The author organised and conducted the prospective study of laser therapy for advanced rectosigmoid cancer (chapter 9). All patients were treated, or their treatment closely supervised, by the author or Professor S G Bown. Data collection and analysis for patients with incurable rectosigmoid cancer who had received surgical treatment at University College Hospital (chapter 10) was performed by the author aided by Dr V Komborozos, a visiting surgical fellow.